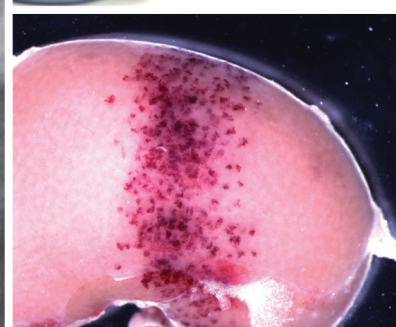
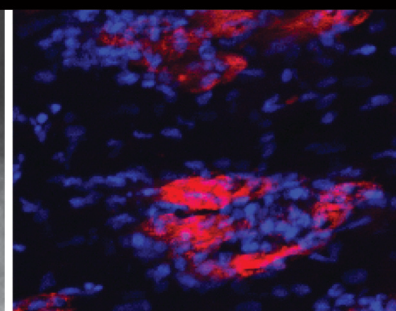


# THE SAFE USE OF ULTRASOUND IN MEDICAL DIAGNOSIS

Edited by Gail ter Haar

3rd Edition



# **The Safe Use of Ultrasound in Medical Diagnosis**

**3rd Edition**

**Edited by Gail ter Haar**

We should like to acknowledge the support of the British Medical Ultrasound Society, the European Federation of Societies for Ultrasound in Medicine and Biology, and the National Physical Laboratory (UK). Without their generosity this revision would not have been possible.

The British Institute of Radiology  
36 Portland Place, London W1B 1AT, UK  
[www.bir.org.uk](http://www.bir.org.uk)

Published in the United Kingdom by The British Institute of Radiology

© 1991 The British Institute of Radiology

© 2000 The British Medical Ultrasound Society & The British Institute of Radiology

© 2012 The Authors



This book is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

Some rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical or photocopying, recording, or otherwise for commercial purposes, or altered, transformed, or built upon, without the prior written permission of the British Institute of Radiology

First published 1991 (978-0-905749-28-0)

Second edition 2000 (978-0-905749-42-6)

Third edition 2012 (978-0-905749-78-5)

British Library Cataloguing-in Publication data

A cataloguing in record of the publication is available from the British Library

ISBN 978-0-905749-78-5 (print)

ISBN 978-0-905749-79-2 (eBook)

A print version of this book can be purchased from the BIR website

The British Institute of Radiology has no responsibility for the persistence or accuracy of URLs for external or third-party internet websites referred to in this publication, and does not guarantee that any content on such websites is, or will remain, accurate or appropriate

All opinions expressed in this publication are those of the respective authors and not the publishers. The publishers have taken the utmost care to ensure that the information and data contained in this publication are as accurate as possible at the time of going to press. Nevertheless the publishers cannot accept any responsibility for errors, omissions or misrepresentations howsoever caused. All liability for loss, disappointment or damage caused by reliance on the information contained in this publication or the negligence of the publishers is hereby excluded

# Contents

<b>Contributors</b>		<b>iv</b>
<b>Preface</b>		<b>v</b>
<b>Chapter 1</b>	<b>Introduction</b>	<b>1</b>
	<i>Gail ter Haar</i>	
<b>Chapter 2</b>	<b>The propagation of ultrasound through tissue</b>	<b>4</b>
	<i>Francis A. Duck</i>	
<b>Chapter 3</b>	<b>The acoustic output of diagnostic ultrasound scanners</b>	<b>18</b>
	<i>Adam Shaw and Kevin Martin</i>	
<b>Chapter 4</b>	<b>Ultrasound-induced heating and its biological consequences</b>	<b>46</b>
	<i>Charles C. Church and Stanley B. Barnett</i>	
<b>Chapter 5</b>	<b>Non-thermal effects of diagnostic ultrasound</b>	<b>69</b>
	<i>J. Brian Fowlkes</i>	
<b>Chapter 6</b>	<b>Radiation force and its possible biological effects</b>	<b>81</b>
	<i>Hazel C. Starritt</i>	
<b>Chapter 7</b>	<b>Bio-effects—cells and tissues</b>	<b>91</b>
	<i>Gail ter Haar</i>	
<b>Chapter 8</b>	<b>The safe use of contrast-enhanced diagnostic ultrasound</b>	<b>105</b>
	<i>Douglas L. Miller</i>	
<b>Chapter 9</b>	<b>Epidemiological prenatal ultrasound studies</b>	<b>125</b>
	<i>Kjell Å. Salvesen</i>	
<b>Chapter 10</b>	<b>Safety standards and regulations: the manufacturers' responsibilities</b>	<b>134</b>
	<i>Francis A. Duck</i>	
<b>Chapter 11</b>	<b>Guidelines and recommendations for the safe use of diagnostic ultrasound: the user's responsibilities</b>	<b>142</b>
	<i>Gail ter Haar</i>	
<b>Glossary</b>		<b>159</b>
<b>Index</b>		<b>163</b>

# Contributors

## **Dr Stanley B. Barnett, MSc, PhD**

11/147 Darley St. West, Mona Vale, NSW 2103, Australia  
E-mail: shirlstan2004@yahoo.com

## **Dr Charles C. Church, MSc, PhD**

National Center for Physical Acoustics, University of Mississippi, MS 38655, USA  
E-mail: cchurch@olemiss.edu

## **Professor Francis A. Duck, PhD, DSc**

3 Evelyn Rd, Bath BA1 3QF, UK  
E-mail: f.duck@bath.ac.uk

## **Professor J. Brian Fowlkes, PhD**

Department of Radiology, University of Michigan, Medical Science I, 1301 Catherine,  
Room 3226C, Ann Arbor, MI 48109-5667, USA  
Department of Biomedical Engineering, University of Michigan, 3315 Kresge Research Building III,  
204 Zina Pitcher Place, Ann Arbor, MI 48109-0552, USA  
E-mail: fowlkes@umich.edu

## **Dr Kevin Martin, BSc, PhD, FIPEM**

Department of Medical Physics, University Hospitals of Leicester,  
Infirmary Square, Leicester LE1 5WW, UK  
E-mail: kevin.martin42@btinternet.com

## **Dr Douglas L. Miller, PhD**

Basic Radiological Sciences Division, Department of Radiology, University of Michigan SPC 5667,  
3240A Medical Science Building I, 1301 Catherine Street, Ann Arbor, MI 48109, USA  
E-mail: douglm@umich.edu

## **Dr Kjell Å. Salvesen, MD, PhD**

Department of Obstetrics and Gynaecology, Clinical Sciences, Lund University,  
Box 117, SE-221 00 Lund, Sweden  
E-mail: pepe.salvesen@ntnu.no

## **Mr Adam Shaw, BA, MA (Cantab)**

Acoustics and Ionizing Radiation Division, National Physical Laboratory,  
Hampton Road, Teddington TW11 0LW, UK  
E-mail: adam.shaw@npl.co.uk

## **Dr Hazel C. Starritt, PhD**

Medical Physics and Bioengineering, Royal United Hospital, Combe Park, Bath BA1 3NG, UK  
E-mail: hazelstarritt@nhs.net

## **Dr Gail ter Haar, MA, PhD, DSc**

Institute of Cancer Research, 15 Cotswold Road, Belmont, Sutton SM2 5NG, UK  
E-mail: gail.terhaar@icr.ac.uk

# Preface

It is an oft observed fact that safety sessions at congresses are seldom well attended, and that the sneaky insertion of a lecture on a safety-related topic into a specialist session may be regarded by some as the opportunity for a coffee break, but the fact remains that the safe use of diagnostic ultrasound is the responsibility of the person conducting the scan. In order for appropriate judgements to be made, the practitioner must be knowledgeable about the hazards and risks involved in performing an ultrasound examination, and this book aims to provide this basic knowledge. Leading world experts in the fields of ultrasound physics, biology, standards and epidemiology have contributed chapters, written at a level that is intended to be accessible to everyone, whatever their background. Each chapter is extensively referenced to allow readers to delve deeper into a topic of interest if they so wish.

Ultrasound has an unprecedented safety record, but that does not mean that we can be cavalier about its use. What is evident from the information presented in this book is that there are many gaps in our knowledge about ultrasound safety. Many of the studies on which we base our information and recommendations have been carried out in animal models whose relevance to the human is not fully understood, ultrasound exposure conditions which have little relevance to diagnostic ultrasound pulses, or on scanners that are no longer in common clinical use. While this is useful information, it must always be interpreted with care.

It must be remembered that “absence of evidence of harm is not the same as absence of harm” (Salvesen *et al.*, 2011). It is never possible to prove a negative, all we can do is to use increasingly more sensitive tests and assays. It is for these reasons that professional societies continue to support committees whose remit is to inform and educate users about the safe use of ultrasound, so that ultrasound imaging can continue to enjoy its reputation as a technique whose benefits far outweigh any potential risk.

The publication of the third edition of this book would not have been possible without the generous support of the British Medical Ultrasound Society, European Federation of Societies for Medical Ultrasound and the National Physical Laboratories to whom I am extremely grateful.

Gail ter Haar  
London, November 2012

## Reference

Salvesen KÅ, Lees C, Abramowicz J, Brezinka C, ter Haar G, Maršál K. 2011. Safe use of Doppler ultrasound during the 11 to 13 + 6-week scan: is it possible? *Ultrasound Obstet Gynecol*, 37, 625–628.



# Chapter 1

## Introduction

**Gail ter Haar**

*Institute of Cancer Research, Sutton, UK*

The decision by the British Medical Ultrasound Society (BMUS), the European Federation of Societies for Ultrasound in Medicine & Biology (EFSUMB) and the UK National Physical Laboratory (NPL) to sponsor the revision of this publication on the topic of the safety of diagnostic ultrasound in medical practice at this time is entirely appropriate. In England alone, over two and a half million obstetric ultrasound scans (about four for every live birth) are performed every year ([Department of Health, 2012](#)). Many of these are carried out using the new generations of ultrasound scanners, which have the potential to produce significantly higher acoustic outputs than their predecessors (see [Chapter 3](#)). Ultrasound imaging has become more sophisticated and new techniques such as tissue harmonic imaging, pulse coding and contrast-enhanced imaging are becoming more common, bringing with them not only increased diagnostic capabilities, but also uncharted waters as far as safety considerations are concerned. This is not unusual; we have a track record of safety studies lagging behind clinical applications—there are, for example, no epidemiological studies concerned with the use of pulsed Doppler techniques. This state of affairs is not to be condoned, and there is now considerable effort being put into understanding the way in which an ultrasonic beam interacts with tissue in terms of its heating potential, and the probability of inducing mechanical effects such as acoustic cavitation, so that there is more chance of predicting and preventing the occurrence of an unwanted bio-effect.

During the early 1990s a change was made by the Food and Drug Administration (FDA) in the USA that has affected all those using ultrasound for medical diagnosis. Output levels had been set in the 1980s simply on the basis that such conditions had been in use before, with no evidence of hazard. The change allowed intensities previously reserved only for peripheral vascular studies to be used for all studies, including first-trimester scanning. No epidemiological or other evidence was then, or is now, available to support the assertion of safety at these higher exposures. The FDA change resulted in the widespread availability of high specification pulsed Doppler and Doppler imaging modes for uses in addition to cardiovascular applications, including obstetrics. Recognizing the difficulty of establishing resilient safety management for this change, the FDA decided to pass the responsibility for safe management to the user. Manufacturers

are now able to use higher exposures than before, provided that the equipment displays “safety indices”. These, the thermal index (TI) and the mechanical index (MI), have been designed to inform the user of conditions which might give rise to safety concerns during any scanning session. For those using ultrasound equipment, these changes in philosophy are of central importance to their clinical practice. The management of safety has become a partnership between manufacturers, whose responsibility it is to design and make safe equipment, and the users whose responsibility it is to understand how to operate the equipment safely. The primary purpose of this book is to inform users about the principles and evidence on which this safe practice depends.

Two biophysical mechanisms, heating and cavitation, have become central to safety judgements. In order to assist those using diagnostic ultrasound equipment to make their own judgements on safety, the two safety indices mentioned above were introduced. The TI gives an approximation to the greatest temperature rise which could occur in exposed tissue. This tissue warming (a more realistic word to describe what may happen than “heating”) results from the energy deposited in the tissue by ultrasound absorption. The highest local temperatures occur in bone *in vivo*, since this tissue absorbs the ultrasound waves most strongly. The theory for MI describes the resonant behaviour of gas bubbles in liquids, which could cause damage from “inertial cavitation”. Gas bodies are essential precursors to this process and there is no experimental evidence that inertial cavitation occurs at diagnostic ultrasound levels in their absence. However, there are two situations *in vivo* where gas bodies may be exposed to diagnostic ultrasound. These are during the use of gas-bubble ultrasound contrast agents, and when ultrasound exposes tissue which naturally contains gas, such as the lung or intestines. These are discussed in [Chapters 5 and 8](#).

When considering the safe use of ionizing radiation, the use of the ALARA (as low as reasonably achievable) principle is widespread and entirely appropriate. It is often brought up in the context of the safety of ultrasound exposures. Here it should be used with caution. If the assumption is correct that heating and cavitation are the two prime mechanisms by which hazardous bio-effects can be brought about, then, at exposure levels that lie below the thresholds for their occurrence (see [Chapters 4 and 5](#)) there is no reason for keeping exposures low, provided these thresholds are not exceeded. However, where exposure levels have the potential to move above the threshold then it is entirely appropriate to invoke the ALARA principle in an attempt to minimize potential hazard. At exposures below the thresholds, the risk/benefit judgement depends on uncertainties about the validity of these thresholds, and also about uncertainties of the existence and effects of other bio-effects mechanisms.

A problem that has bedevilled the study of ultrasound bio-effects is the lack of a consistent method of describing “dose”. There are no separate units to describe the level of ultrasound exposure incident on tissue (kerma would be used to describe this aspect of an X-ray beam) and the ultrasound “dose” to the tissue (here units of Gray are used for X-rays). A problem arises in ultrasound dosimetry, with ultrasound fields being described in terms of pressure or intensity, neither of which give a measure of energy deposition. Either “free-field” or *in situ* values are given. *In situ* values have been “derated” to account for tissue attenuation

(see [Chapters 2 and 3](#)). Often, the precise nature of the parameter quoted in the published bio-effects literature is not given. This situation has led to problems of interpretation of much of the early safety literature in terms of its relevance to diagnostic ultrasound exposures. However, more rigour is now being applied (and, increasingly, required by professional journals) and we can look forward to more clinically relevant safety studies coming out of research laboratories.

The intended readership of this book includes all clinical users of diagnostic ultrasound, including sonographers, radiologists and obstetricians, together with those using ultrasound in other clinical areas such as general practice, cardiology and vascular studies. It is also intended to provide fundamental information about ultrasound safety to those in clinical training. In addition, the book should be of value to clinical and research scientists engaged in the development of new ultrasound diagnostic methods. The book has been structured to aid interpretation of the “on-screen” labelling which is now used very widely on ultrasound scanners (see [Chapters 4–6](#)), to inform the user of the current status of bio-effects research (see [Chapters 7–9](#)); and to review the regulations and recommendations regarding use of diagnostic ultrasound (see [Chapters 10 and 11](#)).

The BMUS and EFSUMB have Safety Committees. One of the functions of these Groups is to ensure that their members are kept informed about issues of safety. This book arose originally, in part, as a result of an awareness of this responsibility. This revision has been co-sponsored by BMUS, EFSUMB and NPL. Another effective vehicle for circulating and updating safety information is the internet. The websites of the BMUS and EFSUMB Safety Committees provide a valuable resource containing safety statements, tutorial articles and literature reviews. The American Institute for Ultrasound in Medicine (AIUM) also publishes safety related information on their Website ([www.aium.org](http://www.aium.org)), as does the World Federation for *Ultrasound in Medicine & Biology* (WFUMB; [www.wfumb.org](http://www.wfumb.org)).

Ultrasound has an enviable record for safety. Nevertheless, modern scanners are capable of warming tissue *in vivo*, applying stress to tissue and, under some circumstances, damaging fragile structures adjacent to gas. It is essential that in the enthusiastic search for greater diagnostic efficacy the pre-eminent place gained by ultrasound as a safe diagnostic mode is not prejudiced. It is the responsibility of all those engaged in the diagnostic use of ultrasound to ensure that this is so.

## Acknowledgement

This chapter is a revised version of [Chapter 1](#) in the second edition. The contribution of Francis Duck to that chapter is acknowledged.

## Reference

Department of Health. 2012. <http://www.dh.gov.uk>.

# Chapter 2

## The propagation of ultrasound through tissue

**Francis A. Duck**

*University of Bath, Bath, UK*

### Summary

- Ultrasonic waves in the frequency range 1–20 MHz are widely used for medical diagnostic applications.
- Exposure is usually given in terms of peak rarefaction pressure, total acoustic power and acoustic intensity.
- *In situ* exposure may be estimated using simple tissue models.
- The two main bio-effects mechanisms are heating and mechanical processes.
- The most likely tissues to experience heating are bone and adjacent soft tissues.
- The most likely tissues to experience mechanical damage are those adjacent to gas: at the lung surface, in the intestine and with contrast agents.
- Non-linear acoustic effects are particularly significant during propagation through fluids such as water and amniotic fluid.

### 2.1 Introduction

The term ultrasound describes a mechanical wave, similar in character to audible sound, but at frequencies greater than 20 kHz, or 20,000 cycles per second. For medical applications frequencies typically above 1 MHz are used. These are at least 100 times more rapid than the oscillations that can be detected by the ear. In this chapter, a description is given of the way in which waves of this frequency travel through the body, emphasizing those aspects that may be important when making judgements about the safe management of diagnostic uses of ultrasound.

Particular emphasis will be given to the propagation characteristics in the frequency range between 1 MHz and 20 MHz. At such frequencies, practical use is made of these waves in clinical medicine for diagnostic, therapeutic and destructive purposes, and therefore their propagation characteristics are of particular interest and have been most fully studied. From a knowledge of the wave velocities and of the degree to which tissues

Ultrasound describes mechanical waves above 20 kHz

Frequencies between 1 MHz and 20 MHz are used for diagnostic ultrasound

absorb, scatter and reflect ultrasound, it is possible, in principle, to predict the manner by which ultrasound propagates within, and interacts with, the body. This chapter has two parts. In the first, a general overview is given of ultrasonic wave propagation, and of the properties of body tissues that affect it. In the second, this knowledge is used to describe what may happen to a pulse of ultrasound as it travels into tissue, so setting the biophysical basis for the later discussions of ultrasound safety.

## 2.2 Ultrasound wave propagation

Ultrasound is propagated in a manner identical to that of audible sound, through the displacements of the molecules constituting the medium in which the wave is travelling. It is thus a fundamentally different wave phenomenon from electromagnetic waves such as radio waves, infrared radiation and X-rays. The ultrasonic wave may propagate in the same direction as the displaced particles, in which case it is called a longitudinal compressional wave. Alternatively the particles may oscillate transversely, perpendicularly to the direction of propagation. Such a wave is termed a transverse or shear wave. Though shear waves can propagate in solids, and may therefore travel in calcified tissues such as bone or tooth, they are of little relevance in soft tissue, which can barely support them at ultrasonic frequencies.

The longitudinal wave is therefore of primary importance for medical applications of ultrasound. In a longitudinal wave, individual molecules or particles in the medium oscillate sinusoidally about a fixed location, moving forward and backward along the direction of propagation of the wave energy (Figure 2.1). As the particles move forward they become closer to those ahead, so increasing both the local density and the local pressure in the medium. Following their maximum forward displacement, the particles return towards and beyond their equilibrium location, resulting in a slight density reduction, and a reduction in local pressure. The difference between the ambient pressure (approximately atmospheric pressure) and the local pressure as the wave passes is called the “acoustic pressure”. This may be a compression (pressure above ambient) or a rarefaction (pressure below ambient). The greatest value of the acoustic pressure is of considerable importance when discussing aspects of safety concerning mechanical hazard. In particular, the “peak rarefaction pressure” is strongly related to cavitation events (see later). In diagnostic scanners these acoustic pressures can reach more than 2 MPa at the transducer face, or about 20 atmospheres. Referring to the rarefaction pressure, this means that the tissue is being pulled apart with a strength equal and opposite to about 20 atmospheres compression. The reason that it does not usually rupture is twofold. First, tissue, like water, can withstand this stress under many conditions. Second, the stress lasts for a very short time: at 1 MHz the rarefaction lasts only 0.5  $\mu$ s, and this period becomes progressively shorter as the frequency increases.

The distance between one compression (or rarefaction) and its immediate neighbour defines the wavelength,  $\lambda$  (Figure 2.1). At any particular frequency,  $f$ , the wavelength,  $\lambda$ , can be calculated from a knowledge of the velocity  $c$  (see below), using the expression  $\lambda = c/f$ . At 1 MHz the wavelength in soft tissues is typically between 1.5 mm and 1.6 mm,

Longitudinal waves are much more important than shear waves in soft tissues at diagnostic frequencies

The ultrasonic wave consists of compressions and rarefactions

Adjacent compressions are separated by one wavelength, typically 0.1–1 mm in soft tissues at common diagnostic frequencies

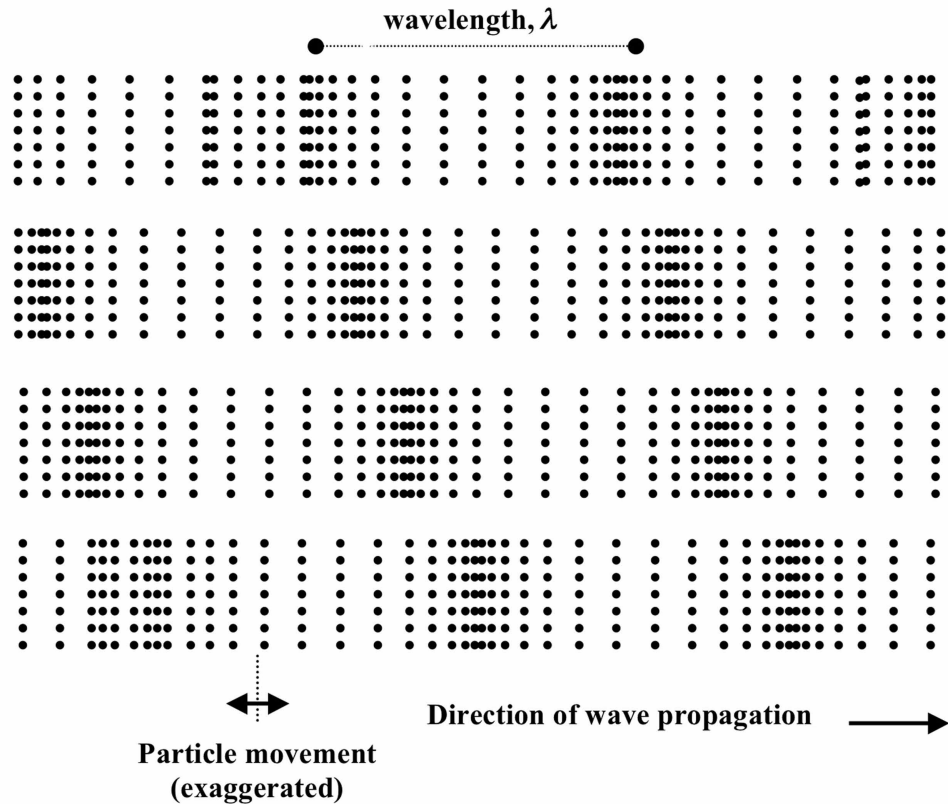


Figure 2.1. A diagram representing the progression of a longitudinal compressional wave moving forward by about half its wavelength. The time delay between each wave and the one below it is about  $\lambda/6c_0$ , where  $c_0$  is the speed of the wave. The dots represent the particles, which do not progress with the wave, but oscillate about an undisturbed position.

whereas at the same frequency the wavelength in bone is between 3mm and 4mm, because the wave travels about twice as fast in bone as in soft tissue (Table 2.1).

Standing waves  
are rare *in vivo*

Under very specific circumstances a standing wave can also be generated. This occurs when part of the energy in a longitudinal compressional wave is reflected back and interacts with the incoming wave, forming an interference pattern. Although such an arrangement can be generated in the laboratory, it is rare for conditions that may give rise to standing waves to occur in an ultrasonic field within the body. Moreover, for pulsed ultrasound, interference only occurs transiently, and very close to the reflecting surface.

### 2.2.1 Wave propagation speed

Wave speed  
depends  
on density  
and elastic  
properties

The speed at which an ultrasonic wave propagates is controlled by the mechanical properties of the medium. For liquids and soft tissues the speed of the wave,  $c_0$ , depends on the compressibility and the undisturbed density  $\rho_0$ . Solids support both longitudinal waves and shear waves, whose speeds depend on the elastic moduli of the solid. However, simple equations are difficult to apply directly to biological solids, including bone. This is partly because the mechanical properties of some tissues depend on direction, and

Table 2.1. Representative values for some acoustic properties of tissues at body temperature. Note that these are representative values only, and there are very wide variations of tissue properties for bone and soft tissues: Blood and amniotic fluid are better characterized. Values taken from [Duck \(1990\)](#), [ICRU \(1998\)](#) and [Verma et al. \(2005\)](#).

	Cortical bone	Non-fatty tissue	fat	Blood	Amniotic fluid
Propagation speed ( $\text{m s}^{-1}$ )	3635	1575	1465	1584	1534
Characteristic acoustic impedance ( $10^6 \text{ kg m}^{-2} \text{ s}^{-1}$ )	6.98	1.66	1.44	1.68	1.54
Attenuation coefficient at 1 MHz ( $\text{dB cm}^{-1}$ )	20	0.6	1.0	0.15	0.005
Attenuation coefficient frequency dependence	n/a	1.2	1.0	1.2	1.6
Non-linearity coefficient, B/A	n/a	7.0	10.0	6.1	n/a

consequently so do their ultrasonic properties. This dependence on direction is termed anisotropy.

Values for the wave speed of ultrasound through selected tissues are given in [Table 2.1](#). This table gives representative estimates of the speed with which ultrasound propagates in the range from 1 MHz to 10 MHz, at body temperature, in normal adult human tissues. Tissues from a particular organ, for example the liver, have a range of properties that may depend on age, sex, disease state, perfusion and even dietary habits. An increase in either water or fat content leads to a decrease in wave speed. Both fatty breast and fatty liver tissue have a lower wave speed than comparable normal tissue. Foetal tissues also have slightly lower speed than comparable adult tissue, but this is because of their higher water content. The presence of collagen, particularly in tendon, skin and arterial wall, gives rise to slightly higher speeds than in other soft tissues.

Speed through tissue depends on fat, collagen and water content

### 2.2.2 Specific acoustic impedance and interface reflections

When the particles of the medium move in response to an ultrasonic wave ([Figure 2.1](#)), there is a particle velocity associated with this movement. (This is quite distinct from the speed with which the wave travels.) Oscillations of particle velocity,  $v$ , and acoustic pressure,  $p$ , in a plane progressive wave are in phase: that is, the particles move fastest when the acoustic pressure is greatest.  $p$  and  $v$  are also proportional, and the constant of proportionality  $p/v$  is called the specific acoustic impedance,  $Z$ . A simple analysis shows that the acoustic impedance is equal to  $\rho_0 c_0$ . Knowledge of the acoustic impedance of a particular tissue is not, of itself, of great importance. The significance of this quantity is demonstrated only when considering the reflection and transmission of an ultrasonic wave as it passes across a boundary between two materials with different  $Z$ , or when small-scale variations in  $Z$  result in scattering. Acoustic impedance differs little between different soft tissues, and between soft tissues and water. The greatest differences occur at the interface between soft tissue

Changes in specific acoustic impedance control transmission and reflection at interfaces

## 2 The propagation of ultrasound through tissue

and bone where about one-half of the incident intensity is reflected, and at the interface between soft tissue and gas, which reflects almost all the incident wave. This second example is also interesting in that it is a so-called “pressure release interface” which causes the pressure wave to change phase. The compression in the wave is reflected as a rarefaction, and vice versa. The reflection process does not depend on the frequency of the wave, the same fraction being reflected from a plane soft-tissue/bone interface at 10 MHz as at 1 MHz.

### 2.2.3 Attenuation, absorption and scatter of ultrasound by tissue

Thus far in the discussion, no mention has been made of energy loss in the tissue through which the ultrasonic wave passes. This energy loss, or attenuation, gives rise to energy deposition in body tissues. The attenuation of a plane sound wave at a single frequency is described by the expression

$$p_x = p_0 e^{-2\alpha x} \quad (2.1)$$

where the initial acoustic pressure amplitude  $p_0$  has decreased to  $p_x$  after a travelling a distance  $x$  (see Figure 2.2).  $\alpha$  is the amplitude attenuation coefficient, with units of neper per centimetre,  $\text{Np cm}^{-1}$ . The relative reduction in amplitude or intensity is often expressed on a decibel scale, when the value is  $8.68\alpha \text{ dB cm}^{-1}$ .

The attenuation depends on the frequency of the wave. It is greater at higher frequencies. For soft tissues the dependence on frequency is approximately linear. It is common therefore to give values of the attenuation coefficient for tissue in units of decibel per centimetre per megahertz,  $\text{dB cm}^{-1} \text{ MHz}^{-1}$ .

Both absorption and scattering contribute to the reduction in acoustic pressure amplitude when an ultrasonic wave propagates through tissue. Therefore the total attenuation

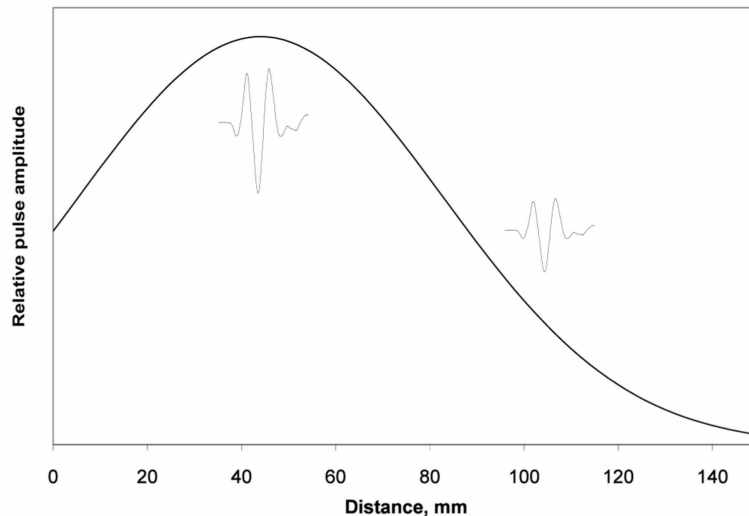


Figure 2.2. A diagram showing the alteration in amplitude with depth of an ultrasound pulse propagating into tissue. This example is for a 3 MHz beam, focused at 70 mm, propagating through tissue with an attenuation coefficient of  $0.5 \text{ dB cm}^{-1} \text{ MHz}^{-1}$ .

Attenuation is described as an exponential loss of pressure amplitude with distance

Attenuation coefficient of tissue depends linearly on frequency, approximately

coefficient  $\alpha$  can be expressed as  $(\alpha_a + \alpha_s)$ , where  $\alpha_a$  is the absorption coefficient and  $\alpha_s$  is the scattering coefficient. For soft tissues, attenuation is strongly dominated by absorption in the low-megahertz range, with scatter losses contributing no more than 10% to the total attenuation (Duck, 1990). For calculations involving energy loss the appropriate property is the attenuation coefficient for intensity,  $2\alpha$ .

The processes by which ultrasonic energy is absorbed by tissues are complex, and not fully understood. The frequency dependence differs from that of a simple liquid like water, for which attenuation over this frequency range depends on the square of the frequency. Representative values for some tissues are included in Table 2.1, which gives both the attenuation coefficient at 1 MHz and its frequency dependence. As a rule of thumb the average attenuation coefficient in soft tissue at any frequency is often taken as being  $0.5 \text{ dB cm}^{-1} \text{ MHz}^{-1}$ . The fraction of the input energy that is deposited in soft tissue, up to specified depths and for beams at 2 MHz, 3 MHz, 5 MHz and 10 MHz is shown in Figure 2.3.

The scattering of sound from tissue is anisotropic (depends on direction) and arises from small-scale variations in density and/or bulk compressibility, and hence in sound velocity. In the low-megahertz range there is strong coherent (i.e. in phase) forward scatter with generally weak scattering in all other directions. Only the very low-level backscattered component contributes to pulse-echo imaging, and this constitutes a vanishingly small fraction of the incident energy. The integrated backscattered energy from soft tissue may be as low as 50 dB below (that is, 0.00001 of) the incident energy, which implies that essentially all of the energy entering the body is deposited in the tissue.

Both absorption and scatter contribute to attenuation: in soft tissue, absorption dominates

For most diagnostic beams, 90% of the power is deposited within the first 5 cm of tissue

Essentially all the acoustic power incident entering through the skin surface is absorbed in the body tissues

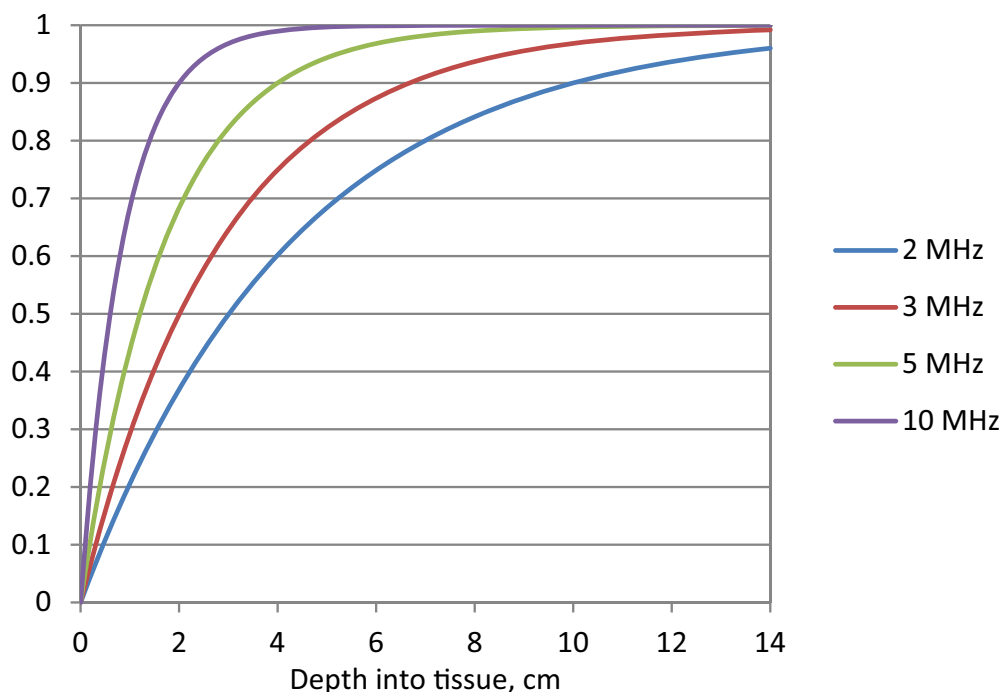


Figure 2.3. The fraction of the acoustic power leaving the transducer which is deposited in soft tissue up to a particular depth, depending on frequency. An absorption coefficient of  $0.5 \text{ dB cm}^{-1} \text{ MHz}^{-1}$  has been assumed.

## 2 The propagation of ultrasound through tissue

Bone attenuates much more than soft tissue

Attenuation in bone is much greater than in soft tissue. Attenuation coefficients in the range  $10\text{--}20\text{ dB cm}^{-1}$  have been reported at 1 MHz for cortical and skull bone. Attenuation in trabecular bone is highly variable, probably due to the contribution from scatter.

### 2.2.4 Beam structure and frequency content

Diagnostic pulses are typically shorter than  $1\mu\text{s}$  and contain a spectrum of frequencies

In practice, a number of other characteristics of beams of sound are significant for the complete description of the transmission of ultrasound through tissues. The structure of a beam of ultrasound close to its source can be highly complex (Humphrey and Duck, 1998). Of particular practical interest are the beams from the pulsed transducers that are widely used in medical diagnostic applications. Such sources emit very short pulses, being typically only two or three cycles, about  $0.5\mu\text{s}$ , in duration. The energy in these pulses of ultrasound is contained in a band of frequencies extending both above and below the resonant frequency of the ultrasound transducer that forms the source.

Focusing increases the intensity by up to 50 times, excluding attenuation effects

Diagnostic beams are also focused. This is done to reduce the beam width in order to improve imaging resolution. Focussing has the additional effect of increasing the acoustic pressure and intensity (see below) in the focal zone. The degree of focussing is weak, however, giving an increase in pressure amplitude of no more than about a factor 7, equivalent to a gain in intensity of about 50. In tissue, this increase is reduced because of attenuation of the tissue lying between the transducer and the focus.

### 2.2.5 Acoustic power and intensity

Acoustic power is a measure of the rate of energy flow

The total acoustic power emitted by the transducer is of central importance when considering its safe use. Acoustic power is a measurement of the rate at which energy is emitted by the transducer measured in watts: that is, joules per second. Acoustic powers in diagnostic beams vary from less than 1 mW to several hundred milliwatts. All this power is absorbed by the tissue, and, as a result, the temperature of the tissue is raised slightly. Although the power is delivered in very short pulses, it is more relevant to heating to average out the effects and to consider only the average power over many seconds.

Maps of acoustic intensity describe the spatial distribution of power

Whilst acoustic power is important, it is also relevant to describe how that power is distributed throughout the beam and across a scanning plane, so that local “hot-spots” may be quantified. This variation in “brightness” is measured as acoustic intensity, which is obtained by averaging the power over an area. The practical unit of measurement is milliwatt per square centimetre,  $\text{mW cm}^{-2}$ . The area may cover the whole beam, or a very local part of the beam. A commonly quoted intensity is the “spatial-peak temporal-average intensity,  $I_{\text{spta}}$ ”, which is the greatest intensity in the beam, where the beam is “brightest”. For an unscanned beam, such as that used for pulsed Doppler or M-mode, this will be in the focal zone: for a scanned beam, it may occur much closer to the transducer, particularly for sector scan formats.

Acoustic power and spatial-peak time-average intensity only give information about energy deposition when averaged over extended periods of time. Other acoustic quantities are used when it is necessary to describe the magnitude of the pulse itself; for example,

when considering mechanical effects which might result from the interaction of a single pulse with tissue, rather than a series of pulses. The most fundamental of these is the peak rarefaction pressure,  $p_r$ . The two other quantities, which are also used to describe the magnitude of the pulse, are the mechanical index, which is calculated directly from the peak rarefaction pressure (see [Chapter 10](#)), and the pulse-average intensity which describes the “brightness” of each pulse.

Rarefaction pressure, mechanical index and pulse-average intensity all describe the size of the ultrasound pulse itself

### 2.2.6 Estimates of *in situ* exposure

It is not generally possible to measure the acoustic field within the body directly. This difficulty has meant that alternative methods have been developed to give estimates of acoustic quantities such as power, acoustic pressure and intensity within the tissue during scanning, so-called “estimated *in situ* exposure”. Ideally, a numerical model would be used to predict pulse wave propagation through body tissues, taking account of all absorption, scattering, refraction and non-linear processes, and recognizing that the body tissues form a three-dimensional distribution of varying acoustic properties. The extreme complexity of this approach has led to a practical simplification, which is used at present whenever “estimated *in situ* exposure” is required.

Very simple models are generally used to estimate *in situ* exposure

All calculations are based upon measurements of the acoustic pressure in water. The tissue is modelled with uniform, homogeneous attenuating properties, with an attenuation coefficient of  $0.3 \text{ dB cm}^{-1} \text{ MHz}^{-1}$ . The selection of this value for attenuation coefficient, which is lower than the average for soft tissues alone (see [Table 2.1](#)), is justified by the view that it safely takes account of propagation through both soft tissue (with a slightly higher loss) and fluids (with lower loss). On average this method should overestimate the local exposure. Whilst this may be generally true, it must also be emphasized that *in situ* exposures estimated using this very simple model can only be taken as gross approximations to actual exposures.

$0.3 \text{ dB cm}^{-1} \text{ MHz}^{-1}$  allows a safety margin for estimated *in situ* exposure for many situations

## 2.3 Non-linear propagation effects

Thus far the discussion has assumed that the ultrasonic wave is governed by linear laws of acoustic propagation. This may be a poor approximation to what actually happens when ultrasonic pulses travel through tissue. So-called “finite-amplitude” effects occur, the terminology coming from the need to describe theoretically waves apart from those with vanishingly small amplitudes. These effects are of practical importance when considering exposure measurement, and the biophysical effects of ultrasound ([Duck, 2002](#)). An initially sinusoidal pressure wave of finite amplitude does not retain its sinusoidal waveform as it propagates. The compressions in the wave travel forward faster than the associated rarefactions partly because the speed of sound depends on density. This results in a distortion of the wave, in which the compressions catch up on the preceding rarefactions, ultimately forming a pressure discontinuity or shock. A comparison between the pulse-pressure waveform at two distances from a transducer is shown in [Figure 2.4](#). This shows the distortion in wave shape, which has been caused by several centimetres travel through water, with its accompanying acoustic shock separating the highest amplitude rarefaction and compression. The amount of non-linear distortion increases with several factors: the

Non-linear propagation causes waveform distortion and acoustic shock formation

## 2 The propagation of ultrasound through tissue

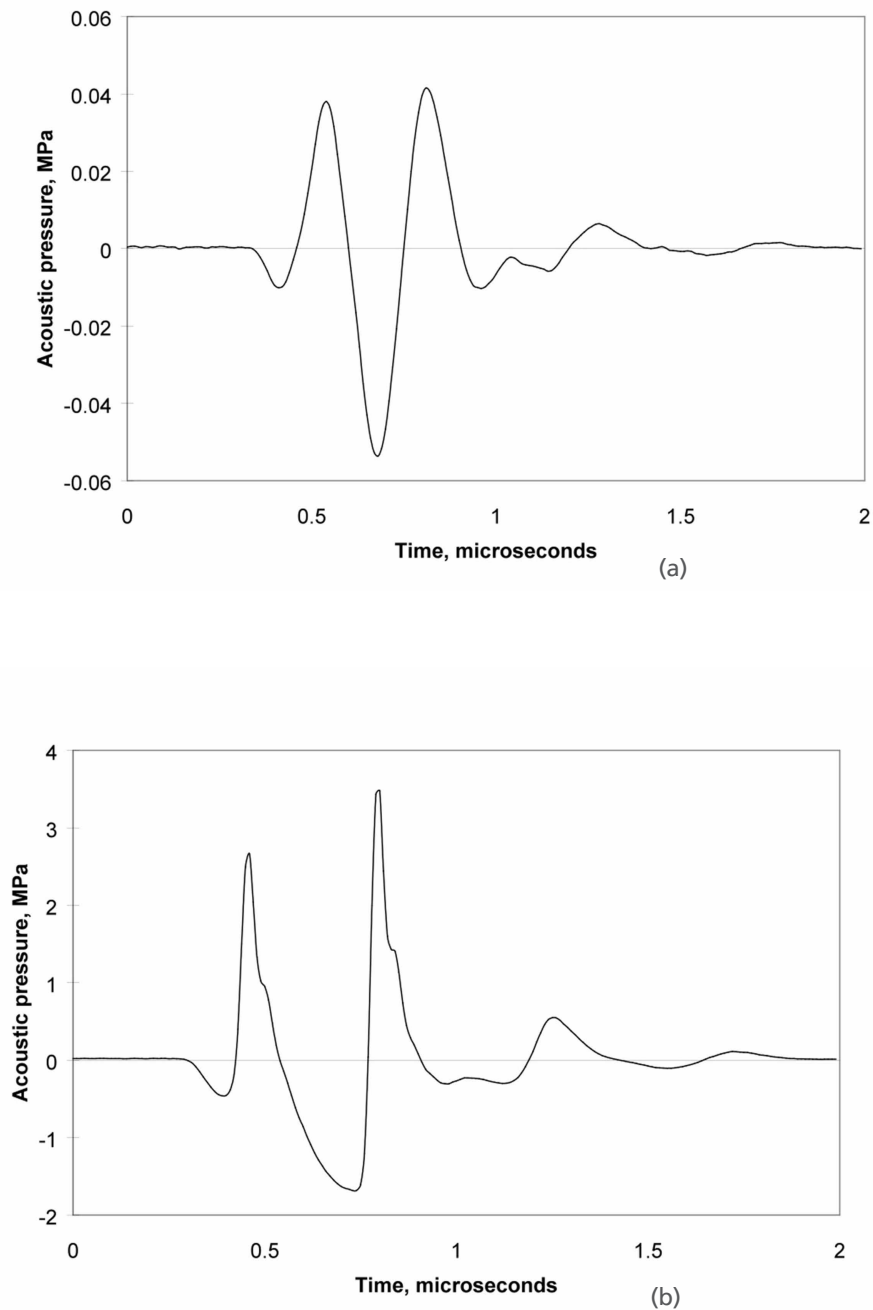


Figure 2.4. Two pressure pulses measured in water at the focus of the same 3.5 MHz diagnostic transducer, (a) one at low amplitude and (b) the other at high amplitude. The high-amplitude pulse shows strong waveform distortion and acoustic shock (an abrupt change from rarefaction to compression).

frequency and amplitude of the wave; the non-linear coefficient of the medium; and the distance travelled by the wave.

As a result of the distortion caused by the non-linear propagation of the wave, its frequency content is altered and energy passes from the fundamental frequency into harmonics (overtones). The propagation of such shocked waves is associated with additional energy absorption, which enhances, sometimes significantly, the propagation losses and deposition of energy. Eventually the phenomenon of acoustic saturation occurs. This describes the condition where, as the wave amplitude at the transducer is increased, none of this additional wave energy arrives at some distance away from the transducer, because all additional acoustic energy leaving the transducer is lost through the process of excess energy absorption. In practice, the generation of acoustic shocks is common when ultrasonic pulses generated by medical imaging systems propagate through water. It is predicted that severe waveform distortion and perhaps full shock generation may also occur within the fluid spaces *in vivo*, because of their low attenuation. Examples include propagation within urine in the bladder or in the amniotic fluid within a pregnant uterus. Propagation through soft tissue inhibits the formation of high levels of harmonic because of greater absorption losses.

Distorted waves are rich in harmonics, resulting in increased attenuation

Non-linear effects are significant in discussions of ultrasound safety for two main reasons. First, all estimates of acoustic exposure within the body are based on measurements in water, in which non-linear effects are strong, and no correction is applied when estimating *in situ* exposure. It has been predicted that acoustic saturation can limit the effectiveness of the present Food and Drug Administration limits for the control of ultrasound exposure (see [Chapter 10](#)), particularly for longer focal depths and higher frequencies ([Duck, 1999](#)). The second reason is that harmonics can enhance the deposition of energy in tissue, which may in turn increase warming and radiation forces.

In non-linear beams *in situ* exposures can be underestimated and bio-effects may be accentuated

## 2.4 Mechanisms for effects on tissue

The preceding sections have presented in outline the main important processes that occur during the propagation of an ultrasonic wave through tissue. As a result of a variety of absorption processes, energy is deposited in the tissue. The response of the tissue will depend in part on the mechanism for this deposition, and thus on one of several alternative properties of the beam. It is conventional to consider two broad categories: thermal effects and mechanical effects. Broadly, mechanical effects can best be predicted from knowledge of individual pulses, whilst thermal effects can best be predicted from knowledge of energy flow over an extended time period. In addition, as will be detailed below, the tissue response is modified considerably by the presence of bone, gas and fluid spaces.

The two main bio-effects mechanisms are heating and mechanical processes

### 2.4.1 Heating

Acoustic energy may convert to heat, transferred into the tissue by a variety of absorption processes. The rate per unit volume at which heat is produced,  $dQ/dt$ , is equal to  $2\alpha_a I$ , where  $\alpha_a$  is the amplitude absorption coefficient (which increases with frequency) and  $I$  is the intensity of the wave. The initial rate of temperature rise is equal to  $2\alpha_a I/C$  where  $C$  is

## 2 The propagation of ultrasound through tissue

Tissue warming depends on acoustic intensity and beam size, and on tissue absorption coefficient, perfusion and thermal properties

the heat capacity of the medium. Subsequent heating depends on the width of the beam. Broader beams can cause higher temperatures for a given peak intensity than do narrow, more highly focused beams. The steady-state temperature also depends on the thermal conductivity of the tissue and on the effects of blood perfusion. An “effective thermal conductivity” is commonly used in calculations to allow for convective heat loss due to blood flow. However, perfusion becomes important only in the wider parts of the beam, away from the focal zone.

Primary bone heating is markedly higher than soft tissue warming. Tissue adjacent to bone will experience secondary warming

Tissues with higher absorption coefficients can get warmer than those with less absorption. So, the surfaces of calcified bone absorb energy strongly, and heat more than soft tissues. Transmission into the bone, and hence its increase in temperature, may be reduced for angles of incidence other than those near normal. Foetal bones absorb energy more strongly than the surrounding foetal soft tissue, and this difference becomes greater as the foetal bones calcify. A 30-fold increase in absorption coefficient has been reported as the foetal bone matures (Drewniak *et al.*, 1989). Adjacent soft tissues can experience secondary heating from thermal conduction into the tissue from the bone.

Acoustic cavitation occurs when bubbles are driven by an ultrasonic field

### 2.4.2 Mechanical effects: cavitation and radiation pressure

When a gas bubble in a liquid experiences the variations in pressure of an acoustic wave its size is driven to change, expanding during the period of decreased pressure and contracting during the compression half-cycle of the wave. This behaviour is termed acoustic cavitation. For low values of peak acoustic pressure, oscillations in bubble radius largely follow variations in pressure. As the peak acoustic pressure increases, the bubble becomes unstable as it contracts, collapsing catastrophically under the inertia of the surrounding liquid. Such cavitation is therefore termed “inertial” to distinguish it from stable or non-inertial cavitation. The term acoustic cavitation is also used to refer to the creation of bubbles in a liquid by an acoustic field at nucleation sites, such as microscopic impurities, surface roughness on the container or even small-scale local density variations.

Bio-effects of acoustic cavitation arise from shear forces, and free-radical formation

Complex mechanical forces are exerted on the surrounding fluid, on any surface adjacent to the bubble, and between one bubble and its neighbours. Biologically, probably the most important of these are the shear forces exerted at the bubble surface. Mechanical forces of this sort are associated with both non-inertial and inertial cavitation, although clearly they are significantly higher in the latter case. Chemical action is also possible. The adiabatic conditions associated with extremely rapid bubble compression during inertial cavitation result in very high instantaneous temperatures within the bubble. These can result in the creation of highly reactive free-radical chemical species.

Gas in lung, intestine and contrast materials increases the likelihood of mechanical damage to tissue

It is highly improbable that either form of cavitation can be generated at diagnostic levels within soft tissues or fluids in the body, in the absence of gas-filled ultrasound contrast agents. However, there are two conditions when the presence of gas may result in mechanical trauma to adjacent soft tissue, caused by a cavitation-like process: at the surface of the lung, and in the intestine.

Finally, tissues may experience a range of other forces from the passage of an ultrasonic wave (see [Chapter 6](#)). In particular, a radiation stress is exerted within tissues and fluids as the pulse propagates, and also at interfaces where there is a change of acoustic impedance. When exerted within a liquid this force causes acoustic streaming, and the fluid moves in the direction of the pulse propagation. This radiation stress is of much lower magnitude than that associated with bubble activity, but exists universally and does not require the presence of gas bodies.

Low-level radiation stress always accompanies ultrasound wave propagation

## 2.5 The passage of an ultrasonic pulse through tissue

Based on the preceding discussion, and at the risk of some minor repetition, we are now in a position to follow what happens when a real ultrasonic transducer generates a series of acoustic pulses, which then propagate through tissue. The pulses are generated by a broadband piezoelectric transducer. Such transducers are inherently poor in their efficiency of transferring electrical energy to acoustic energy, and as a result heat is dissipated in the transducer: it warms up. It is probable that the greatest tissue heating during diagnostic ultrasound arises from this cause ([Calvert \*et al.\*, 2007](#)), and it should be considered seriously when thermally sensitive tissues lie close to the transducer, as in ophthalmic scanning.

Pulsed ultrasound transducers generate heat

The penetration of the pulse into the tissue depends on the effectiveness of the acoustic coupling to the tissue. For skin-coupling the attenuation coefficient of the dermal and sub-dermal layers may also have a strong effect, since it may be high depending strongly on hydration, and fat and collagen content. The acoustic pulse contains a broad spectrum of frequencies centred approximately at the resonant frequency of the piezoelectric source. The amplitude and intensity of the wave reduces with distance at a rate of about  $0.5 \text{ dB cm}^{-1} \text{ MHz}^{-1}$ ; for a 3.5 MHz wave, the amplitude will be reduced by one-half, and the intensity by a factor of four ( $-6 \text{ dB}$ ) after travelling about 4 cm, mostly due to viscous and relaxation absorption processes. The remaining energy is scattered, effectively spreading the beam, and this scattered energy may undergo further scattering interactions. An extremely small fraction of the energy returns to the transducer.

The majority of the transducer output power is absorbed in the superficial tissue layers

If there is a repetitive sequence of pulses, as in most diagnostic applications, the tissue will be warmed as a result of the absorption of acoustic energy. The temperature rise depends on the time-averaged acoustic intensity, the acoustic absorption coefficient, the thermal properties of tissue (heat conduction and specific heat), tissue perfusion (blood flow), beam size and scanning mode and the period of time the transducer is held in one position. The tissue also experiences a small transient force in the direction of propagation each time a pulse passes. If the pulse passes through a liquid, it will move in the direction of the pulse propagation: a series of pulses will cause acoustic streaming.

The tissue is slightly warmed, and slightly stressed during diagnostic scanning

The pulse spectrum alters as the wave propagates. In soft tissue this alteration is dominated by the frequency-dependent attenuation of the tissue. As a result, higher frequencies in the pulse spectrum reduce in proportion to those at lower frequencies, so lowering the mean frequency in the spectrum of the pulse. For a pulse of very high amplitude, finite-amplitude effects also come into play and some energy is passed to

The pulse frequency spectrum alters as the pulse propagates

Bone heats preferentially, and will warm surrounding tissues

higher-frequency harmonics. This latter effect is more pronounced during transmission through fluids, however, where it is the dominant mechanism modifying the pulse spectrum.

As the wave propagates farther into the tissue it may reach a clear acoustic interface between media of differing acoustic properties. If the second medium is bone, about half the energy in the wave is reflected and half enters the bone. The pattern of reflected energy will depend somewhat on the scattering properties of the tissue-to-bone boundary, and the subsequent propagation of this scattered wave through soft tissue is difficult to predict. Standing waves are very unlikely to form. The remaining energy that enters the cortical bone may propagate as longitudinal, shear or surface waves, all of which are rapidly absorbed, resulting in a local temperature rise. This bone heating causes secondary heating of the surrounding soft tissues by thermal conduction.

Tissues next to a gas boundary are particularly vulnerable to mechanical damage

Almost all of the incident wave energy is reflected from any boundary between soft tissue and gas. This gas may exist within the alveoli of the lung, within the intestine or at the exit site of the beam. Also, gas bubbles may be artificially introduced to act as a contrast medium in blood. Such tissue-to-gas interfaces constitute very large alterations of acoustic impedance and the resulting pressure wave is, to a first approximation, of equal amplitude and opposite phase to that of the incoming wave. Mechanical stress experienced by soft tissue at a tissue-to-gas interface can be sufficient to cause permanent damage to membranes (causing lysis of erythrocytes in the presence of bubbles, for example) or to weak connective tissue structures, especially tissues with low shear strength (causing, for example, lung capillary bleeding). Were inertial cavitation to occur, extreme conditions of temperature and pressure could be locally generated, which in principle could lead to free-radical generation. This has not been demonstrated *in vivo*. Apart from mechanical effects, the interaction between the acoustic wave and bubbles can also generate heat locally, because of a general increase in absorption coefficient.

Another interface of interest is that from soft tissue into fluid. Little energy is reflected since the acoustic impedance change across the boundary is slight. The wave emerges into a space containing, for example, blood, amniotic fluid or urine. Scatter is minimal, absorption is low and finite-amplitude distortion processes are not strongly suppressed. The wave therefore carries frequency components through the fluid that are substantially higher than those generated by the transducer, especially in the focal zone. When this pulse reaches a further fluid-to-tissue boundary, much of its high frequency content will be deposited in the superficial tissue layers, leading to greater warming and radiation stress than from equivalent undistorted pulses.

## 2.6 Conclusion

The propagation of ultrasound and the mechanisms of action between ultrasonic waves and tissue are now well understood. The generation of this knowledge has been largely stimulated by the widespread use of ultrasound in the low-megahertz frequency

Liquids *in vivo* accentuate non-linear effects

range in diagnostic and therapeutic medicine. Much is still unclear, however, about the detailed interaction at a microscopic level of these interactions and mechanisms. Furthermore, the thresholds and conditions for cavitation, and the importance of finite-amplitude transmission within tissue, and the relevance of radiation stress still require clarification.

## References

- Calvert J, Duck F, Clift S, Azaim H. 2007. Surface heating by transvaginal transducers. *Ultrasound Obstet Gynecol*, 29, 427–432.
- Drewniak JL, Carnes KI, Dunn F. 1989. *In vivo* ultrasonic heating of fetal bone. *J Acoust Soc Am*, 86, 1254–1258.
- Duck FA. 1990. Acoustic properties of tissue at ultrasonic frequencies. In *Physical Properties of Tissue, a Comprehensive Reference Book*. London, UK: Academic Press, pp. 73–135.
- Duck FA. 1999. Acoustic saturation and output regulation. *Ultrasound Med Biol*, 25, 1009–1018.
- Duck FA. 2002. Nonlinear acoustics in diagnostic ultrasound. *Ultrasound Med Biol*, 28, 1–18.
- Humphrey VF, Duck FA. 1998. Ultrasonic fields: structure and prediction. In *Ultrasound in Medicine*, Duck FA, Baker AC, Starritt HC (editors). Bristol, UK: Institute of Physics Publishing, pp. 3–22.
- ICRU. 1998. ICRU Report 61: Tissue Substitutes, Phantoms and Computational Modelling in Medical Ultrasound. Bethesda, MD: International Commission on Radiation Units and Measurements.
- Verma PK, Humphrey VF, Duck FA. 2005. Broadband measurements of the frequency dependence of attenuation coefficient and velocity in amniotic fluid, urine and human serum albumin solutions. *Ultrasound Med Biol*, 31, 1375–1381.

# Chapter 3

## The acoustic output of diagnostic ultrasound scanners

Adam Shaw<sup>1</sup> and Kevin Martin<sup>2</sup>

<sup>1</sup>Acoustics and Ionizing Radiation Division, National Physical Laboratory, Teddington, UK

<sup>2</sup>Department of Medical Physics, University Hospitals of Leicester, Leicester, UK

### Summary

- Four important acoustic output quantities are the peak rarefaction pressure ( $p_r$ ), the spatial-peak temporal-average intensity ( $I_{\text{spta}}$ ), the temporal-average acoustic power ( $W$ ) and the temperature of the transducer face ( $T_{\text{surf}}$ ).
- The measurement of acoustic outputs in clinical environments requires appropriate equipment and techniques.
- In general,  $I_{\text{spta}}$ ,  $W$  and  $T_{\text{surf}}$  are greatest for spectral Doppler mode and least for B-mode. For all three quantities there is considerable variation between different transducers and machine models. Values of  $p_r$  do not vary much between modes.
- Surveys since 1991 demonstrate that  $p_r$  values have increased steadily.  $I_{\text{spta}}$  values in B-mode have shown the greatest increases and now overlap the range of pulsed Doppler values.
- Maximum mechanical index values declared by manufacturers are biased towards the Food and Drug Administration (FDA) maximum permitted level. Manufacturer declared values of thermal index are on average much lower than the FDA normal maximum level, but still significant in relation to acoustic safety in obstetric and neonatal scanning.

In the previous chapter, some of the parameters that may be used to characterize the beams and pulses from diagnostic ultrasound systems have been described. It was shown that these parameters could be used to assess the likelihood of tissue heating or cavitation during exposure. The aim of this chapter is to explain how relevant acoustic parameters can be measured for diagnostic systems and how these parameters are affected by user controls. Values of acoustic parameters and their trends for modern diagnostic systems are also reviewed.

## 3.1 Acoustic output parameters

### 3.1.1 Acoustic pressure

A point within the ultrasound beam experiences successive cycles of compression and rarefaction during the passage of an ultrasound pulse (see Figure 3.1a).

The magnitude of the pressure changes is characterized by the peak compression and rarefaction pressures, which are the greatest values during the pulse. The peak rarefaction pressure  $p_r$  can be used in assessing the risk of occurrence of cavitation or other gas-body activation events. The peak rarefaction pressure changes with position in the beam and is greatest in the focal region. Acoustic pressure is normally measured in water using a hydrophone (see later).

The peak rarefaction pressure in an ultrasound beam is used to assess the risk of cavitation

### 3.1.2 Acoustic power

Each pulse transmitted into the tissue medium carries acoustic energy [measured in joules (J)] which is gradually absorbed and deposited in the tissue. The rate at which energy is transmitted into tissue from the transducer by this means is the total acoustic power  $W$ ,

Absorption of acoustic power in tissues causes tissue heating and radiation stress

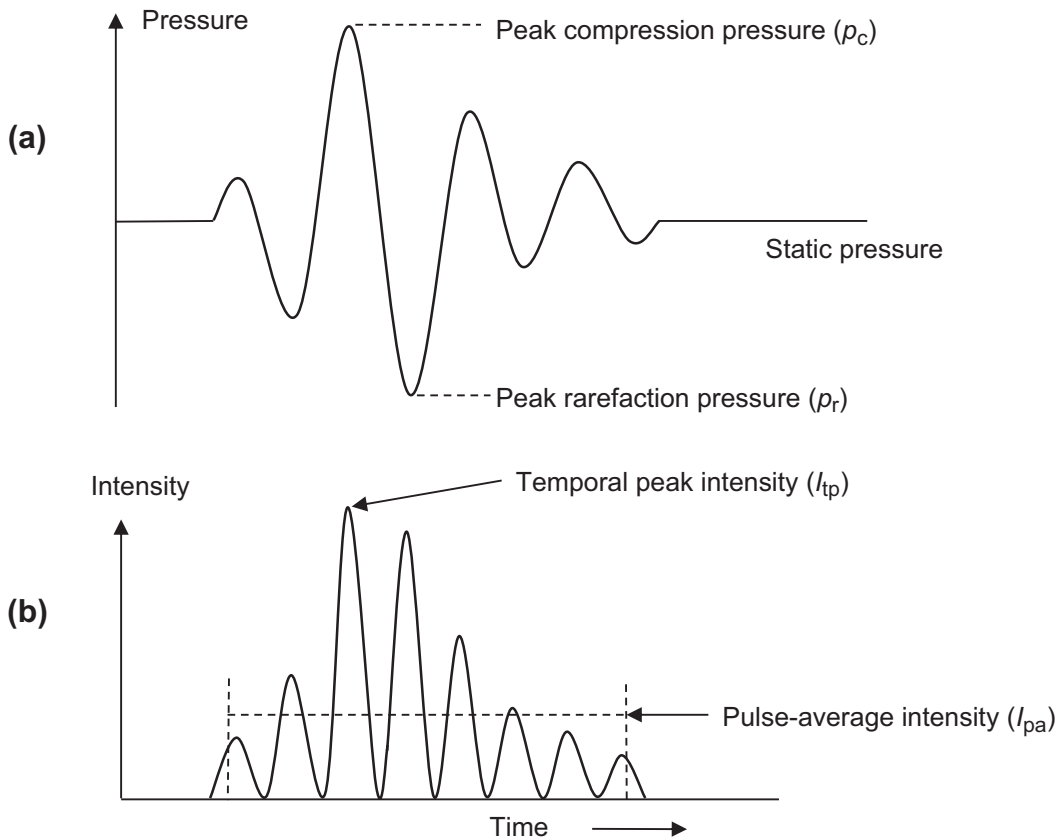


Figure 3.1. (a) The peak compression and rarefaction pressures are the maximum and minimum values of pressure in the medium during the passage of an ultrasound pulse. (b) The intensity is related to the pressure squared and is always positive. The temporal-peak intensity is the maximum value during the pulse. The pulse-average intensity is the average value over the duration of the pulse.

measured in watts (W) ( $1 \text{ W} = 1 \text{ J s}^{-1}$ ). This is the average power over many transmit pulse cycles. A medium which absorbs the acoustic power from the transducer of course heats up, but it is also subject to a radiation force, which is proportional to the absorbed power. This force results in stresses within the tissue [an effect which is now being exploited in acoustic radiation force imaging] and in acoustic streaming within fluid-filled regions such as the bladder or cysts.

#### 3.1.3 Intensity

The intensity in the ultrasound beam is a measure of the flow of acoustic power through a given cross-sectional area and is measured in  $\text{W m}^{-2}$  or  $\text{mW cm}^{-2}$  (see Figure 3.2). In plane waves, intensity is related to the square of acoustic pressure by the equation:

$$I = p^2 / Z \quad (3.1)$$

where  $Z$  is the acoustic impedance of the medium (see Chapter 2). Hence, intensity values can be derived from measurements of acoustic pressure.

During the passage of an ultrasound pulse, the pressure and hence the intensity, vary with time. Figure 3.1 shows corresponding pressure and intensity waves during a pulse. Note that because intensity is related to the square of pressure, its value is always positive. The peak value of intensity during the pulse is called the temporal-peak intensity  $I_{\text{tp}}$ . An alternative and more widely used measure of intensity during the pulse is the pulse-average intensity  $I_{\text{pa}}$ . The pulse-average intensity is more useful as it is more immune to changes in the shape of the pulse than the temporal-peak intensity.

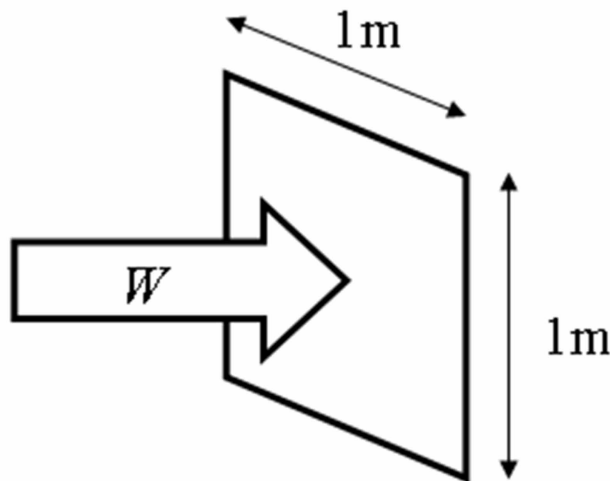


Figure 3.2. Intensity is the power  $W$  in watts flowing through unit area, e.g.  $1 \text{ W m}^{-2}$ .

Intensity is related to the square of acoustic pressure and is always positive

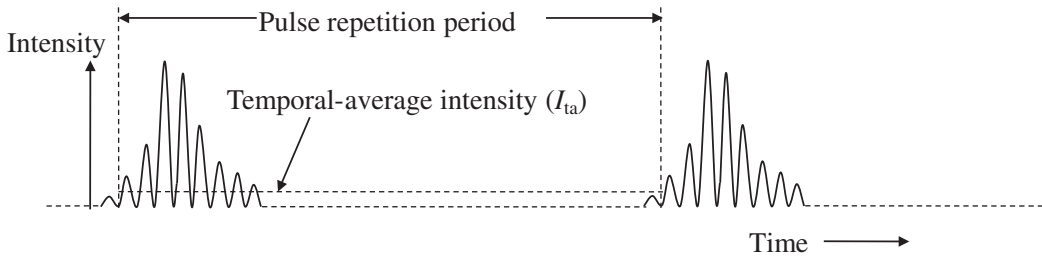


Figure 3.3. The intensity waveform is repeated with every pulse-echo cycle. The temporal-average intensity is the average value over a complete pulse-echo cycle and is much lower than the pulse-average intensity.

Where the ultrasound beam is stationary, *e.g.* for a pulsed Doppler beam, the pulse waveform is repeated at the pulse repetition frequency. Where the longer term effects of exposure to the beam are of interest, *e.g.* in assessing potential for tissue heating, it is useful to measure the temporal-average intensity ( $I_{ta}$ ). This is the value of intensity averaged from the start of one pulse to the start of the next (or other similar point). This value is much lower than  $I_{pa}$  as it includes the long “OFF” period between pulses (Figure 3.3). For scanned modes, where the beam is swept through the region of interest, the point of interest in the tissue may be exposed only once in each scan of the beam and the average must be taken over a complete scan repetition period.

Intensity varies with time and position in the beam. Temporal-average intensity is much lower than that during the pulse

As described in Chapter 2, the intensity varies with position in the beam as well as with time. Hence it is possible to specify intensity at a particular location in the beam, such as at the point where it is maximum. This is the spatial-peak value. Alternatively, it is possible to calculate a value averaged over the beam cross-sectional area, known as the spatial average value (Figure 3.4). The following are the most commonly quoted intensity parameters.

- $I_{sppa}$  (Spatial-peak pulse-average intensity): The pulse average-intensity measured at the location where it is maximum.
- $I_{spta}$  (Spatial-peak temporal-average intensity): The temporal-average intensity measured at the location where it is maximum.
- $I_{sata}$  (Spatial-average temporal-average intensity): The temporal-average intensity averaged across the beam cross section (at a particular range from the transducer).

### 3.1.4 Free-field and derated values

When acoustic pressure or intensity is measured using a hydrophone, the measurement is normally made in water, which has almost no attenuation. These are normally called free-field quantities. To estimate pressure values that might exist in soft tissue in the same ultrasound beam, the measured pressure values are “derated”, by an amount that depends on the attenuation of the tissue. Most soft tissues have an attenuation of between 0.5 and 1.0 dB cm<sup>-1</sup> MHz<sup>-1</sup>. When calculating the safety indices (next section), a lower attenuation of 0.3 dB cm<sup>-1</sup> MHz<sup>-1</sup> is assumed (in case some of the path is fluid-filled) and the derated value of peak rarefaction pressure is denoted as  $p_{r,0.3}$ . That is, the value  $p_r$

Pressure and intensity are normally measured in water using a hydrophone. These “free-field” values may then be derated to estimate the values that would be expected in tissues, assuming an attenuation of 0.3 dB cm<sup>-1</sup> MHz<sup>-1</sup>

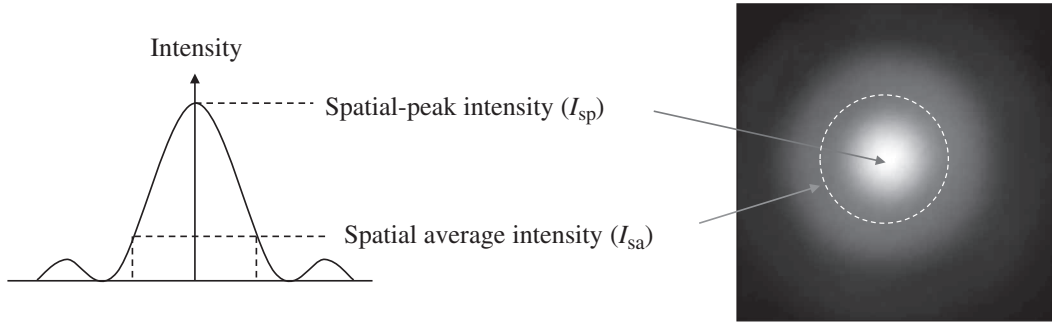


Figure 3.4. The values of the various intensity parameters change with position in the beam also. The highest value in the beam is the spatial-peak intensity. The average value over the area of the beam is the spatial average intensity.

measured in water, is reduced by  $0.3fz$  dB to estimate the value  $p_{r,0.3}$  that would exist in tissue, where  $f$  is the frequency of the pulse (in MHz) and  $z$  is the range (in cm) from the transducer at which the measurement was made. This is a reasonable approximation to a “worst-case” safety index, but it does not usually give the best estimate of the field in real tissue. Nevertheless, in most cases where “derated” values are reported, the derating factor used is  $0.3 \text{ dB cm}^{-1} \text{ MHz}^{-1}$ .

The same process may be applied to values of intensity such as  $I_{\text{spta}}$  or  $I_{\text{sppa}}$ . Such derated values of intensity are used by the Food and Drug Administration (FDA) in the USA to regulate output levels from diagnostic ultrasound systems (see [Chapter 10](#)).

### 3.1.5 Safety indices

The pressure, intensity and power parameters detailed above describe the acoustic field in water (free-field) or in tissue (derated) and are related to the field that the patient is exposed to during diagnosis. Such parameters were widely used to monitor the acoustic outputs of early ultrasound systems. On their own however, they were not good indicators of the risk of adverse effects. Current standards and regulations refer to parameters that are intended to relate more directly to cavitation and tissue heating: these are the mechanical index (MI) and the thermal index (TI) ([IEC62359, 2010](#); see also [Chapter 10](#)). MI is intended to indicate the probability of occurrence of inertial cavitation, while TI is an indicator of the likely maximum temperature rise in tissues exposed to the ultrasound field. Although these indices can provide useful information to the user, they are not perfect and are based on a set of very specific assumptions. A particular criticism of TI is that it ignores the self-heating of the transducer, and so greatly underestimates the temperature rise within about 5 mm of the transducer. For some applications this region may contain sensitive tissue (see later section on Measurement of Temperature).

#### 3.1.5.1 Mechanical index

MI is defined by:

$$\text{MI} = \frac{p_{r,0.3}}{\sqrt{f}} \quad (3.2)$$

Safety indices MI and TI are used to indicate the risk of cavitation and the probable temperature rise in tissue exposed to an ultrasound beam

Here,  $p_{r,0.3}$  is the maximum value of derated peak rarefaction pressure (in MPa) in the beam. This is measured by recording  $p_r$  at a range of depths in water and derating the values to find the maximum value of  $p_{r,0.3}$ . The centre frequency in the pulse is  $f$  MHz. The equation for MI is based on a model which assumes the presence of bubble nuclei in the tissue. It predicts that inertial cavitation is more likely at higher values of  $p_{r,0.3}$  and at lower frequencies. According to the theory, cavitation should not be possible at values less than 0.7.

### 3.1.5.2 Thermal index

TI gives an indication of the likely maximum temperature rise in tissue due to absorption of ultrasound.

It is defined by:

$$TI = W/W_{deg} \quad (3.3)$$

Here,  $W$  is the current acoustic output power from the transducer and  $W_{deg}$  is the power required to raise the temperature of the tissue by 1 °C. The likely maximum temperature rise depends on the type of tissue and on the operating conditions of the ultrasound system. As temperature rise in tissue is strongly influenced by the presence of bone, 3 versions of TI are used to model the anatomical conditions. These are (i) TIS, which assumes exposure of uniform soft tissue, (ii) TIB, which assumes that a layer of bone is present in or close to the focal region of the beam and (iii) TIC, a model which assumes the presence of bone just under the tissue surface. American Institute for Ultrasound in Medicine and International Electrotechnical Commission (IEC) standards include agreed formulae for calculating the indices for scanned and unscanned beams and for beam apertures greater than or less than 1 cm<sup>2</sup>. These standards include a requirement that MI or TI is displayed to the user if either value can exceed 1.0 under any operating condition.

Three different models are used to calculate TI to account for the presence and relative position of bone in the beam. These are TIS, TIB and TIC

### 3.1.6 Transducer temperature rise

In addition to heating due to absorption of ultrasound, the temperature of tissues near the transducer is strongly influenced by the temperature of the transducer itself. Ultrasound pulses are produced by applying an electrical signal to the transducer. Some electrical energy is dissipated in the element, lens and backing material, causing transducer heating. Electronic processing of received signals in the transducer head may also result in electrical heating. Conduction of heat from the transducer face can result in temperature rises of several degrees Celsius in superficial tissues. Maximum allowable transducer surface temperatures ( $T_{surf}$ ) are specified in IEC standards (see Chapter 10). These are 50 °C when the transducer is transmitting into air and 43 °C when transmitting into a suitable phantom. This latter limit implies that skin (typically at 33 °C) is permitted to be heated by up to 10 °C. Transducer heating is a significant design consideration in complex transducers and in some circumstances these temperature limits may effectively restrict the acoustic output that can be achieved.

The temperature of the transducer face can be raised due to electrical energy losses in the transducer, resulting in heating of adjacent tissues. Transducer temperature is limited by international standards

Independent measurements are important to make sure the scanner meets necessary standards, to check manufacturers' data and to support research

## 3.2 The need for independent measurement

Modern ultrasound scanners have become so complex and have so many different output combinations that it is effectively impossible for anyone other than the original manufacturer or a very specialized laboratory to attempt a full measurement of the output. So, with most modern scanners displaying thermal and mechanical indices (see also [Chapter 10](#) on regulations) why would anyone else want to undertake any measurements? Of course, not all hospitals can be expected to make complex output measurements but there are several important reasons why there must be a capability within any healthcare system to make detailed independent measurements.

The first is a duty of care to those being scanned and the need to ensure that equipment is “fit for purpose”, meets all necessary standards and is properly maintained. Measurements may be needed prior to acceptance on purchase, for routine QA in compliance with local or national quality systems, or when a potential fault is reported. Software upgrades by field engineers pose a special problem, since the systems are controlled by software and the acoustic output may potentially change whenever such an upgrade takes place. Report 102 from the Institute of Physics and Engineering in Medicine ([IPEM, 2010](#)) deals with QA in detail.

The second reason is to act as a check on the manufacturers. CE marking of equipment in Europe is mostly based on self-declaration by the manufacturer, and not on independent evaluation. Although the CE marking process in a company is in principle subject to audit, this essentially concentrates on management systems, not on the “correctness” of acoustic measurements. Apart from measurement problems, record-keeping lapses are always a possibility with the ongoing process of hardware and software revisions potentially leading to the output of a particular machine being substantially different to that of another machine, apparently of the same make and model and revision, or to the manufacturer's published value. It is perhaps not surprising, therefore, that manufacturers' reported output data has not always been completely reliable ([Jago \*et al.\*, 1995](#)).

The third reason is to support research, for example into biological response to ultrasound or into the use of higher output modes for diagnosis, especially of the foetus, embryo or neonate, or of the brain and central nervous system. It is tempting but completely wrong, to suppose that the on-screen MI and TI is enough to somehow “characterize” the exposure. Anyone thinking about undertaking research must think carefully in advance about the output measurements required to support it: [ter Haar \*et al.\* \(2011\)](#) have presented guidelines for correctly reporting exposure conditions.

## 3.3 Measurement methods and equipment

A detailed description of how to make output measurements is beyond the scope of this book but the following sections give a description of the principles, considering pressure, intensity, output power and temperature rise. Report 102 from the Institute of Physics and Engineering in Medicine ([IPEM, 2010](#)) gives practical guidance for which measurements are suitable for QA and the maintenance of diagnostic scanners; more general advice

on setting up and using measurement systems can be found in [Preston \(1991\)](#), [Lewin and Ziskin \(1992\)](#), and [Szabo \(2004\)](#). The measurement of temperature rise is perhaps the most easily accessible measurement, with output power not too far behind. Measuring pressure or intensity distributions is a much more specialized task; nevertheless, it is logical to deal with this most complex issue first.

### 3.3.1 Measurement of pressure and intensity

#### 3.3.1.1 Pressure

The fundamental component that allows the acoustic pressure to be monitored and measured is the hydrophone. This is essentially a high frequency microphone for use underwater that produces a voltage waveform when it is placed in an ultrasonic field. The type preferred for use in diagnostic fields is the membrane hydrophone (available from, *e.g.* Precision Acoustics Ltd, Dorchester, UK; ONDA Corporation, Sunnyvale, CA; and Sonora Medical Systems Ltd, Longmont, CO, amongst others) which is chosen for its even response over a wide range of frequencies. In this type of hydrophone, the pressure-measuring element is the small central area of a polymer membrane (polyvinylidene fluoride—PVDF), stretched across a circular support ring ([Figure 3.5](#)). The diameter of this ring (typically 80 mm) is sufficient to accommodate the full B-mode ultrasound field from a medical ultrasound probe. A small central region of the film (typically less than 0.5 mm in diameter) is piezoelectrically active: it is desirable for this area to be as small as possible, since the voltage produced represents the spatial average of the acoustic pressure over this area.

The sensitivity of a membrane hydrophone increases slowly with frequency up to its resonance frequency (approximately 60 MHz for a 16  $\mu\text{m}$  thick membrane). However, a more constant frequency response can be obtained by amplifying the hydrophone output in a low-noise preamplifier with a frequency response that is deliberately matched to be complimentary to that of the hydrophone. Due to non-linear propagation effects which can result in the generation of high frequency harmonics in the pulse waveform, the international standard [IEC62127-1 \(2007\)](#) recommends that the output of the hydrophone and preamplifier should vary by less than  $\pm 6\text{ dB}$  over a frequency range extending to 3 octaves above the acoustic working frequency, or to 40 MHz, whichever is the smaller.

Acoustic pressure is measured with a calibrated hydrophone connected to an oscilloscope

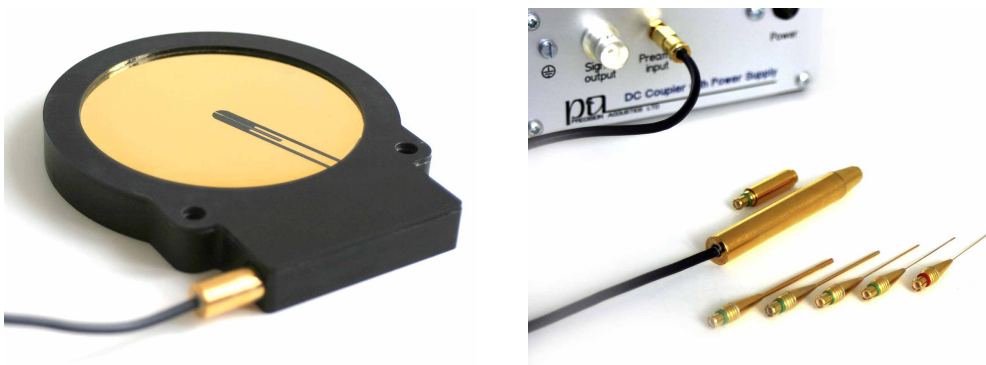


Figure 3.5. Membrane hydrophone (left) and needle hydrophones (right). Photographs courtesy of Precision Acoustics Ltd.

### 3 The acoustic output of diagnostic ultrasound scanners

Good quality modern membrane hydrophones will normally meet this requirement, even without a matched amplifier.

Membrane hydrophones are more accurate but probe hydrophones are cheaper

Although membrane hydrophones offer the most faithful reproduction of the pressure waveform, they are expensive (approximately £8000 in 2011). Another type of hydrophone is the probe (or needle) hydrophone in which the active PVDF element is placed on the end of a hollow tube (or needle). The needle perturbs the ultrasound field resulting in a sensitivity which varies more strongly with frequency, especially below 3 MHz. However, they are cheaper to buy (from about £1200 in 2011), and their needle shape offers advantages in some situations. Fibre-optic hydrophones are also available in which the pressure field modulates the amount of light reflected from the end of an optical fibre but these are more normally used in high intensity therapeutic ultrasound (HITU or HIFU) fields where piezoelectric hydrophones might get damaged.

Generally, the hydrophone is mounted in a water tank on a three-axis manipulator that allows it to be moved within the transducer field. The signal from the hydrophone is monitored on an oscilloscope, from which  $p_r$  can be measured directly. The use of a digital oscilloscope allows other pulse parameters, such as centre frequency, to be calculated in real-time if required. The hydrophone calibration should be traceable to national standards (for instance at the National Physical Laboratory). Measurement uncertainty depends on the particular application but it is typically less than  $\pm 10\%$  for acoustic pressure parameters, and  $\pm 21\%$  for intensity parameters (95% confidence level).

#### 3.3.1.2 Intensity

Intensity is not measured directly. It is calculated from the pressure waveform

Intensity is a measure of the rate of energy flow through an area. Although there are some prototype sensors for measuring intensity based on heating (Wilkens, 2010a,b; Hodnett and Zeqiri, 2009; Zeqiri *et al.*, 2011), in practice intensity is not measured directly but is calculated from measurements of pressure using a hydrophone as described in the previous section on pressure. The basic assumption that is made in calculating intensity is called the “plane-wave assumption” which says that the instantaneous intensity,  $I(t)$ , is related to the instantaneous pressure,  $p(t)$  by the relationship:

$$I(t) = \frac{p^2(t)}{\rho c} \quad (3.4)$$

where  $\rho$  is the density of water and  $c$  is the speed of sound in water. Although this relationship is not strictly true everywhere, it is a good approximation throughout most diagnostic fields and is used in international standards (IEC62127-1, 2007).

To measure  $I_{ta}$ , the contributions from all pulses in the scanframe must be included

The determination of temporal-average intensity,  $I_{ta}$ , is particularly challenging for scanned imaging modes because many separate pulses contribute to the energy flowing through a particular point. Modern, deep memory digital oscilloscopes have, however, made it much easier than in the past, since it is now possible to capture every pulse in the scanframe—even for combined modes—as long as a trigger signal can be obtained from the scanner. In the absence of such a dedicated trigger signal, it is possible to trigger directly on the hydrophone waveform to capture all pulses that exceed some small

pressure. Of course this will miss the contribution from the smallest pulses and can also capture electrical pickup which is not part of the acoustic signal. An analogue alternative is the method developed by [Martin \(1986\)](#) in which the signal from the hydrophone is first amplified in a power amplifier and then input to a commercial electrical power sensor to measure the time-averaged electrical power generated by the hydrophone without the need for a synchronizing trigger: this is proportional to the temporal-average intensity. A digital equivalent to this is to continuously digitize the hydrophone signal. With both the analogue and digital versions, the electrical noise power should be assessed and, if significant, corrected for.

### 3.3.1.3 Hydrophone measurement systems

Turnkey commercial hydrophone measurement systems which integrate a measurement tank, positioning system, hydrophone, digital oscilloscope and software are available from Precision Acoustics Ltd, Onda Corporation and Sonora. They are not designed to deal with scanned modes of operation “out of the box” but additional software capture and analysis routines can be written to do this. Although they are sometimes mounted on a very large trolley, these systems are essentially more suited to use in a fixed location ([Figure 3.6](#)).

A measurement system which is no longer commercially available but is still being used in some centres, and which was designed specifically to deal with scanned operating modes, is the NPL Ultrasound Beam Calibrator ([Preston; 1988; Shaw and Preston, 1995](#)). This is a sophisticated system, based on a linear array of hydrophone elements whose outputs

Complete hydrophone measurement systems can be bought

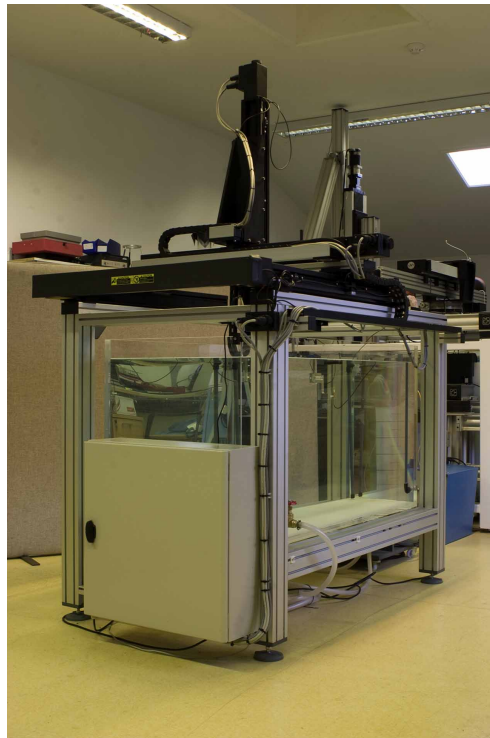


Figure 3.6. The UMS3 hydrophone scanning system. Photograph courtesy of Precision Acoustics Ltd.

are sampled in rapid succession to give an effectively real-time profile of the pressure or intensity distribution across a beam. The array is formed on a PVDF membrane stretched across a support ring, in a similar way to the single element membrane hydrophone described previously. Multielement array hydrophones are available from Precision Acoustics Ltd.

Those preferring to build their own measurement system for lower cost could also look at the approach taken in Newcastle General Hospital (UK). They designed a lightweight and compact system, suitable for transportation by car between base and a hospital site, and by a small trolley within a hospital. Since access to most scanning systems is limited by the need to cause minimal disruption to the normal clinical workload, it was designed to be quick and easy to assemble at the measurement site. It has been used to make measurements on over a thousand combinations of probes and modes on a wide range of diagnostic ultrasound scanners in the north of England. It uses the analogue method developed by [Martin \(1986\)](#) for monitoring  $I_{ta}$  in real-time. A block diagram of the system is shown in [Figure 3.7](#).

#### 3.3.2 Measurement of output power

A radiation force balance (RFB) provides a convenient way of measuring the acoustic power from diagnostic equipment in hospital departments. This method makes use of the fact that ultrasound exerts a force on a target that is directly proportional to the total power absorbed or reflected by the target [guidance can be found at [http://www.npl.co.uk/acoustics/ultrasound/research/best-practice-guide-to-measurement-of-acoustic-output-power-\(introduction\)](http://www.npl.co.uk/acoustics/ultrasound/research/best-practice-guide-to-measurement-of-acoustic-output-power-(introduction))]. It is preferable to use a flat absorbing target rather than the conical reflecting target which is sometimes seen. The use of a flat target simplifies corrections for non-perpendicular incidence (see below), and allows the distance between the probe and the target to be reduced, thereby reducing errors due to absorption of high frequency harmonics associated with the non-linear propagation of ultrasound waves in water. Conical targets should not be used in focused fields ([IEC61161, 2006](#)).

The force on an absorbing target is approximately  $68 \mu\text{g per mW}$  of incident power. Since the output power of diagnostic scanners is typically between a few milliwatts and

Power is best measured using a calibrated RFB fitted with an absorbing target

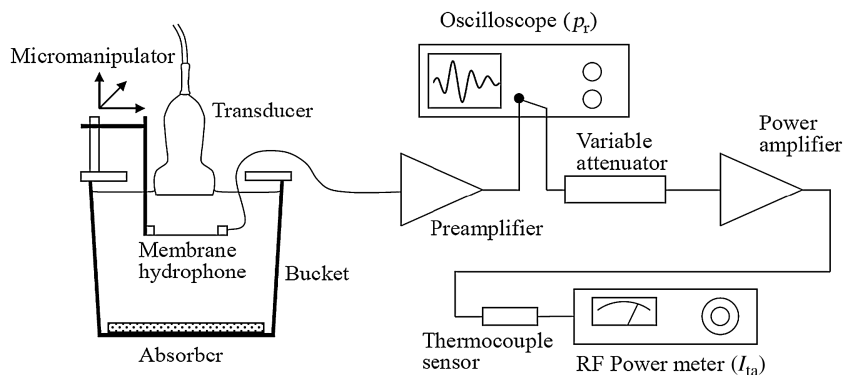


Figure 3.7. Principle features of the portable "hydrophone in a bucket" system developed in Newcastle.

a few hundred milliwatts, a balance resolution of 0.01 mg is required for measurements at the lower end of this power range although, with care, a resolution of 0.1 mg is adequate for powers above about 20 mW. This high sensitivity means that air currents and vibrations transmitted from the surroundings can be a problem.

The balance calibration should be traceable to national standards (*e.g.* at the National Physical Laboratory), its performance may be checked using a checksource (a transducer and drive unit that delivers a beam of known acoustic power) or, in some cases, by applying a known weight. The use of a checksource is preferable to weights since it will also verify the acoustic performance of the target. If the ultrasonic field is strongly convergent (*e.g.* some strongly focused stationary beams), divergent (*e.g.* sector scanners in scanning mode) or obliquely incident on the target (*e.g.* angled Doppler or sector scan beams), then an appropriate “ $\cos \theta$ ” correction factor should be estimated and applied. With care, an uncertainty of 10–15% is achievable.

Commercial RFBs suitable for the diagnostic power range are available from Onda Corporation, Ohmic Instruments Co. (Easton, PA) and Precision Acoustics. All use a top-loading configuration (see Figure 3.8): in the first two, the target is suspended in a small water tank; in the third, the target actually forms the water tank in what is sometimes called an “acoustic well” (Sutton *et al.*, 2003). Some large transducers may not fit tall of these RFBs. Especially when measuring powers less than 50 mW, the transducer must be held solidly in a stationary clamp, the transducer cable should be supported to stop it swinging or moving, and it may be necessary to cover the RFB to protect it from draughts (even a cardboard box can be very effective).

It is quite possible to make a RFB. The most important consideration is the need for a high quality absorbing target: the best material for this the 2-layer polyurethane material called “HAM-A” from Precision Acoustics Ltd (Zeqiri and Bickley, 2000).

Several centres still use a design of RFB which is no longer available and which is often called the “Bath Balance” (Perkins, 1989). This was a development of an earlier design by Farmery and Whittingham (1978). This is a closed system in which the transducer is placed horizontally against a membrane on the side of a small chamber in which the target hangs from a pivot.

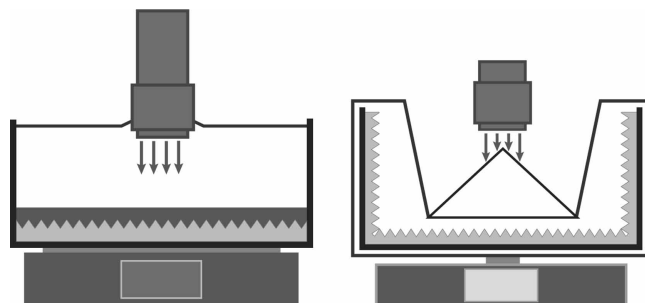


Figure 3.8. Two schematic RFB configurations showing the absorbing well (left) and suspended target (right) types.

There is a radiation force of about  $68 \mu\text{g}$  per mW of acoustic power

An angle correction may be necessary (*e.g.* for angled Doppler or scanning sector probes)

Commercial RFBs are available. It is also possible to make an RFB

TI “at surface”  
can be measured  
using an RFB

It is possible to use an RFB to determine some forms of the TI. The TI “at surface” is calculated either from total acoustic power or from the power emanating from a 1 cm square region of the transducer face. The use of an RFB with suitable mask allows this latter quantity to be measured.

#### 3.3.3 Measurement of temperature

The safety standard IEC60601-2-37 (2007) limits the temperature of the transducer surface to less than 50°C when running in air and to less than 43°C when in contact with a phantom at 33°C (for externally applied transducers) or at 37°C (for internal transducers). It is often these temperature limits (rather than a limit on  $I_{\text{spta}}$  or MI) that restrict the acoustic output of a transducer.

$T_{\text{surf}}$  in air can be  
measured most  
conveniently  
using an  
infra-red camera

The most practical way to check compliance with the limit in air is to use an infrared camera, which can be bought for between £1000 and £2000. Lower cost options are to use small wire thermocouples or single-point infra-red thermometers but IR cameras have the advantage that the location of the hottest part of the transducer is visible (Figure 3.9) so the measurement process becomes much faster and easier: the hottest part is not always in the middle of the transducer (Hekkenberg and Bezemer, 2004). In addition, thermocouples can perturb the temperature field leading to higher or lower values; and the spot-size on many infra-red thermometers is relatively large (1–2 mm), leading to spatial-averaging. The value of the surface emissivity is usually adjustable on the camera and should be set to give the correct temperature value when the transducer is “cold” *i.e.* at room temperature before ultrasound is applied. It is often instructive to see how the temperature distribution changes when the operating mode is changed or other scanner controls are adjusted. The measurement should be carried out over 30 min but it is often obvious long before that if the temperature is likely to approach the threshold value.

$T_{\text{surf}}$  on tissue is  
estimated using  
a phantom and  
a miniature  
thermocouple

Measurement of surface temperature with the probe in contact with a phantom (Hekkenberg and Bezemer, 2004; Calvert and Duck, 2006) is more complicated but a phantom to mimic skin over soft tissue is available from the National Physical Laboratory. This consists of an agar gel covered with a layer of silicone rubber and meets the specification of IEC60601-2-37 (2007). A thermal sensor is not usually included, so users must supply their own: flat, metal film thermocouples have been widely used [*e.g.* type CO2-K from Omega Engineering, Manchester, (UK)]. Thin wire thermocouples can also be

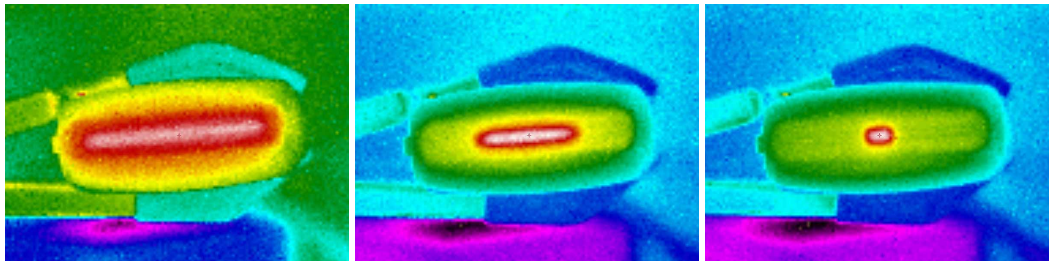


Figure 3.9. Infra-red images of a linear array transducer operating in B-mode (left—maximum = 27.7°C), colour-flow (centre—maximum = 31.5°C) and PW Doppler mode (right—maximum = 31.6°C).

used but, in either case, it is preferable to avoid type T thermocouples since the thermal conductivity of copper is very high and distorts the temperature field more than other types. Again, it is often instructive to observe how the temperature varies as the scanner controls are adjusted (Figure 3.10).

Thermal phantoms can be made to mimic particular tissue paths and have an important role in evaluating any potential hazard arising from ultrasound-induced heating. Shaw *et al.* (2011) used a phantom designed to mimic the neonatal head to estimate the temperature rise at several locations in the head due to scanning through the fontanel at typical clinical settings. They found that approximately 35% of the configurations studied gave a temperature increase at the phantom skin surface in excess of 6 °C in less than 10 min. They also found that there was no useful correlation between the displayed TI and the temperature measured in the phantom: the average skin surface temperature on the phantom was 6 times larger than the average TI value. This is because the model for calculating TI completely ignores the self-heating of the transducer, which is actually the dominant factor governing  $T_{\text{surf}}$ . The use of phantoms is not restricted to measurement of surface temperature (Shaw *et al.*, 1998, 1999; IEC62306, 2006).

$T_{\text{surf}}$  on tissue is usually much higher than the TI value

### 3.4 Control settings that give the highest output levels

Awareness of the control settings that are likely to give the highest output levels is important both for users wishing to avoid high outputs and reduce the MI or TI value for safety reasons, and to measurers who are trying to maximize the output. Those who look for worst-case values must have an understanding of the operating principles of the particular machine, since the number of different possible combinations of control settings can run into millions. The nature and range of controls is constantly changing with the evolution of new scanning features, so provision of a rigid universal protocol is not possible. Controls on some of the newer machines can have quite unexpected effects, as manufacturers often arrange for, say, drive voltages or pulse repetition frequencies to change automatically when controls are set in a way which would otherwise cause a particular safety parameter, such as  $I_{\text{spta}}$  or TI, to exceed a predetermined limit. However,

Awareness of the control settings is important for users wishing to avoid high outputs and reduce the MI or TI value for safety reasons

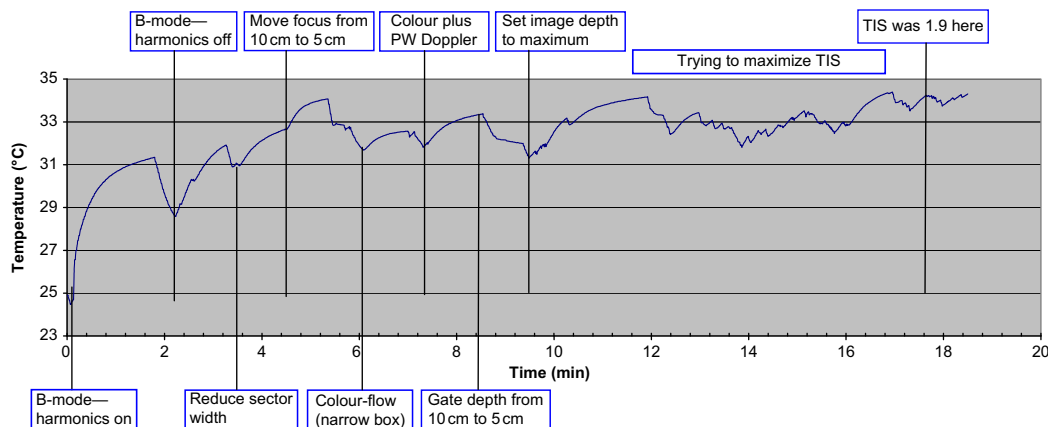


Figure 3.10. Example showing the variation in the surface temperature of a 3 MHz linear array transducer as scanner settings are adjusted.

### 3 The acoustic output of diagnostic ultrasound scanners

Measurement of “worst-case” settings requires an understanding of the operating principles of the particular machine, since the number of different possible combinations of control settings can run into millions

High power is often associated with longer focal depths

$I_{\text{spta}}$  can be increased when using the write-zoom control in B-mode, and with a narrow colour box in colour Doppler modes

The position of the highest intensity in tissue may not be within the zoom or colour box itself

published protocols can provide useful guidance (Henderson *et al.*, 1994; Whittingham, 2000; IPEM, 2010) and help to reduce the search to manageable proportions.

Apart from the obvious example of setting the output power control to maximum, there are a few general observations that can be made about producing high output levels. In general, the effects of controls on output levels depend upon the operating mode, but selecting a deep transmission focus often involves an increase in acoustic power whichever mode is chosen. This is because manufacturers often arrange for the transmission aperture to be increased if a deep transmission focus is selected, in order to maintain a narrow beam width and good sensitivity at depth. Apart from the effect of the larger aperture, the drive voltage applied to each element may also be increased to compensate for the greater attenuation anticipated for deep targets. Linear and curvilinear arrays give the greatest opportunity to vary the aperture. For smaller sector scanners and phased arrays, most of the aperture is used even for small depths. The power may not increase so much with display depth, because to do so would result in a higher energy density (and hence excessive temperature) at the transducer face.

When operating in B-mode, the increase in power usually associated with a deep focus setting will also increase  $I_{\text{spta}}$ . Activation of a write-zoom box is another way by which  $I_{\text{spta}}$  is increased, particularly if the box is narrow. Unlike read-zoom, which simply magnifies part of the stored image, write-zoom involves a selected area being re-scanned at a higher line density. This leads to higher temporal-average intensities, since the probe continues to transmit the same energy per second, but this is restricted to a narrower area. Write-zoom may also lead to a higher pulse repetition frequency, since there is no need to wait for echoes from beyond the box, and this will increase temporal-average power and  $I_{\text{spta}}$  even further. Since the transmission focus (or multiple foci) is usually automatically set to lie within the box, the highest  $I_{\text{spta}}$  and power levels in B-mode are usually associated with a fairly deep and narrow zoom-box. A similar effect, only at generally higher output levels, also occurs with the colour box in colour Doppler modes, *e.g.* colour-flow mapping mode or colour Doppler power mode. Again, this may be less marked for smaller sector scanners and phased arrays than for linear or curvilinear arrays. It is sometimes possible to adjust the sector angle from a sector scanner or phased array. Reducing the angle can often increase the frame rate and so increase  $I_{\text{spta}}$  and surface temperature.

Note that the position at which the  $I_{\text{spta}}$  occurs is not generally within the zoom-box itself, but rather at a depth close to that of minimum slice thickness. Nevertheless, selection of a zoom-box still increases  $I_{\text{spta}}$ , since it reduces the width of the scanned field at all depths, including that at the minimum slice thickness. Also note that, on some machines, if the write-zoom or colour box is moved to the very great depths, the power and  $I_{\text{spta}}$  may not be as large as at a less extreme depth setting, since the aperture may not be able to expand any further, yet the pulse repetition frequency will be lower.

In stationary beam modes, such as M-mode and spectral Doppler, temporal-average intensities are directly proportional to temporal-peak intensities, provided the pulse

repetition frequency (prf) remains constant. Thus, with this proviso, control settings that maximize  $p_r$  will be those that also maximize  $I_{\text{spta}}$ . A large  $p_r$  and hence  $I_{\text{spta}}$  is usually produced if the operator-controlled focus (which acts in the scan plane) is set close to the (fixed) elevation focus, since this increases the strength of focussing in a three-dimensional sense. However, as discussed above, setting the focus (or range-gate in the case of spectral Doppler) to a greater depth may well increase the transmission aperture and drive voltage, and hence produce even greater pressures and intensities near the scan-plane focus. Only practical measurement can establish which of these two effects will produce the greatest  $p_r$  and  $I_{\text{spta}}$ .

In spectral Doppler mode, a high Doppler frequency scale setting, or the selection of “high prf” mode, is likely to produce a higher power and  $I_{\text{spta}}$ . In themselves, these prf-related controls would not be expected to affect  $p_r$  values, but manufacturers sometimes arrange for drive voltages, and hence pressure amplitudes, to be reduced for safety reasons if a high prf is selected. A short range-gate is likely to give higher  $p_r$  values, since drive voltages are usually reduced as gate length increases, again for safety reasons. The effect of range-gate length on power and  $I_{\text{spta}}$  is difficult to predict, for the same reason.

The use of harmonic imaging modes is often accompanied by higher  $p_r$  (to generate more non-linearity) leading to greater output power and higher  $I_{\text{spta}}$ .

## 3.5 Acoustic output values

### 3.5.1 Independent measurements of acoustic outputs

Measurements of acoustic exposure parameters from diagnostic ultrasound systems have long been of interest for assessing their acoustic safety. The first surveys of acoustic outputs to include real-time B-scan array systems (c.f. static B-scanners) were published in 1978 (Carson *et al.*, 1978) and 1985 (Duck *et al.*, 1985), when this technology was relatively new. Although the number of array systems studied in these reports is small (two and four respectively) and some of the measurement methods differ from those now used, the values are of interest because they are so much lower than those reported more recently for current systems. These early reports are discussed in more detail later.

The most comprehensive surveys of acoustic output values for ultrasound systems using real-time transducers were published or carried out in the 1990s (Duck and Martin, 1991; Henderson *et al.*, 1995; Whittingham, 2000). These surveys were carried out in the UK by NHS medical physics departments, independently of the equipment manufacturers and relate to systems in active clinical use at the time of measurement. The measurement methods used were based on the principles described above, *i.e.* using a PVDF membrane hydrophone in a water bath to measure acoustic pressure and a RFB to measure acoustic power. In all 3 surveys, the active element of the hydrophone used was 0.5 mm in diameter.

In these surveys, the spatial-peak values of pressure and the intensity parameters given were those measured in water at the point in the acoustic field where they achieved their

The highest  $p_r$  in spectral Doppler mode is commonly associated with the shortest range-gate, and lowest prf. A high Doppler frequency scale setting, or the selection of “high prf” mode, is likely to produce a higher power and  $I_{\text{spta}}$ .

Several surveys of acoustic exposure parameters were carried out in the 1990s. These reported peak values of pressure and intensity measured in water under worst-case conditions

### 3 The acoustic output of diagnostic ultrasound scanners

maximum value. No derating of values, as used in the measurement and calculation of safety indices (see above) was applied. In each case, the ultrasound system controls, for the particular mode of operation (e.g. B-mode or colour Doppler), were manipulated to achieve the highest value of the parameter of interest (e.g.  $p_r$  or  $I_{\text{spta}}$ ), i.e. the worst-case value. As described above, the operating conditions and hydrophone locations required to give worst-case values of  $p_r$  and  $I_{\text{spta}}$  in each mode of operation are likely to be quite different.

Mean and median values of  $p_r$  from the three 1990s surveys in 3 modes of operation are of the order of 2.4 MPa, with much overlap in the ranges of values, but a slow upward trend

For all three surveys, measurement data from all types of real-time transducer (linear/curved array, phased array, mechanical, transcutaneous and intracavity) are combined. The survey by [Duck and Martin \(1991\)](#) included data from 108 real-time transducers and 44 scanners from 19 manufacturers. Pulsed Doppler measurements were from 17 systems from 11 manufacturers. [Henderson et al. \(1995\)](#) studied 82 scanners and 223 transducers from 18 manufacturers. The data from [Whittingham \(2000\)](#) related to similar measurements made in the period 1995–1998. The survey by [Duck and Martin \(1991\)](#) gave values for peak compression and rarefaction pressures,  $I_{\text{spta}}$ ,  $I_{\text{sppa}}$  and acoustic power. As the 2 later surveys gave values only for peak rarefaction pressure,  $I_{\text{spta}}$  and acoustic power, values for these 3 parameters are reviewed here to allow identification of trends.

[Table 3.1](#) gives the range, median and mean values of peak rarefaction pressure quoted by the three surveys above in real-time B-mode, pulsed Doppler and colour Doppler modes.

Values for peak rarefaction pressure for all modes and surveys are typically in the range 0.5–5 MPa with mean and median values of the order of 2.4 MPa. For each individual survey, there is much overlap in the ranges of pressure values for the three modes of

Values of  $I_{\text{spta}}$  from the 1990s surveys were highest in pulsed Doppler mode (mean > 1 W cm<sup>-2</sup>) and least in B-mode. There was a strong upward trend in  $I_{\text{spta}}$  in B-mode but little change in pulsed Doppler values

Table 3.1. Worst-case values of peak rarefaction pressure (MPa) as measured in water. Data taken from [Duck and Martin \(1991\)](#), [Henderson et al. \(1995\)](#) and [Whittingham \(2000\)](#) (1998 survey). The number of transducers for which measurements are included is  $n$ .

	1991	1995	1998
B-mode			
Range	0.6–4.3	0.4–5.5	0.5–4.6
Median	2.1	2.4	2.4
Mean	2.1	2.4	2.6
$n$	108	190	100
Pulsed Doppler			
Range	0.2–3.8	0.7–5.3	0.6–5.5
Median	1.6	2.1	2.4
Mean	1.8	2.2	2.4
$n$	42	118	82
Colour Doppler			
Range	0.9–3.9	0.5–4.2	0.8–4.9
Median	2.3	2.4	2.6
Mean	2.4	2.4	2.8
$n$	18	87	79

operation, although in the 1991 survey, the mean and median values in pulsed Doppler mode are somewhat lower. Comparison of values across the three surveys shows a gradual trend to higher values and less difference between modes of operation.

**Table 3.2** gives values for  $I_{\text{spta}}$  from the 1991, 1995 and 1998 surveys in B-mode, pulsed Doppler and colour Doppler.

Values for  $I_{\text{spta}}$  in all modes and surveys show much wider ranges of values than for peak rarefaction pressure. There are also substantial differences in mean and median values for the 3 modes of operation. In the 1991 survey, there is a clear progression in mean values from B-mode to colour Doppler mode to pulsed Doppler mode, with almost an order of magnitude increase between modes. Mean and median values of  $I_{\text{spta}}$  in pulsed Doppler are greater than  $1 \text{ W cm}^{-2}$ . High values of  $I_{\text{spta}}$  would be expected in pulsed Doppler mode due to the use of a stationary beam, whereas in B-mode, the beam is scanned across the full image and in colour Doppler mode across the region of the colour box. Across the surveys, there is a strong upward trend in  $I_{\text{spta}}$  values in B-mode and to a lesser extent in colour Doppler mode, but no clear trend in pulsed Doppler mode.

**Table 3.3** gives values for acoustic power from the 1991, 1995, and 1998 surveys in B-mode, pulsed Doppler and colour Doppler. Values for acoustic power show relatively small differences between modes with typical mean values being of the order of 100 mW. Typical values for the 1995 and 1998 surveys in B-mode and pulsed Doppler mode are higher than those from the 1991 survey, especially in B-mode.

Values of acoustic power from the 1990s surveys showed small differences between modes with mean values in colour Doppler and pulsed Doppler of the order of 100 mW

Table 3.2. Worst-case values of spatial-peak temporal-average intensity ( $\text{mW cm}^{-2}$ ) as measured in water. Data taken from [Duck and Martin \(1991\)](#), [Henderson et al. \(1995\)](#) and [Whittingham \(2000\)](#) (1998 survey). The number of transducers for which measurements are included is  $n$ .

	1991	1995	1998
B-mode			
Range	0.3–177	0.3–991	4.2–600
Median	6.0	34	94
Mean	17	106	175
$n$	101	194	100
Pulsed Doppler			
Range	110–4520	173–9080	214–7500
Median	1140	1180	1420
Mean	1380	1659	1610
$n$	42	118	82
Colour Doppler			
Range	25–511	21–2050	27–2030
Median	96	290	330
Mean	148	344	470
$n$	19	87	79

Table 3.3. Worst-case values of acoustic power (mW). Data taken from [Duck and Martin \(1991\)](#), [Henderson et al. \(1995\)](#) and [Whittingham \(2000\)](#) (1998 survey). The number of transducers for which measurements are included is  $n$ . No values for acoustic power in colour Doppler mode were given in the 1991 survey.

	1991	1995	1998
B-mode			
Range	0.53–350	0.3–285	4–256
Median	7.1	75	51
Mean	19.1	77.8	64
$n$	51	45	29
Pulsed Doppler			
Range	8.7–210	10–440	11–324
Median	42	100	129
Mean	63.5	124	144
$n$	20	39	22
Colour Doppler			
Range		15–440	35–295
Median		90	118
Mean		119	138
$n$		29	22

### 3.5.2 Manufacturer declared acoustic outputs

Although, to the knowledge of the authors, no further independent surveys of acoustic outputs from clinical ultrasound systems have been published since 2000, acoustic output data for more recent models are available from equipment manufacturers. As part of the regulatory systems for medical ultrasound devices in Europe and the USA, manufacturers must declare acoustic output values to demonstrate the acoustic safety of their equipment (see [Chapter 10](#)). In the USA, the FDA requires manufacturers to declare maximum values of MI and TI for each transducer and mode of operation and demonstrate that these are within prescribed limits ([FDA, 2008](#)). The format of the declaration is essentially the same as that in the international standard [IEC60601-2-37 \(2007\)](#). For medical ultrasound systems to be placed on the market in the European Union, manufacturers must demonstrate compliance with the essential safety requirements of the European Medical Devices Directive ([European Communities, 1993](#)). Acoustic safety may be demonstrated by declaring acoustic output values in compliance with [IEC60601-2-37 \(2007\)](#) or [IEC61157 \(2007\)](#) although no upper limits are enforced. IEC61157 includes a requirement to declare maximum values for peak rarefaction pressure and  $I_{\text{spta}}$  for each transducer and mode of operation. These must be measured in water at the location where they achieve maximum value, with no derating applied and hence may be compared with the independent survey values discussed in the previous section. [Martin \(2010\)](#) has reported values of peak rarefaction pressure ( $p_r$ ) and  $I_{\text{spta}}$  from such IEC61157 declarations for ultrasound systems on the market in 2008. These are shown in [Table 3.4](#).

Table 3.4. Manufacturer declared values for maximum in-water peak rarefaction pressure ( $p_r$ ) and  $I_{\text{spta}}$  from [Martin \(2010\)](#). The number of transducers for which measurements are included is  $n$ .

	$p_r$ (MPa)	$I_{\text{spta}}$ (mW cm <sup>-2</sup> )
B-mode		
Range	2.3–6.4	20–1100
Median	3.7	273
Mean	3.9	341
$n$	79	79
Pulsed Doppler		
Range	2.1–6.7	271–2830
Median	4.2	749
Mean	4.2	860
$n$	79	79
Colour Doppler		
Range	1.4–6.7	51–1480
Median	4.2	450
Mean	4.1	466
$n$	79	79

In this manufacturer declared data, mean and median values of  $p_r$  are of the order of 4 MPa, with much overlap between modes in the ranges of values. The highest mean and median values are in colour Doppler and pulsed Doppler modes rather than B-mode. There is still a progression in mean and median values for  $I_{\text{spta}}$  from B-mode to colour Doppler to pulsed Doppler but the differences between the modes are much smaller than those in the surveys reported earlier. In the declared data, the mean  $I_{\text{spta}}$  value in pulsed Doppler is approximately 2.5 times that in B-mode, whereas in the 3 independent surveys, this ratio varies between 9.2 and 81.

As described earlier, it is now more common to characterize the acoustic output of ultrasound systems in terms of safety indices, which indicate the risk of cavitation or heating, rather than using measured exposure parameters such as pressure and intensity. [Martin \(2010\)](#) reported declared values of MI and TI from four ultrasound equipment manufacturers. These are maximum values achievable under worst-case operating conditions.

Under FDA rules, the maximum permitted value for MI is 1.9 and the maximum measured value plus the uncertainty in the measurement must be within this limit. For TI, the normal maximum value is 6.0.

[Table 3.5](#) gives manufacturer declared values of MI (combined from 4 manufacturers), TIS, TIB and TIC in B-mode and pulsed Doppler from [Martin \(2010\)](#). The ranges of MI values for B-mode and pulsed Doppler are the same, consistent with the large overlap in ranges for the declared values of  $p_r$  in [Table 3.4](#). Maximum MI values are less than the permitted maximum of 1.9 due to the need to allow for measurement

Mean values of  $p_r$  declared recently by manufacturers are of the order of 4 MPa, with much overlap between modes. Declared values of  $I_{\text{spta}}$  were highest in pulsed Doppler but with much more overlap between modes than in earlier surveys

Maximum values of MI declared by manufacturers are of the order of 1.25 (mean) in B-mode and pulsed Doppler with ranges extending to 1.7

### 3 The acoustic output of diagnostic ultrasound scanners

Table 3.5. Declared values of MI (combined manufacturer values), TIS, TIB and TIC in B-mode and pulsed Doppler mode from [Martin \(2010\)](#).

	MI	TIS	TIB	TIC
B-mode				
Range	0.2–1.7	0.5–4.1	0.02–4.0	0.1–5.9
Mean	1.25	0.99	0.78	1.7
<i>n</i>	177	131	86	92
Pulsed Doppler				
Range	0.2–1.7	0.08–5.0	0.26–7.0	0.15–6.6
Mean	1.23	1.1	2.3	1.8
<i>n</i>	147	138	145	87

uncertainty. The relatively high mean values of MI (of the order of 1.25) suggest that many transducers are capable of producing an MI near to the FDA regulatory limit.

Mean declared values of TIS, TIB and TIC in both modes are much lower than the normal maximum FDA value of 6.0, showing that many transducers are not capable of producing this value. For some transducers, this may be due to the transducer temperature reaching the regulatory limit before a high TI value is achieved. Mean declared values of TIS and TIB in B-mode and TIS in pulsed Doppler mode are all of the order of 1.0, reflecting the fact that the same mathematical model is used for TIS and TIB for scanned modes (*e.g.* B-mode) and TIS in unscanned modes for apertures  $<1 \text{ cm}^2$  (*e.g.* pulsed Doppler). Mean values for TIC in both modes and TIB in pulsed Doppler mode are higher.

[ter Haar \(2008\)](#) reported values for TI and MI obtained from a survey of ultrasound users in the UK. These values were reported in 2 categories: (i) the default values obtained at switch-on or with each new patient and (ii) the maximum values achieved during an individual patient scan. Hence the values from this survey represent typical MI and TI values found in clinical use rather than worst-case system values. In this study, values were reported according to the clinical application of the scan rather than the mode of operation. Of the 48 abdominal scans reported, 44 were B-mode or B-mode with harmonic imaging and 4 included use of colour Doppler. TI values were reported as TIS for 36 scans and TIB for 5. In the obstetric category, 66 scans were reported as B-mode, 30 as colour Doppler and 19 included pulsed Doppler (other reports did not specify mode of operation). TI values were reported as TIS for 20 scans, TIB for 72 scans and TIB/TIS/TIC for 31.

[Table 3.6](#) gives the maximum values of MI and TI recorded during abdominal and obstetric scans. Although the equipment used in this study was not the same as that for manufacturer declared values, both studies related to equipment that was available in 2008. The large overlap in the ranges of the manufacturer and clinical values of MI suggest that the full range of available MI values may be used in clinical practice. Mean values of maximum MI used in clinical practice are of the order of 60–75% of the maximum

Mean manufacturer declared values of TI are generally much lower than the FDA limit of 6.0

Maximum values of MI reported during clinical use cover a similar range to manufacturer declared maximum values but are lower on average

Table 3.6. Maximum values of MI and TI recorded during abdominal and obstetric scans by clinical users (from [ter Haar, 2008](#)).

	MI <sub>max</sub>	TI <sub>max</sub>
Abdominal		
Range	0.4–1.6	0.1–0.8
Mean	0.97	0.56
<i>n</i>	48	46
Obstetric		
Range	0.2–1.6	0.1–2.5
Mean	0.74	0.98
<i>n</i>	220	167

available. Direct comparison between clinical and manufacturer declared TI values is more difficult due to the mixture of modes of operation and types of TI reported in the clinical study. However, the range and mean TI values reported for abdominal scans were significantly lower than the worst-case manufacturer TI values. Maximum TI values reported for obstetric applications were higher than for abdominal scans, presumably due to the use of pulsed Doppler in many of the cases.

Maximum TI values reported for abdominal scans are lower than the maximum B-mode values declared by manufacturers

### 3.5.3 Trends in acoustic outputs

The acoustic output surveys from the 1990s described above showed gradual increases through that decade in mean and median values of peak rarefaction pressure in B-mode, colour Doppler and pulsed Doppler. Mean and median values of  $I_{\text{spta}}$  in B-mode and colour Doppler increased more strongly. More recent trends can be revealed by comparing values from these surveys to manufacturer declared values. In making this comparison, it must be taken into account that the measurement equipment used and measurement uncertainties may not be the same. Also the manufacturer values may represent the maximum from a small batch of the same type of transducer and system model. [Figure 3.11](#) shows graphically the range and mean values for peak rarefaction pressure from the 1990s surveys and the manufacturer declared values (from [Martin, 2010](#)). Mean manufacturer declared values of  $p_r$  were of the order of 4 MPa, representing an increase of the order of 50% in mean B-mode and colour Doppler values and 75% in pulsed Doppler since 1998.

Peak rarefaction pressures declared by manufacturers (2010) are 50–75% higher than those reported in a 1998 measurement survey

[Figure 3.12](#) shows a similar comparison of survey and manufacturer declared values of  $I_{\text{spta}}$  in the three modes of operation. In B-mode, the upward trend observed in the 1990s surveys has continued. The mean value in 2010 ( $341 \text{ mW cm}^{-2}$ ) was almost twice that measured in 1998 ( $175 \text{ mW cm}^{-2}$ ). However, in pulsed Doppler mode, a downward trend is seen; the mean declared value of  $I_{\text{spta}}$  was approximately half that reported in 1998. In colour Doppler mode, the mean  $I_{\text{spta}}$  value was similar to that reported in 1998. A further important observation which emerges from this comparison is that the opposing trends in B-mode and pulsed Doppler has resulted in much overlap in the ranges of  $I_{\text{spta}}$  values for the three modes of operation. It is no longer the case that  $I_{\text{spta}}$  values in pulsed Doppler are many times greater than in B-mode.

Maximum  $I_{\text{spta}}$  values declared by manufacturers (2010) showed an increase for B-mode but a reduction for pulsed Doppler mode compared to 1998 survey values, resulting in increased overlap in values between modes

### 3 The acoustic output of diagnostic ultrasound scanners

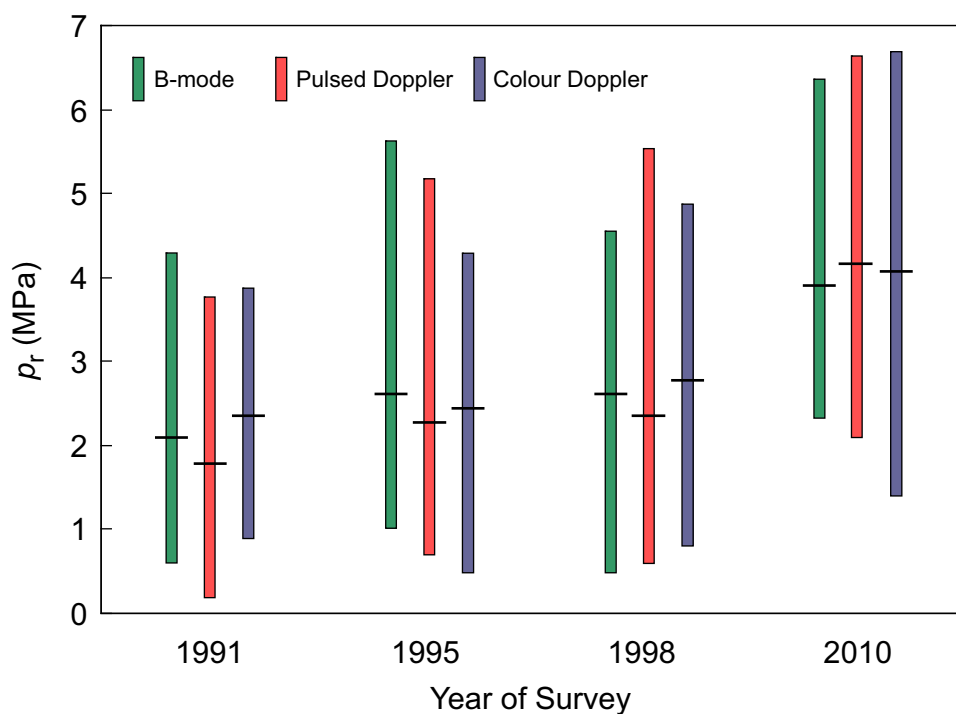


Figure 3.11. Manufacturer declared values of peak rarefaction pressure ( $p_r$ ) in (2010) compared to 3 previous surveys in B-mode, pulsed Doppler and colour Doppler (from [Martin, 2010](#)).

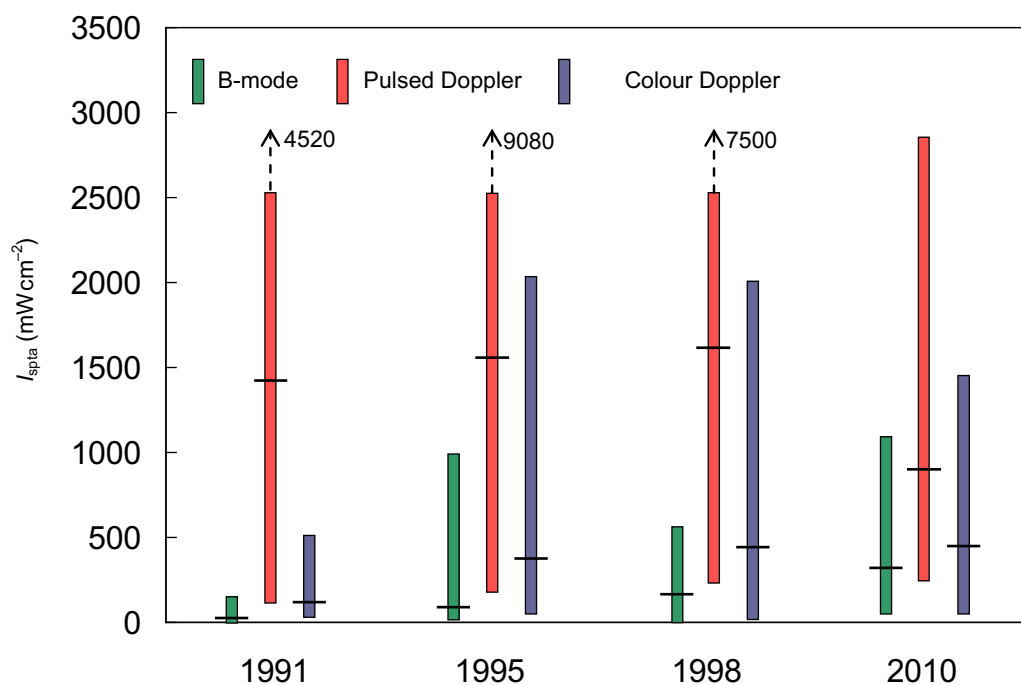


Figure 3.12. Manufacturer declared values of spatial-peak temporal-average intensity ( $I_{spta}$ ) in (2010) compared to 3 previous surveys in B-mode, pulsed Doppler and colour Doppler mode (from [Martin, 2010](#)).

### 3.6 Discussion

In previous years, those carrying out output measurements on scanners have tended to concentrate on finding the settings which give the maximum output. This is still appropriate for regulatory purposes but, with the extreme complexity of modern scanners, it is debatable whether it is worth the effort of trying to identify these settings in a hospital environment. They may not even be particularly relevant to hospital users and patients. There are two alternative approaches which seem to be more efficient and relevant outside of the regulatory environment. The first is to measure the presets. Almost all ultrasound exams start with the selection of a clinical “preset” appropriate for the type of scan being undertaken and, although practice varies between individuals, it is common that relatively few settings that affect the output (such as display depth and scan mode) are adjusted during the scan. So the output of the preset is a fair representation of the output during a typical scan of that type. The use of the preset also provides a way of reproducing the output configuration for instance to look for changes over time or following hardware or software upgrades: some presets could be “locked” and dedicated to testing. Testing could involve hydrophone measurements but even simpler testing with an RFB or a thermal phantom would provide useful tests of consistency.

It may be more useful to measure the clinical presets and to validate displayed indices than to try to maximize output

A second approach is to validate the displayed MI and TI values. Limited validation can be carried out using an RFB to measure power, although more thorough validation requires hydrophone measurements. Determination of MI and TI requires a measurement of power and measurements of  $p_r$  and  $I_{ta}$  along the beam-axis. There is a strong case for saying that every medical physics department with an ultrasound responsibility should be capable of validating the displayed indices and should do this as part of acceptance testing when scanners are purchased. Users are expected to make risk-benefit judgements based on the values displayed and need to be reassured that they are reliable. A system targeted to making only these measurements could be more compact and economical than a more general hydrophone system. A prototype of such a system has been assembled at the National Physical Laboratory.

To ensure the safe use of ultrasound in diagnosis, it is important for clinical users to have some awareness and understanding of the acoustic output of their equipment and how it is affected by the way in which they operate it. Review of reported values for acoustic output parameters shows that maximum values for some parameters may now be more than 2 orders of magnitude greater than those reported for the first real-time B-mode transducers. [Carson \*et al.\* \(1978\)](#) reported a maximum value for  $I_{spta}$  of  $15.9 \text{ mW cm}^{-2}$  and [Duck \*et al.\* \(1985\)](#) a maximum value of  $2.5 \text{ mW cm}^{-2}$  for early linear array transducers operating in B-mode. In 2010, a worst-case value in real-time B-mode of  $1100 \text{ mW cm}^{-2}$  was declared for this parameter by an ultrasound system manufacturer ([Martin, 2010](#)). While the developments in ultrasound technology that have taken place over this time scale have resulted in huge improvements in image quality and system performance, it is now clear that they have also resulted in some significant increases in acoustic output levels, particularly in B-mode.

Maximum values for some parameters are more than 100 times greater than those reported for the first real-time B-mode scanners

### 3 The acoustic output of diagnostic ultrasound scanners

Some new imaging methods require higher output: regulations may eventually be modified to allow more effective use of emerging techniques

The review given above of acoustic output surveys from the 1990s and more recent manufacturer declared outputs showed steady increases in the mean values of peak rarefaction pressure in B-mode, pulsed Doppler and colour Doppler. Such increases would be expected from manufacturers' efforts to improve transducer efficiency and focussing methods, thus allowing the use of higher frequencies for a given application. Acoustic pressure levels are now effectively regulated by the FDA through the maximum permitted values of MI. MI increases with  $p_r$  but reduces with the square root of frequency and there is evidence (Martin, 2010) that some manufacturers are working to this regulatory limit, using higher  $p_r$  values at higher frequencies.

More recent developments in technology may have influenced acoustic pressure and MI values. For example, harmonic imaging requires the use of high acoustic pressures to generate harmonics in the pulse waveform via non-linear propagation. Harmonic imaging (Tranquart *et al.*, 1999) may also be associated with higher MI values, as some harmonic imaging methods also require the transmit frequency to be reduced. Shear wave techniques (Bercoff *et al.*, 2004) must make use of the highest permissible output levels to generate acoustic radiation stress in tissues. It is possible that existing regulations may be modified to permit the use of higher outputs.

The largest changes in acoustic output values over the last 20 years have been in  $I_{\text{spta}}$  levels for real-time B-mode. In the 1991 survey, the mean value of this parameter in B-mode was smaller than that in pulsed Doppler by a factor of 84. This would be expected due to the use of a stationary beam in pulsed Doppler mode and the use of relatively long pulses and high prf. However, in the manufacturers' declared values from 2010, this ratio was reduced to 2.5. While there had been a reduction in the mean value of  $I_{\text{spta}}$  in pulsed Doppler mode, the mean value in B-mode had increased from 17 to 341 mWcm<sup>-2</sup>. The 2010 data also showed much overlap in the ranges of values for these 2 modes.

Values for  $I_{\text{spta}}$  in B-mode have presumably increased over this time due to improvements in transducer efficiency and focussing methods. New pulse sequencing techniques designed to increase frame rates and the use of longer coded pulses (Chiao and Hao, 2005) would also contribute to this increase. Corresponding increases in the already high values in pulsed Doppler would be restricted by FDA limits on  $I_{\text{spta}}$  (Chapter 10).

Maximum achievable TI values declared by manufacturers, on average, are low compared to the FDA normal maximum permitted value of 6.0. Mean values of TIS and TIB in B-mode and TIS in pulsed Doppler mode are of the order of 1.0 or less. The mean TIB value declared for pulsed Doppler (2.3) was more than twice this value. Mean values for TIC in B-mode and pulsed Doppler were 1.7 and 1.8. While these values may seem low in relation to the maximum FDA value, they are still significant in acoustic safety terms. For obstetric and neonatal transcranial scanning, the BMUS safety guidelines (BMUS, 2010) recommend that scanning time is restricted for any TI value greater than 0.7. For a TIB of 2.3, it is recommended that the duration of such scans be restricted to 4min. Maximum TI values used in obstetric scanning as reported by ultrasound users

BMUS recommends that obstetric scanning time is limited for TI more than 0.7

(ter Haar, 2008) are more reassuring. The majority of TI values used in obstetric scanning were less than 0.7 with a mean value of 0.44. Of the 231 obstetric scans reported, only three were identified that did not conform to the BMUS guidelines in terms of TI level and scanning time.

## Acknowledgements

The authors would like to acknowledge the contribution of Dr Tony Whittingham who wrote the equivalent chapter in the second edition of this book. We have reused some parts of his original chapter.

## References

- Bercoff J, Tanter M, Fink M. 2004. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. *IEEE Trans Ultrason Ferroelectr Freq Control*, 51, 396–409.
- BMUS. 2010. Guidelines for the Safe Use of Diagnostic Ultrasound Equipment. Available at: [bmus.org](http://bmus.org).
- Calvert J, Duck FA. 2006. Self-heating of diagnostic ultrasound transducers in air and in contact with tissue mimics. *Ultrasound*, 14, 100–108.
- Carson PL, Fischella PS, Oughton TV. 1978. Ultrasonic powers and intensities produced by diagnostic ultrasound equipment. *Ultrasound Med Biol*, 3, 341–350.
- Chiao RY, Hao X. 2005. Coded excitation for diagnostic ultrasound: a system developers perspective. *IEEE Trans Ultrason Ferroelectr Freq Control*, 52, 160–170.
- Duck FA, Martin K. 1991. Trends in diagnostic ultrasound exposure. *Phys Med Biol*, 36, 1423–1432.
- Duck FA, Starritt HC, Aindow JD, Perkins MA, Hawkins AJ. 1985. The output of pulse-echo ultrasound equipment: a survey of powers, pressures and intensities. *Br J Radiol*, 58, 989–1001.
- European Communities. 1993. Council directive 93/42/EEC of June 1993 concerning medical devices. *Off J Eur Communities*, 169.
- Farmery MJ, Whittingham TA. 1978. A portable radiation-force balance for use with diagnostic ultrasonic equipment. *Ultrasound Med Biol*, 3, 373–379.
- FDA. 2008. Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers. Rockville, MD: Food and Drug Administration.
- Hekkenberg RT, Bezemer RA. 2004. On the development of a method to measure the surface temperature of ultrasonic diagnostic transducers. *J Phys Conf Ser*, 1, 84. doi: 10.1088/1742-6596/1/1/019.
- Henderson J, Jago J, Willson K, Whittingham TA. 1994. Development of protocols for measurement of maximum spatial peak temporal average intensity from scanners operating in pulsed Doppler and colour Doppler modes. *Br J Radiol*, 67, 716.
- Henderson J, Willson K, Jago J, Whittingham TA. 1995. A survey of the acoustic outputs of diagnostic ultrasound equipment in current clinical use in the Northern Region. *Ultrasound Med Biol*, 21, 699–705.
- Hodnett M, Zeqiri B. 2009. A novel sensor for determining ultrasonic intensity. In Proceedings of the 38th Annual Symposium of the Ultrasonic Industry Association (UIA), Muratore R, Hodnett M (editors). doi: 10.1109/UIA.2009.5404029.

- IEC60601-2-37 Edition 2. 2007. Medical Electrical Equipment – Part 2-37: Particular Requirements for the Basic Safety and Essential Performance of Ultrasonic Medical Diagnostic and Monitoring Equipment. Geneva, Switzerland: International Electrotechnical Commission.
- IEC61157 Edition 2.0. 2007. Standard Means for the Reporting of the Acoustic Output of Medical Diagnostic Ultrasonic Equipment. Geneva, Switzerland: International Electrotechnical Commission.
- IEC61161 Edition 2.0. 2006. Ultrasonics – Power Measurement – Radiation Force Balances and Performance Requirements. Geneva, Switzerland: International Electrotechnical Commission.
- IEC62127-1 Edition 1.0. 2007. Ultrasonics – Hydrophones – Part 1: Measurement and Characterization of Medical Ultrasonic Fields up to 40 MHz. Geneva, Switzerland: International Electrotechnical Commission.
- IEC/TS62306 Edition 1.0. 2006. Ultrasonics – Field Characterisation – Test Objects for Determining Temperature Elevation in Diagnostic Ultrasound Fields. Geneva, Switzerland: International Electrotechnical Commission.
- IEC62359 Edition 2.0. 2010. Ultrasonics – Field Characterization – Test Methods for the Determination of Thermal and Mechanical Indices Related to Medical Diagnostic Ultrasonic Fields. Geneva, Switzerland: International Electrotechnical Commission.
- IPEM Report 102. 2010. Quality Assurance of Ultrasound Imaging Systems, Stephen Russell (editor). York, UK: Institute of Physics and Engineering in Medicine.
- Jago J, Henderson J, Whittingham TA, Willson K. 1995. How reliable are manufacturers' reported acoustic output data? *Ultrasound Med Biol*, 21, 135–136.
- Lewin PA, Ziskin MC (editors). 1992. Ultrasonic Exposimetry. Boca Raton, FL: CRC Press.
- Martin K. 1986. Portable equipment and techniques for acoustic power output and intensity measurement. In *Physics in Medical Ultrasound*, Evans JA (editor). London, UK: IPEM.
- Martin K. 2010. The acoustic safety of new ultrasound technologies. *Ultrasound*, 18, 110–118.
- Perkins MA. 1989. A versatile force balance for ultrasound power measurement. *Phys Med Biol*, 34, 1645–1651.
- Preston RC. 1988. The NPL ultrasound beam calibrator. *IEEE Trans Ultrasonics Ferroelectr Freq Control*, 35, 122–138.
- Preston RC (editor). 1991. Output Measurements for Medical Ultrasound. London, UK: Springer-Verlag.
- Shaw A, Memoli G, Duck FA, Osborne J, Robinson H, Bartle D, *et al.* 2011. Neonatal Transcranial Ultrasound – Thermal Hazard and Risk Assessment. NPL Report. Teddington, UK: National Physical Laboratory.
- Shaw A, Pay NM, Preston RC. 1998. Assessment of the Likely Thermal Index Values for Pulsed Doppler Ultrasonic Equipment – Stage II: Experimental Assessment of Scanner/Transducer Combinations. NPL Report CMAM 12. Teddington, UK: National Physical Laboratory.
- Shaw A, Pay NM, Preston RC, Bond AD. 1999. A proposed standard thermal test object for medical ultrasound. *Ultrasound Med Biol*, 25, 121–132.
- Shaw A, Preston RC. 1995. The NPL ultrasound beam calibrator: cost effective measurements to IEC61157. In *Proceedings of the World Congress on Ultrasonics*, Herbertz J (editor). pp. 923–926.

- Sutton Y, Shaw A, Zeqiri B. 2003. Measurement of ultrasonic power using an acoustically absorbing well. *Ultrasound Med Biol*, 29, 1507–1513.
- Szabo TL. 2004. Ultrasonic exposimetry and acoustic measurements. In *Diagnostic Ultrasound Imaging: Inside Out*, Szabo TL (editor). Burlington, MA: Elsevier Academic Press.
- ter Haar G. 2008. Results of a survey of exposure conditions used in ultrasound scans in the U.K., February 2007. *Ultrasound*, 16, 110–113.
- ter Haar G, Shaw A, Pye S, Ward B, Bottomley F, Nolan R, *et al.* 2011. Guidance on reporting ultrasound exposure conditions for bio-effects studies. *Ultrasound Med Biol*, 37, 177–183.
- Tranquart F, Grenier N, Eder V, Pourcelot L. 1999. Clinical use of ultrasound tissue harmonic imaging. *Ultrasound Med Biol*, 25, 889–894.
- Whittingham TA. 2000. The acoustic output of diagnostic machines. In *The Safe Use of Ultrasound in Medical Diagnosis*, ter Haar G, Duck FA (editors). 2nd Edition. London, UK: BMUS/BIR.
- Wilkens V. 2010a. A thermal technique for local ultrasound intensity measurement: part 1. Sensor concept and prototype calibration. *Meas Sci Technol*, 21, 115805 (8 pp.).
- Wilkens V. 2010b. A thermal technique for local ultrasound intensity measurement: part 2. Application to exposimetry on a medical diagnostic device. *Meas Sci Technol*, 21, 115806 (10 pp.).
- Zeqiri B, Bickley CJ. 2000. A new anechoic material for medical ultrasonic applications. *Ultrasound Med Biol*, 26, 481–485.
- Zeqiri B, Zauhar G, Hodnett M, Barrie J. 2011. Progress in developing a thermal method for measuring the output power of medical transducers that exploits the pyroelectric effect. *Ultrasonics*, 51, 420–424.

# Chapter 4

## Ultrasound-induced heating and its biological consequences

Charles C. Church<sup>1</sup> and Stanley B. Barnett<sup>2</sup>

<sup>1</sup>National Center for Physical Acoustics, University of Mississippi, Oxford, MS, USA

<sup>2</sup>Mona Vale, NSW, Australia

### Summary

- Developing tissues of the embryo and foetus are particularly susceptible to damage by heating, and the effects can have serious consequences.
- The induction of teratogenic effects depends on a combination of the elevation above normal physiological temperature and the duration for which the increased temperature is maintained.
- A threshold dose of 0.5 min exposure to an increase of 4°C above normal body temperature may be hazardous to embryonic and foetal development.
- In late pregnancy, the heated volume is small compared with the size of the foetus, and consequent biological effects may be difficult to detect unless a major neural pathway is perturbed.
- Simple grey scale B-mode imaging is not capable of producing harmful temperature increases in tissue.
- A diagnostic exposure that produces a maximum temperature rise of 1.5°C above normal physiological levels (37°C) does not appear to present a risk from thermal effects in humans for an imaging session of less than 30 min.
- There are uncertainties in predicting *in situ* temperature increases in the embryo and foetus, and it is therefore prudent to use the minimum output consistent with obtaining the required diagnostic information.

### 4.1 Introduction

The normal human core temperature is generally accepted to be 37°C with a diurnal variation of  $\pm 0.5$ –1°C (Mellette *et al.*, 1951; Hardy, 1961), although  $36.8 \pm 0.4$ °C may be the true mean for large populations (Mackowiak *et al.*, 1992). Temperature in the human foetus is higher than maternal core body temperature by 0.3–0.5°C during the entire gestation (Asakura, 2004), but in the third trimester (near-term) the temperature of the

foetus is higher by 0.5 °C than that of its mother (Macaulay *et al.*, 1992). Biological tissues absorb ultrasound, resulting in heating above normal physiological temperatures, and an increase in temperature of sufficient magnitude and duration can damage or kill biological tissues. These facts are well known to most professional users of diagnostic ultrasound equipment. However, the details of the relationship between exposure to heat and the resulting effects are less well understood, even by those who use ultrasound every day.

Temperature fundamentally affects biochemical, physiological and reproductive processes of all living organisms. Mild increases in temperature, of less than 1 °C, may simply slightly accelerate cellular processes with no overall detrimental effect. Excessive temperature increase can be lethal (Raaphorst *et al.*, 1979; Dewey *et al.*, 1977; Dewey, 1994). Moderate temperature increases may arrest or retard cell division (Mazza *et al.*, 2004). The effects of a moderate rise above normal physiological temperature can have important consequences for developing embryos or foetuses, particularly if the central nervous system is involved. The actively dividing cells of the embryonic and foetal central nervous system are known to be highly susceptible to changes in temperature (Edwards, 1969b; Webster and Edwards, 1984; Shiota, 1982, 1988). Interference with neural tissue is likely to have significant consequences on growth and development.

Elevated temperatures may have deleterious effects on foetal and embryonic cells and tissues

Medical ultrasonography continues to enjoy increasingly widespread use as an effective diagnostic clinical tool. Improvements in resolution and image quality have been particularly valuable in obstetrics. Pulsed Doppler (PD) spectral flow analysis and Doppler colour flow imaging (CFI) techniques offer the potential to increase diagnostic effectiveness and may prove to be valuable diagnostic tools in early pregnancy. There is a growing trend to apply new applications of ultrasound, including Doppler, at earlier stages in pregnancy, although benefits have not necessarily been demonstrated. Particularly noteworthy is the recent movement towards use of spectral Doppler to measure foetal heart rate in the first trimester. Owing to the small size of the target, practitioners unfamiliar with the technique may require unnecessarily long exposures to obtain the same data that may be had using older procedures requiring lower outputs. Furthermore, the introduction of novel imaging modalities in ever more sophisticated ultrasound equipment can be accompanied by substantial increases in acoustic output (Martin, 2010). This has important consequences for the risk of producing thermal bio-effects as the amount of heat deposited in biological tissue during ultrasonic examinations is directly related to intensity.

Diagnostic ultrasound is assumed to be safe. This opinion is supported by a general lack of independently confirmed adverse effects from ultrasound exposure in mothers or children. However, these conclusions have limited relevance to the way ultrasound is currently used in medicine. For example, there are no epidemiological data relevant to the increased acoustic outputs available with modern equipment (see Chapters 3 and 9). The acoustic outputs of ultrasound scanners in clinical use have increased substantially in recent years and are now capable of producing significant heating effects in some applications (WFUMB, 1992, 1998). A report by Henderson *et al.* (1995) described an increase by a factor of five in the spatial-peak temporal-average intensity ( $I_{\text{spta}}$ ) from B-mode diagnostic equipment in clinical use in the UK during the period 1991–1995. The total acoustic power output in PD mode doubled during that period. More recent

Increasing acoustic output levels mean that there is a greater possibility of biologically significant heating

publications (Duck and Henderson, 1998; Henderson *et al.*, 1997; Whittingham, 2000; Martin, 2010) show that the trend for increasing acoustic output has continued to current levels that are capable of producing biologically significant heating.

While maximum outputs have increased, the only effective regulatory body, the Food and Drug Administration (FDA), has relaxed the upper limit on intensity that can be applied in obstetric ultrasonography in the USA. Under this new scheme (AIUM/NEMA, 1992) equipment that incorporates an output display may deliver acoustic intensity to the embryo or foetus that is almost eight times higher than equipment regulated under the Previous application-specific scheme. The rationale for this change is that the responsibility is placed on the ultrasound diagnostician to make risk/benefit assessments, based on information provided by the equipment output display, and to decide on the appropriate examination exposure conditions for each operating condition. The effectiveness of such risk assessment depends on the accuracy of the information given in the output display and on the ability of the diagnostician to understand it.

The American Institute of Ultrasound in Medicine and the National Electrical Manufacturers Association (AIUM/NEMA, 1992) developed an Output Display Standard that includes the thermal index (TI) as an approximation of temperature increase on which to assess the potential for thermally mediated biological effects. The TI is calculated from the source acoustic power divided by the power needed to raise tissue temperature by 1°C. Whilst there is obvious merit in a system that encourages the end-user to become aware of safety issues, the TI has some limitations: (a) it does not consider the effect of dwell time, *i.e.* duration of temperature increase at a single point in tissue; and (b) it is virtually impossible to predict maximum temperature increase in heterogeneous tissue with accuracy. It has been shown that the TI can underestimate the actual temperature increase in tissue and that manufacturer estimates of intensity, on which the TI is based, can also be significantly in error (Jago *et al.*, 1995). In an assessment of TI for Doppler equipment Shaw *et al.* (1998) concluded “The values of TIS and TIB displayed on the scanner should not be taken as the absolute maximum possible temperature rise. The worst-case temperature rise may be three times higher than the displayed value.”

### 4.2 Mechanism of ultrasound heating

The amount of heating that may be expected is related to the absorption coefficient

The absorption coefficient increases as frequency increases

During clinical ultrasonographic examinations, an ultrasound beam is transmitted into biological tissue. Some of the incident energy is reflected back from interfaces between biological tissues to produce echographic images while some is absorbed and converted to heat (see Chapter 1). The amount of heat generated depends on the type of examination, the acoustic output and the tissue properties. In particular, heating is mostly dependent upon the ability of the tissue to absorb, rather than reflect or disperse, ultrasonic energy. For each tissue, this ability is quantified by its acoustic absorption coefficient. Generally, more dense materials such as bone and teeth have higher absorption coefficients than less dense tissues such as liver or muscle and are, therefore, heated to a greater extent than soft tissue. The absorption coefficient of bone may be as much as 50 times greater than most soft tissue. For example, the average value for brain tissue is  $0.2 \text{ dB cm}^{-1} \text{ MHz}^{-1}$  while that for mineralized bone is  $10 \text{ dB cm}^{-1} \text{ MHz}^{-1}$  (Duck, 1990). As is obvious from the form of the absorption

coefficient, the quantity of thermal energy deposited in tissue by an acoustic wave increases with the frequency of the wave. Thus the higher frequencies used for imaging superficial structures will produce a greater temperature rise in a shorter time than will the lower frequencies needed to penetrate to, and image, regions deeper into the body.

Another important factor for thermal bio-effects is the rate of ultrasound-induced heating. The rate of heat deposition in bone is an order of magnitude faster than in soft tissue. Therefore, from a safety perspective, the tissue that has the greatest potential for bio-effects from ultrasound-induced heating is bone, or developing bone. The extent of risk depends on the acoustic exposure conditions and the sensitivity of the target. Tissues lying close to, or in contact with, bone are also at risk of heating by conduction from the bone. Note that it is particularly important to minimize eye exposures in the foetus and adult due to the relatively low perfusion in the eye, particularly in the lens, which thus has reduced capability for heat dissipation. As actively dividing cells are most susceptible to damage by heat, the foetal cerebral cortex, situated close to the skull bone, is at risk of damage by ultrasound-induced temperature increase.

The extent of thermal risk depends on the heat sensitivity of the target

The volume of heated tissue is determined by the ultrasound beam dimensions. For transcranial insonations the transducer can act as a source of heat and may be an important factor contributing to brain heating (see [Chapter 1](#)). The amount of tissue heating that is achieved is limited by the dissipating effects of conduction and convection. Blood flow plays an important role, such that highly vascular organs such as the liver or kidney are less affected by heating than bone, which has relatively poorly developed vasculature. Narrow focused beams that are used in PD and M-mode applications have a large temperature gradient between the centre of the beam and the surrounding tissue, so that heat is rapidly dissipated by conduction. This is especially true at the focus of static beams. In this case vascular perfusion has little additional cooling effect, *i.e.* there is minimal reduction of the amount of ultrasound-induced heating (NCRP, 1992).

## 4.3 Temperature increase from diagnostic ultrasound

The risk of thermal bio-effects in obstetric ultrasound is assessed from the level of heating in susceptible tissues, such as in the central nervous system. As the greatest temperature increase occurs when bone is situated within the ultrasound beam the temperature elevation induced in obstetric exposures depends on the foetal gestational age; bone becomes denser and thicker with advancing foetal development. Using the mouse skull as a model for human foetal insonation, [Carstensen \*et al.\* \(1990\)](#) recorded temperature elevations greater than 5 °C after 90 s in anaesthetized animals exposed to ultrasound at an intensity ( $I_{\text{spta}}$ ) of 1.5 W cm<sup>-2</sup>. The -6 dB focal beam width was 2.75 mm. The greatest temperature increase was observed in older mice where the rate of rise was such that a 4 °C elevation above the baseline temperature was achieved within 15 s of exposure. The maximum ultrasound-induced temperature increase measured after death was approximately 10% higher indicating that blood perfusion in the living animal provided a modest cooling effect to counteract the heating. [Horder \*et al.\* \(1998a\)](#) showed negligible difference between the live and *post mortem* maximum measured temperature rise at the skull/brain interface in guinea-pig foetuses insonated *in utero* at 57–61 days of

The sites of greatest potential heating are bone surfaces. In the foetus, the amount of heating to be expected rises with increasing calcification

Heat loss from perfusion is less important for narrow beams

gestational age (dga). A mean maximum temperature increase of 4.9 °C was measured at the inner aspect of the skull parietal bone after 120 s exposure to  $I_{\text{spta}}$  intensity 2.5 W cm<sup>-2</sup>. The mean maximum temperature increase was 2 °C at 5 mm depth in the brain.

The transducer is an important secondary source of heat

In older foetuses insonated *in utero* near to term (62–67 dga) the mean maximum temperature increase was reduced by approximately 12% to 4.3 °C as a result of cooling from the more substantially developed cerebral vasculature (Horder *et al.*, 1998b). These studies independently confirmed that significant temperature increase can be produced in bone and nearby tissue, and that blood flow provided minimal cooling effects in narrow focussed ultrasound beams such as those used for diagnostic scanning, including obstetric applications. The later studies measured the temperature increase on the inside of the foetal skull adjacent to the cerebral cortex at a biologically significant site. The acoustic exposure conditions were higher than typical values but were, nevertheless, within the published range of outputs of ultrasonographic equipment (Duck and Henderson, 1998; Martin, 2010).

The transducer provides a substantial source of heating, by conduction, in soft tissue examinations (WFUMB, 1992). This is particularly important for pulsed transducers, which are inefficient in converting electrical to acoustic energy. Heating is localized close to the transducer. This should be taken into consideration for transcranial examinations where the transducer directly heats bone. There are also implications for safety for intracavitary applications, particularly where there is a trend towards increased power outputs in gynaecological examinations using the endovaginal route. There is a potential risk of inadvertently exposing an unknown pregnancy to heat.

### 4.4 Effects of ultrasound-induced heating

Whole-body hyperthermia gives slow rates of heating

Estimates of the risk of thermally mediated adverse bio-effects of ultrasound are based on data from whole-body hyperthermia studies. However, there may be differences in the result of ultrasound-induced heating. When ultrasound energy impinges on biological tissue it results in a temperature rise that is rapid compared to the tens of minutes required to elevate foetal temperature under whole-body heating conditions. Studies of external whole-body heating of rats have reported time constants on the order of 13 min per 1 °C elevation in core temperature (Kimmel *et al.*, 1993). Conventional sources of heating warm the surface of the body, allowing the thermoregulatory system to control core temperature via heat receptors in the skin. Such relatively slow heating can also trigger the synthesis of specific heat-shock proteins that may afford some degree of thermotolerance to dividing cells (Walsh *et al.*, 1987). However, as this process takes up to 15 min there is insufficient time for it to occur as a result of ultrasound-induced heating.

Significant heating by ultrasound requires a stationary beam

In imaging procedures using scanned beams any single point tissue target is interrogated for only fractions of a second each time the beam sweeps past so that there is little opportunity to heat a specific tissue target. To achieve significant amounts of heating requires that the ultrasound beam be fixed in relation to a tissue target so that all the energy in the beam is directed onto that target. This occurs in PD spectral measurement techniques and in some CFI applications, such as, for example, studies of foetal breathing.

The rapid onset of ultrasound-induced heating and its related bio-effects was demonstrated in a study showing abnormalities in proliferating bone marrow cells in adult guinea pigs. An original study reported heating to 42.5–43.5 °C (3–4 °C above normal guinea-pig temperature) in a hot-air incubator for 60 min produced bizarre multisegmented nuclear abnormalities in neutrophils extracted from the femurs (Edwards and Penny, 1985). The bone marrow is the main site for blood formation in the third trimester. When the femur was exposed to ultrasound to elevate the temperature in the bone marrow, the same abnormal nuclear division in neutrophils was produced when ultrasound exposure elevated the temperature by 3.5 °C above normal for 4 min (Barnett *et al.*, 1991). This damage threshold is remarkably similar to that for brain anomalies reported in studies using water immersion heating in different animal species, *i.e.* exposure to a temperature increase of 4 °C for 5 min.

Abnormal division of neutrophils has been observed following heating by ultrasound

The normal homeostatic processes regulate body temperature by increasing the heart rate and blood flow to heated regions of the body. In postnatal life this is carried out through the hypothalamus, which responds to change in the temperature of blood flowing through it. In a study designed to test whether the foetus is able to detect and respond to localized mild temperature increase, Horder *et al.* (1998c) insonated the hypothalamus region of the brain of guinea-pig foetuses *in utero* and measured temperature and foetal heart rate. Insonations for 120 s that produced a temperature increase of 1.5 °C at the sphenoid bone adjacent to the hypothalamus did not elicit a change in the foetal heart rate. Either the foetus is unable to react to localized temperature rise or the extent of temperature increase was not biologically significant. If the latter inference is correct, it is further evidence that a temperature increase of 1.5 °C above normal body temperature does not present a risk to the embryo or foetus. This is consistent with a recommendation of the WFUMB that “A diagnostic exposure that produces a maximum *in situ* temperature rise of no more than 1.5 °C above normal physiological levels (37 °C) may be used clinically without reservation on thermal grounds” (WFUMB, 1998).

There is evidence from sensitive studies using embryo culture systems that the effects of pulsed ultrasound may be enhanced by a moderate temperature increase (Angles *et al.*, 1990; Barnett *et al.*, 1990). Exposure to ultrasound at a spatial peak, temporal-average intensity ( $I_{\text{spta}}$ ) of 1.2 W cm<sup>-2</sup> for 15 min at normal temperature produced no adverse developmental effects. However, when ultrasound was applied together with a modest temperature increase of 1.5 °C (absolute temperature 40 °C) there was a significant retardation of growth and reduction of head:body size. As there are few data on the biological effects of interaction of ultrasound with tissues that have a pre-existing temperature elevation, it is prudent to exercise care when using ultrasound in febrile obstetric patients. The published international consensus is that “Care should be taken to avoid unnecessary additional embryonic and foetal risk from ultrasound examination of febrile patients” (WFUMB, 1998).

Ultrasound scanning of febrile obstetric patients requires particular care

## 4.5 Biological effects of hyperthermia

From the scientific data on biological effects of hyperthermia, it is generally accepted that tissues containing a large component of actively dividing cells are particularly sensitive

to the effects of heat (Dewey *et al.*, 1977). Abnormalities in cellular physiology and biochemical processes can occur following an increase in temperature above normal basal levels. The interference with normal rates of enzyme synthesis and reactions can affect the way cells grow and divide and may even lead to abnormalities in DNA synthesis and repair processes.

### 4.5.1 Prenatal animals

A large body of scientific data clearly shows that there are critical periods during gestation when the embryo and foetus are susceptible to thermal insult (Bell, 1987; Edwards, 1986, 1993; Edwards *et al.*, 1995; Kimmel *et al.*, 1993). During formation of the embryonic neural plate and closure of the neural tube, perturbations can result in severe neural tube defects, retarded brain development, exencephaly and microphthalmia in guinea pigs (Edwards, 1993). Kimmel *et al.* (1993) observed craniofacial anomalies and other foetal skeletal anomalies in rats following maternal exposure to increased temperature. Exposure to heat at pre-organogenesis stages in development can result in cardiovascular abnormalities (Edwards, 1993). If the embryo is heated at later stages (*e.g.* day 13 of gestation in rats) the skeletal and visceral systems can be affected. A moderate temperature increase (2 °C above normal), together with exercise, has been shown to induce a range of teratogenic effects in rats (Sasaki *et al.*, 1995). Non-specific effects such as foetal weight reduction are also associated with intrauterine heating or maternal stress. A brief list of effects observed in animals, the experimental animal studied and the temperature and duration of the exposure, is given in Table 4.1 (Church and Miller, 2007).

One conclusion that may be drawn from Table 4.1 is that different tissues may have different sensitivity to the heating produced by diagnostic ultrasound (*vide* Barnett *et al.*, 1997). Actively dividing foetal neural tissue is highly sensitive to damage by heat (Edwards *et al.*, 1995) while adult tissue is generally more resistant and tolerant. If a transient temperature increase arrests mitotic cell division in the brain during embryonic development the resulting neural deficit may not be restored, although the foetus may continue to develop and appear morphologically normal. Such brain-growth retardation is a common result of hyperthermia in animal experiments (Graham *et al.*, 1998). Developing embryos may mount a protective response to sublethal hyperthermia that temporarily arrests the normal process of cell division. This phenomenon has been observed in the brains of rodents where normal cell division lapsed for up to 8 h following heat treatment (Edwards *et al.*, 1974; Upfold *et al.*, 1989). Meanwhile, heat-shock proteins (hsp) may be synthesized at the expense of normal neural proteins. On recovery, normal cell division resumed with the foetus appearing morphologically normal, albeit smaller and with a substantial neural deficit. In embryonic development a lapse of a few hours can lead to substantial delay or disturbance in neurological development. Non-deforming retardation of brain growth and reduced learning performance are common abnormalities in the offspring of moderately heat exposed pregnant guinea pigs. These defects can be caused both during early and later foetal growth (Edwards, 1993). In general, embryos are more susceptible to damage than foetuses due to the high rate of cellular activity during organogenesis. However, continually developing organ systems such as the brain remain susceptible to heat throughout pregnancy.

Some stages of development are more sensitive to heat damage than others

Actively dividing cells are particularly sensitive to thermal damage

The effects of increased temperature on biological systems have been extensively reviewed (Barnett *et al.*, 1994; Edwards, 1993; Miller and Ziskin, 1989; Edwards *et al.*, 2003; Church and Miller, 2007; Abramowicz *et al.*, 2008; O'Brien *et al.*, 2008). In their study, Edwards *et al.* (2003) made some crucial observations. (1) The relative timing of a particular developmental stage of interest does not scale linearly with the average length of gestation, making extrapolation of animal results to human exposures difficult. For example, the thermally sensitive stage of neural tube closure occurs at day 8.5 in the mouse, day 9.5 in the rat, days 13–14 in guinea pigs, and days 20–28 in humans. Similarly, neurogenesis, neural cell migration and the development of bodily structures occurs during days 12–15 in mice, days 13–18 in rats, days 20–35 in guinea pigs, and days 56–126 in humans. (2) The effect of a given heating regimen will depend on the stage of gestation at which it occurs, regardless of the species involved. For example, hyperthermia during the period of neural tube closure may result in the death of neuronal cells leading to anencephaly, spina bifida or encephalocele, while the same exposure a few days or weeks later (depending on the species) during the period of neuronal cell proliferation for brain development may also

The developing foetus is particularly sensitive to hyperthermia during the period of neural tube closure

Table 4.1. Selected thermally induced teratogenic effects (from Church and Miller, 2007).

Thermal effect	Animal/species	Temperature (°C)	Duration (min.)	Source
Abortion	Monkey	40.6	72	Hendrickx <i>et al.</i> , 1979
Absence of optical vesicles	Rat	43.0	7.5	Walsh <i>et al.</i> , 1987
Anencephaly	Rat	41.0–43.5	40	Edwards, 1968
Behavioural anomalies	Marmoset	41.5	60	Poswillo <i>et al.</i> , 1974
Cardiac and vascular anomalies	Chicken	41.0	3180	Nielson, 1969
Developmental anomalies	Rat	42.0	40	Skreb and Frank, 1963
Exencephaly	Mouse	42.3	5	Webster and Edwards, 1984
Eye defects	Chicken	41.0	1440	Nielson, 1969
Limb, toe & tail defects	Rat	41.0–43.5	40	Edwards, 1968
Micrencephaly	Guinea pig	43.0	60	Edwards, 1969 <sup>a,b</sup>
Microphthalmia	Rat	41.0	60	Germain <i>et al.</i> , 1985
Posterior paralysis	Mouse	43.0	60	Pennycuik, 1965
Resorption	Guinea pig	42.9	60	Edwards, 1967
Scoliosis	Monkey	40.6	72	Hendrickx <i>et al.</i> , 1979
Skeletal defects	Marmoset	41.5	60	Poswillo <i>et al.</i> , 1974
Tooth defects	Rat	38.9	720	Kreshover and Clough, 1953

Hyperthermia  
is a suspected  
teratogen in  
humans

kill cells, but the outcome may be micrencephaly (small brain) rather than anencephaly (no or very rudimentary brain), or simply learning disorders not accompanied by obvious structural abnormalities. The interested reader should consult [Edwards \*et al.\* \(2003\)](#) and [Abramowicz \*et al.\* \(2008\)](#) for more complete discussion of teratogenesis in experimental animals and its relation to potential effects in humans.

### 4.5.2 Prenatal humans

Although relatively few studies on the effects of heating during gestation in humans have been published, many of the abnormalities reported in animal studies have also been observed in humans following *in utero* febrile episodes. For example, [Smith \*et al.\* \(1978\)](#) found that maternal febrile illness producing a body temperature above 38.9 °C in early stages of pregnancy was associated with development of foetal anomalies. In a confirmatory study, [Chambers \*et al.\* \(1998\)](#) reported that the offspring of women who had a “high” fever ( $T \geq 38.9$  °C for at least 24 h) during pregnancy had a increased rate of major malformations, 15.8% compared to 4.5% among controls, as well as an increased incidence of minor malformation. Although none of the differences observed were statistically significant, the authors conclude that high maternal fever early in pregnancy is a human teratogen. Similarly, [Little \*et al.\* \(1991\)](#) demonstrated a statistically significant association between a maternal fever of 38.3 °C for 24h or more and subsequent abdominal wall defects in their offspring. Retrospective studies indicate that mothers of babies with various malformations of the central nervous system experienced increased prevalence of febrile illness during early pregnancy ([Layde \*et al.\*, 1980](#); [Pleet \*et al.\*, 1981](#); [Shiota, 1982](#); [Spraggett and Fraser, 1982](#)). For example, [Pleet \*et al.\* \(1981\)](#) observed a relationship between maternal hyperthermia during weeks 4–14 of gestation and the induction of defects of the central nervous system (mental deficiency), altered muscle tone (hypotonia) and facial anomalies such as microphthalmia or cleft lip. [Fraser and Skelton \(1978\)](#) also found an association between microphthalmia and fever during the first trimester. Epidemiological studies by [Erickson \(1991\)](#) and [Tikkanen and Heinonen \(1991\)](#) have shown a relationship between maternal hyperthermia and congenital heart defects. [Graham \*et al.\* \(1998\)](#) provide a summary of the relationship between maternal hyperthermia and congenital birth defects. Based on the similarity of responses across species, hyperthermia is strongly suspected of being a teratogen in humans ([Edwards, 1986, 2006](#); [Edwards \*et al.\*, 1995](#); [Shepard, 1982, 1989](#); [Suarez \*et al.\*, 2004](#); [Moretti \*et al.\*, 2005](#)).

One report that has had a profound impact on our perception of the potential consequences of foetal hyperthermia is the comprehensive study on the effects of hyperthermia in animals and the potential for exposure to diagnostic ultrasound to induce adverse biological effects in the foetus that was published by [Miller and Ziskin \(1989\)](#). Two of their conclusions warrant special attention here: (1) hyperthermic treatment during gestation resulted in teratogenic effects whose magnitude varied with exposure temperature and duration such that the higher the temperature of the exposure medium, the shorter the time needed to cause an effect; and (2) on a plot of exposure duration versus exposure temperature, a convenient boundary could be drawn below which there were no observed effects. The plot referred to in item 2 is

reproduced here as Figure 4.1. Each point represents either the lowest temperature reported for any duration or the shortest duration for any temperature reported for a given effect. A solid line connecting points indicates multiple data points relating to a single study or effect. The dashed line defines a lower boundary ( $t_{\text{ref}} = t_{43} = 1$ , see below) for observed biologic effects. This analysis was widely read and accepted by the scientific (AIUM/NEMA, 1992; NCRP, 1992, 2002; WFUMB, 1992, 1998; BMUS, 2000; Herman and Harris, 2002) and regulatory (FDA, 1997; IEC, 2007) communities. It provided the rationale for concluding that for obstetric diagnostic ultrasound examinations, a temperature elevation of 1°C or 1.5°C could be applied for any duration without concern for a thermal bio-effect.

However, two significant features of the data underlying Figure 4.1 are easily missed. First, every experiment involved whole-body heating of the maternal animal, generally in either a heated water bath or in a hot-air incubator. This is important because no foetus is heated to the experimental exposure temperature instantaneously. There is always some time lag as the mother's body attempts to compensate for the sudden increase in environmental temperature, so the actual time that the foetus experiences the exposure temperature used in Figure 4.1 will be less than the duration of exposure. Second, different experimental animals have different normal physiological temperatures. This is important because we do not know whether a 2 °C rise in an animal having a normal temperature of 39 °C, *e.g.* the

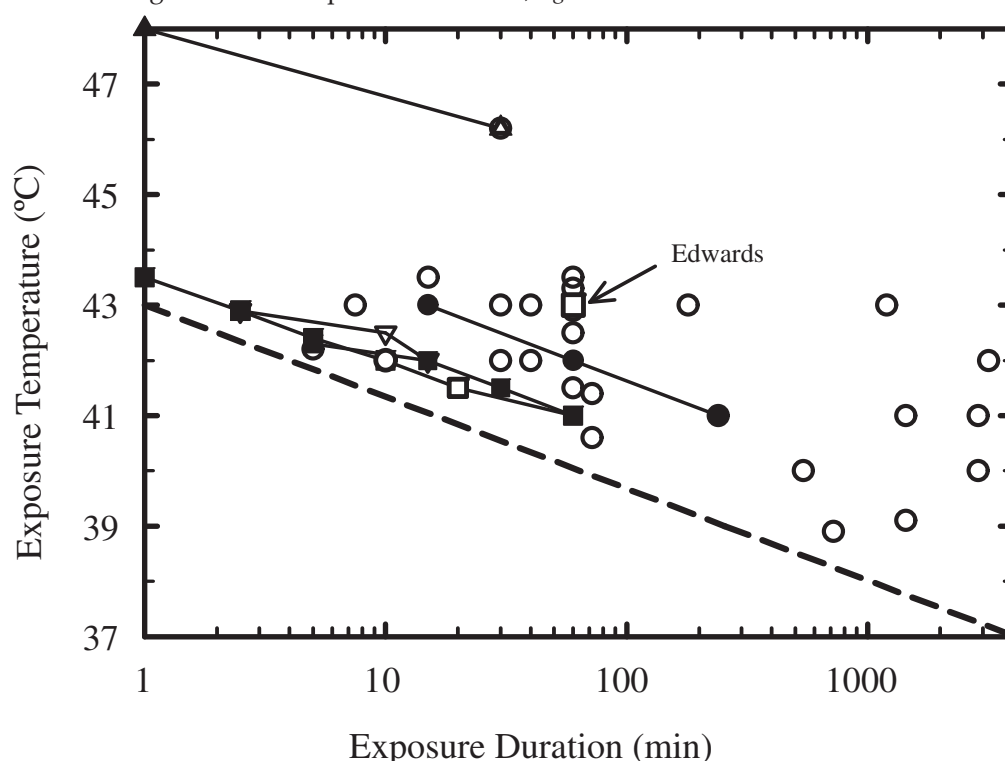


Figure 4.1. Thermally induced biological effects, listed in Table 4 of Miller and Ziskin (1989), that have been reported in the literature and for which the temperature elevation and exposure duration are provided. The dashed line defines a lower boundary ( $t_{43} = 1$ ) for observed biologic effects. The open square and arrowed "Edwards" indicate the exposure temperature and duration (60 min, 43 °C) for the Edwards (1969b) hyperthermia treatment of pregnant guinea pigs; figure taken from Church and Miller (2007).

guinea pig, will have the same effect in an animal with a normal temperature of 37°C such as the human being. In other words, which is the critical factor, the absolute temperature or the change in temperature? Opinions vary, but consider an extreme example: the pigeon lives its entire life at 43°C (Edwards, 1986), a temperature that would be fatal to a human in a matter of days. Therefore, until the question is resolved, prudence dictates that the change in temperature be given greater weight.

### 4.5.3 Postnatal individuals

Most of the preceding discussion has focused on the effects of heating on the embryo or foetus. This is entirely appropriate because prenatal subjects are more sensitive to a wide range of external stimuli than the same individuals would be if the same stimulus occurred later in life. In addition, if a particular ultrasound exposure produces harm in a child or adult, that person can respond in ways that are obvious to the sonographer or physician, but the foetus lacks similar mechanisms for providing direct feedback to the sonographer. While relatively few reports exist relating diagnostic ultrasound exposure conditions to non-foetal thermal effects, a recent report by O'Brien *et al.* (2008) provides a valuable review of the effects of hyperthermia in postnatal subjects.

O'Brien *et al.* (2008) compiled data from a number of sources for temperature thresholds for thermal damage to non-foetal tissue produced by single exposure durations as short as 0.1s, see their Table 2. Using these data, they were able to construct a boundary below which no thermal damage is observed in non-foetal soft tissue. The data and boundary are shown in Figure 4.2; see O'Brien *et al.* (2008) for details. The report suggests that for non-foetal soft tissue and for scanning conditions consistent with conventional B-mode ultrasound examinations for which the exposure durations at the same *in situ* locations would be less than a few seconds, the allowable maximum temperature increase could be relaxed relative to values represented by the conservative boundary line for longer exposures (O'Brien *et al.*, 2008).

## 4.6 Quantification of heating—thermal dose

Thermal dose is used to quantify exposure to heat and compare thermal effects

There is a well-known relationship between an elevation in temperature above the normal physiological level and the time needed to induce a deleterious effect in a biological system (NCRP, 1992, 2002; Edwards *et al.*, 2003; Miller and Ziskin, 1989). Simply put, the higher the temperature rise, the shorter the time needed to produce the effect. Dewey *et al.* (1977) and Sapareto and Dewey (1984) showed that for two exposures at two different temperatures, the ratio of the minimum time  $t_1$  required for the lower temperature  $T_1$  to produce an effect, to the time  $t_2$  required for the higher temperature  $T_2$  to produce the same effect increased by a constant multiple for each degree of temperature difference. For example, if the temperature difference  $T_2 - T_1 = 1^\circ\text{C}$ , then  $t_1/t_2 = R$ , while if  $T_2 - T_1 = 2^\circ\text{C}$ , then  $t_1/t_2 = R^2$ , etc., where  $R$  is the thermal normalization constant. In general,  $t_1/t_2 = R^{T_2 - T_1}$ . The time used to quantify thermal exposures is termed the “thermal dose” ( $t_{\text{REF}}$ ):

$$t_{\text{REF}} = tR^{T_{\text{REF}} - T} \quad (4.1)$$

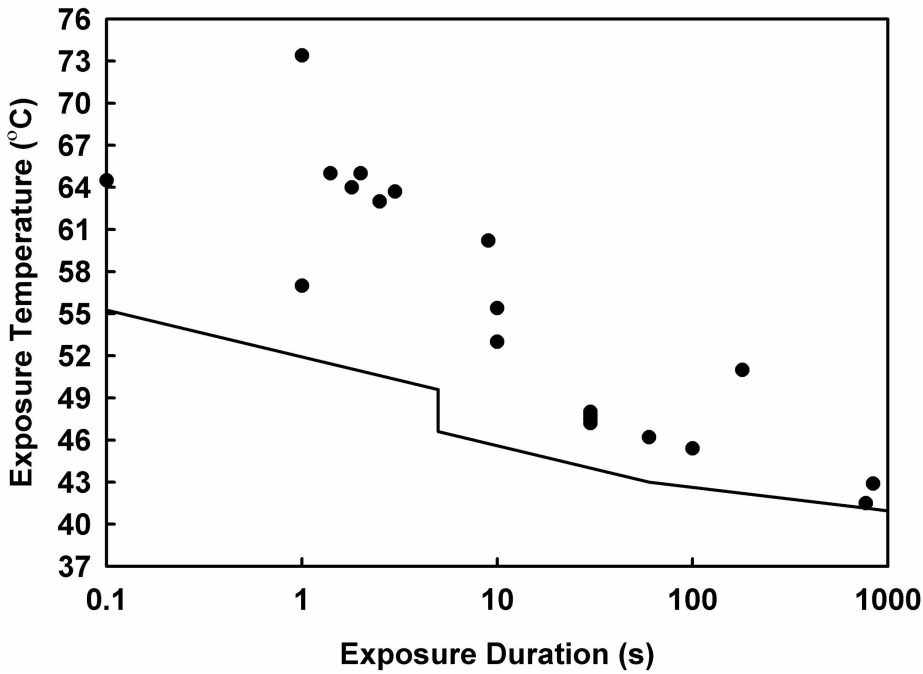


Figure 4.2. Temperature thresholds for damage to non-foetal tissues from single exposures to heat. The solid line represents a conservative boundary for exposure durations in non-foetal soft tissue. See O'Brien *et al.* (2008) for details.

Empirical values of  $R$  vary among species, tissues and biological endpoints. They also are temperature-dependent, with  $R \approx 2$  for  $T > 43^\circ\text{C}$ , increasing by a factor of 2–3 for  $T < 43^\circ\text{C}$ . For simplicity, the values for  $R$  are usually fixed at  $R=2$  for  $T > 43^\circ\text{C}$  and  $R=4$  for  $T < 43^\circ\text{C}$  (Sapareto and Dewey, 1984; Dewey, 1994).

Miller *et al.* (2002) solved the problem of normalizing experimental results obtained in animal species having different core temperatures by subtracting the animal's core temperature  $T_c$  from both  $T_{\text{REF}}$  and  $T$ . In this way, Equation 4.1 may be written:

$$t_{\text{REF}} = tR^{\Delta T_{\text{REF}} - \Delta T} \quad (4.2)$$

where  $\Delta T_{\text{REF}} = (T_{\text{REF}} - T_c)$  and  $\Delta T = (T - T_c)$ . The numerical values of Equations 4.1 and 4.2 are the same, but rather than a fixed reference temperature, the reference is now written in terms of the increase above the animal's core temperature. The effective temperature for a teratological effect simply scales from the animal's normal physiological temperature (Dewey *et al.*, 1977; Raaphorst *et al.*, 1979; Sarge *et al.*, 1995). The transition point for  $R$  is assumed to be at a temperature elevation of 6–7°C. The value of Equation 4.2 is that it normalizes data to a common denominator, the organism's normal temperature and, thus, allows comparison of data among organisms having different core temperatures (Church and Miller, 2007).

Equation 4.2 can be applied to the data depicted in Figure 4.1 and thus normalize them to the increases above each animal's normal physiological temperature. The result of

A temperature rise of 3.5°C for 1 min represents a “safe” thermal dose to the foetus

normalization is shown in Figure 4.3. Each datum was derived from an analysis of a heating–cooling profile of a pregnant laboratory animal (rat, mouse or guinea pig) which yielded fetuses with teratologic anomalies (Miller *et al.*, 2002). The original “safe” boundary line in Figure 4.1, *i.e.*  $t_{43}=1$  min, is now given by  $t_{43-37}=t_6=1$  min, shown by the dashed line. About half of the data points in Figure 4.3 are below this line, showing that temperature exposures previously considered safe because they fell below the boundary in Figure 4.1, *i.e.* below  $t_{43}=1$  min, are actually potentially harmful. A new “safe” boundary might be drawn at  $t_{4.0}=1$  min if it were not for a single point derived from the data of Kimmel *et al.* (1993). While the data collected by Kimmel *et al.* (1993) include seemingly minor anomalies and also those with high natural background rates, prudence suggests that the “safe” line be drawn at  $t_{3.5}=1$  min in Figure 4.3, as shown by the dotted line; this is equivalent to  $t_{4.0}=0.5$  min.

## 4.7 Thresholds for biological effects

Most of the early studies on whole-body heating were not designed *a priori* to identify threshold levels but, instead, set out to demonstrate that severe developmental abnormalities can be produced by heat exposure. In most cases there was no record of

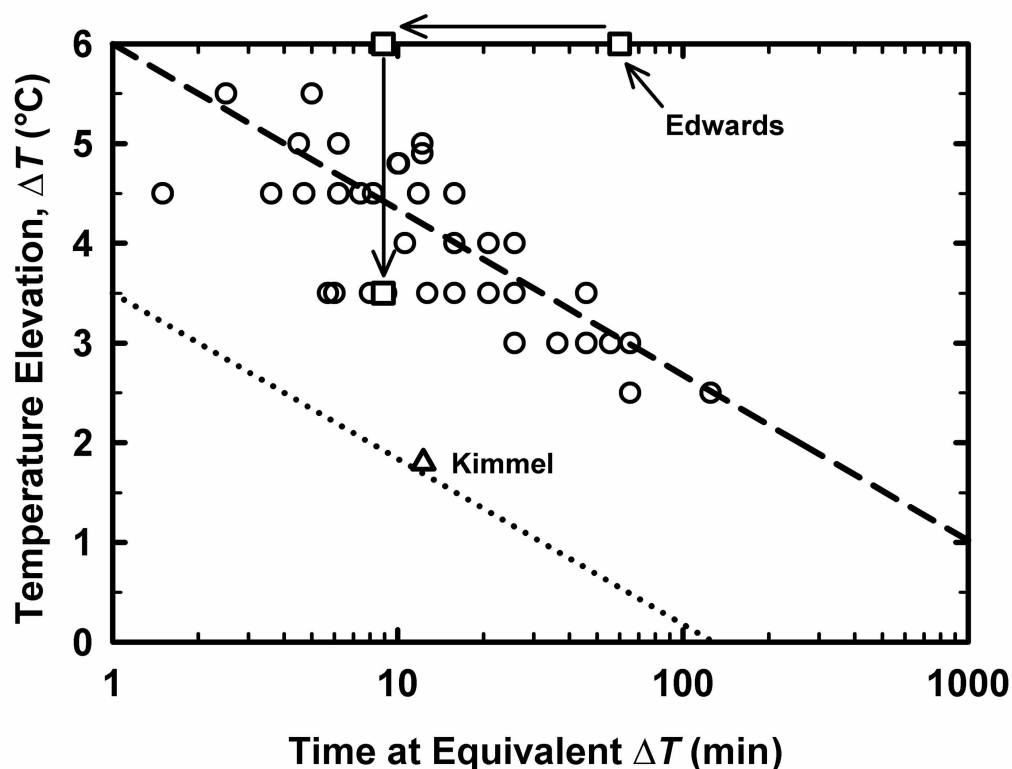


Figure 4.3. Thermal-equivalent core temperature elevations versus time. The dashed line is the equivalent lower boundary ( $t_{43}=1$ ) shown in Figure 4.1, and the dotted line is the lower boundary for the “transformed” data. The open triangle shows the lowest positive-result datum, from Kimmel *et al.* (1993),  $\Delta T=1.8^{\circ}\text{C}$ . The open squares and arrows show the “movement” of the Edwards’ data point from its original location at (60 min, 43 °C) in Figure 4.1 to its “final” location at (8.9 min, 3.5 °C). Adapted from Church and Miller (2007).

either the temperature elevation or the duration for which it was maintained within the foetus. The heat dose was estimated from the maternal core temperature measured *per rectum*.

### 4.7.1 Prenatal individuals

Useful threshold data have been derived from the study by [Germain \*et al.\* \(1985\)](#) which used water immersion as a means of rapid body heating and detected encephalocoeles as the adverse developmental outcome. The normal resting temperature for 50 pregnant rats was measured to be  $38.5 \pm 0.5^\circ\text{C}$  during daylight (*i.e.* when less active, resting). The shortest exposure that produced abnormalities was 1 min at a temperature of  $43.5^\circ\text{C}$  (*i.e.*  $5^\circ\text{C}$  increase above the normal physiological temperature for pregnant rats). The same brain abnormality was observed after 5 min exposure to a temperature elevation of  $4^\circ\text{C}$ . A teratogenic threshold of  $4^\circ\text{C}$  increase in temperature maintained for 5 min was also observed by [Sasaki \*et al.\* \(1995\)](#) in which hyperthermia was achieved in pregnant rats made to swim in a water bath. The majority of brain malformations involved microphthalmia and encephalocoeles. The resting core temperature measured in all rats prior to heat treatment was between  $38^\circ\text{C}$  and  $39^\circ\text{C}$ . Other studies have also reported brain anomalies following prenatal exposure to elevated temperature. For example, exencephaly was produced in mice ([Webster and Edwards, 1984](#)) following intrauterine exposure to  $42.3^\circ\text{C}$  (equivalent to a  $4.3^\circ\text{C}$  increase above normal body temperature), for 5 min. A similar result was reported by [Shiota \(1988\)](#) for exencephaly in mice exposed to a  $4.5^\circ\text{C}$  increase above normal body temperature for 5 min. Exposure to a whole-body temperature increase of  $3.5^\circ\text{C}$  above normal for 10 min produced exencephaly in mice ([Shiota, 1988](#)) and microphthalmia in rats ([Edwards \*et al.\*, 1995](#)).

A temperature rise of  $4.0^\circ\text{C}$  for 0.5 min may represent a threshold for teratological effects

It is instructive to consider the data from [Figure 4.3](#), for which foetal temperature–time profiles are available, in terms of a dose–response relationship. The percentages of foetuses exhibiting major craniofacial anomalies in the reports by [Germain \*et al.\* \(1985\)](#) and [Shiota \(1988\)](#) are plotted as a function of the thermal dose in [Figure 4.4](#). The best-fitting line through the data intersects the  $x$ -axis at approximately 0.5 min, indicating that the data are not inconsistent with the concept of a threshold. Since there is considerable scatter in the data, the exact value of any threshold cannot be determined with much accuracy. The lower 95% confidence interval on the fit intersects the  $x$ -axis at about 4.2 min, suggesting that the threshold is no greater than this value.

Naturally one must be cautious when applying these results to the human population. Tens of millions of newborns are scanned *in utero* each year, and if even a small fraction of ultrasound examinations result in hyperthermia-induced anomalies, this would represent a large number of affected individuals ([Miller \*et al.\*, 2002](#)). A similar situation exists when analysing dose–response data and estimating probability of effects at low doses of ionizing radiation, in spite of the fact that many more studies have been conducted in that area. With this in mind, the most recent report on the Biological Effects of Ionizing Radiation ([BEIR VII; NA/NRC, 2006](#)) adopts a linear no-threshold model for estimating risk from low-level exposures.

Non-foetal soft tissue is at least two orders of magnitude less sensitive to heat than foetal tissue

### 4.7.2 Postnatal individuals

The thermal exposures required to damage a range of non-foetal tissues have been reported in terms of thermal dose (see below) for a variety of animals and humans (Dewey, 1994; Lyng *et al.*, 1991). These doses are given in Table 4.2 for  $t_{43}$ . Since much of the data were obtained from animals having normal physiological temperatures different from that of the human, the doses are also given in terms of a 4 °C temperature rise,  $t_4$ . It is significant that even the smallest value for  $t_4$ , 80 min for damage to the kidney, is more than 2 orders of magnitude greater than the “safe” value determined from Figure 4.4 for the induction of major developmental anomalies in the foetus.

## 4.8 Thermal index

In order to determine the effects of a particular hyperthermic exposure on a particular tissue or organ, it is necessary to know the temperature–time profile of exposure and also to be able to compare a known level of effect produced in the same or similar tissue by a known hyperthermic exposure. This is obviously well beyond what might be expected of any practicing physician or sonographer, no matter how knowledgeable they may be. To provide some level of guidance to users of diagnostic ultrasound, a joint committee

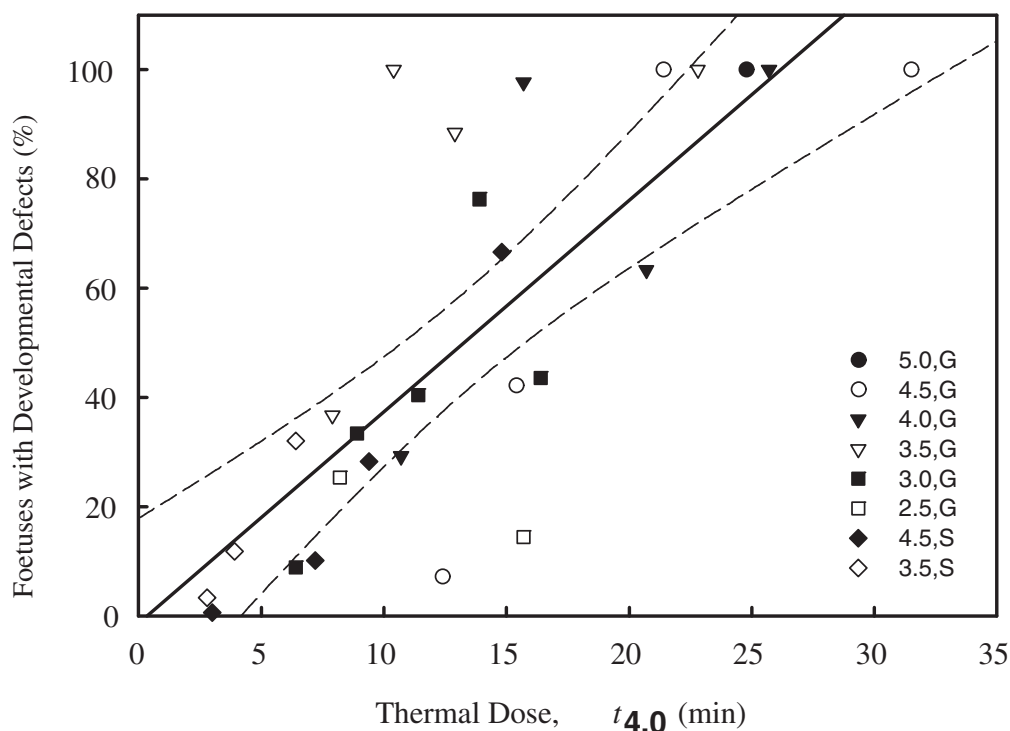


Figure 4.4. Percentage of foetal defects versus  $t_{4.0}$  based on the results of Germain (G) *et al.* (1985) in rats, and Shiota (S) (1988) in mice. The author-specific designations refer to the maximum temperature increase ( $\Delta T$ ) above the measured normal physiological temperature. The solid line is the best fit to the data,  $\% \text{Defects} = 3.893 t_{4.0} - 1.852$ ,  $r^2 = 0.604$ , and the dashed curves give the 95% confidence interval around the fit. Adapted from Miller *et al.* (2002).

Table 4.2. Thermal dose values,  $t_{43}$  and  $t_{47}$ , for selected tissues (adapted from O'Brien *et al.*, 2008).

Tissue	Animal/species	Mean core temperature (°C)	$t_{43}$ (min)	$t_{47}$ (min)
Muscle, fat	Pig	38.5	240	480
Skin	Human, rat, mouse	37, 38, 38	210	3360, 840, 840
Oesophagus	Pig	38.5	120	240
Cartilage	Rat, mouse	38, 38	120	480
Breast	Human	37	100	1600
Bladder	Dog, rabbit	38.5, 39	80	160, 80
Small intestine	Rat, mouse	38, 38	40	160, 160
Colon	Pig, rabbit	38.5, 39	30	60, 30
Liver	Dog, rabbit	38.5, 39	30	60, 30
Brain	Cat, dog	39, 38.5	25	25, 50
Kidney	Mouse	38	20	80

of the AIUM, the NEMA, and the FDA was formed to develop an on-screen display to maintain and enhance patient safety. Their work resulted in the creation of two general indices, the mechanical index (MI) and the TI, to provide information to the user on the output level of their machine and how a change in output would affect the likelihood of inducing a biological effect in the patient. These indices are now part of the regulations governing the manufacture, sale and use of diagnostic equipment in much of the world (FDA, 1997; IEC, 2007, 2010). The MI is discussed in Chapter 5. The TI is discussed in Chapter 2 and below.

The basic definition of the TI is:

$$TI = \frac{W_0}{W_{deg}} \quad (4.3)$$

where  $W_0$  is the source power of the diagnostic ultrasound system, and  $W_{deg}$  is the source power required to increase the temperature of a specific tissue model by 1°C. The model assumes a very low level of attenuation ( $0.3 \text{ dB cm}^{-1} \text{ MHz}^{-1}$ ), thus it will overestimate the temperature rise expected in real tissue. The TI is conservative in this regard. There are three different categories of TI corresponding to different combinations of soft tissue and bone that are commonly encountered while imaging patients. Each category uses one or more models based on system information, including transducer aperture, acoustic beam dimensions and imaging mode. The categories are TIS for soft-tissue imaging, TIB for imaging in a non-scanning mode when bone is at or near the focus, and TIC for imaging when bone is near the surface, *e.g.* adult cranial applications (Abbott, 1999).

Two points should be understood in regard to the MI and TI. First, they are not true safety indices in that no particular value is directly related to any quantifiable level of risk of

The MI and TI enable application of the ALARA principle to ensure patient safety

doing harm to the patient. The MI and TI are output indices because their values are related to specific output parameters and transducer (probe) characteristics. However, it is self-evident that output levels are related to risk in some way, even if the connection between the two remains poorly understood. Second, the MI and TI are relative rather than absolute quantities. In other words, an examination performed at a TI of 2 represents greater risk to the patient than the same examination performed at a TI of 1, although the absolute risk is not necessarily known. Although this fact may be unsettling to some, it is also not particularly important because when properly used, the indices still fulfill their goal of helping to ensure patient safety. This is done by application of the ALARA (as low as reasonably achievable) principle (NCRP, 1990), which ultrasound borrows from radiation biology.

A third point may be made in regard to the TI. The TI does not include time as one of its input parameters. This simplification is necessary owing to the severe technical challenges that must be met and the enormous computational overhead required for a diagnostic machine to determine exactly when it began imaging a region of tissue and when it has been moved to a different region. Various possible solutions to the problem have been proposed (Lubbers *et al.*, 2003; Church, 2007; Ziskin, 2010), but none has yet been adopted by any regulatory agency or manufacturer.

### 4.9 Guidelines for safe use of diagnostic ultrasound

Even though the TI is available on-screen, the user still faces the problem of knowing how long to image a particular tissue or organ. This problem was recently considered by the Safety Group of the British Medical Ultrasound Society (ter Haar, 2010; BMUS, 2010) and by Nelson *et al.* (2009). Both groups recommended restricting the acoustic output to no more than that actually required to obtain the necessary diagnostic information. The BMUS Safety Group provided two levels of their guidelines, one more basic and easily remembered (for obstetric examinations only), and a second that is more detailed in terms of maximum duration of scanning at each of several values for TI for various, specified applications. Nelson *et al.* (2009) provided only a relatively simply set of guidelines. The latter are also, in a few cases, somewhat more conservative in terms of maximum duration for a given TI for obstetric examinations, but they are less conservative for examinations in adults. The guidelines suggested by the two groups for setting and monitoring acoustic output during scanning may be summarized as:

#### 4.9.1 Prenatal examinations

1. TI values less than 0.7 [Nelson, <0.5] should be used unless otherwise required, particularly in the first trimester.
2. More generally, TI values less than 0.7 [Nelson, <0.5] likely can be used for scanning times on an extended basis.
3. TI values greater than 0.5 and up to 1 should be limited to scanning times less than 60 [Nelson, <30] min.
4. TI values greater than 2.5 should be limited to scanning times less than 1 min.

## 4.9.2 Postnatal examinations

1. TI values less than 1 [Nelson, <2] likely can be used for scanning times on an extended basis.
2. TI values greater than 1 and up to 1.5 should be limited to scanning times less than 120 min, for  $1.5 < \text{TIB} \leq 2.0$  to 60 min, for  $2.0 < \text{TIB} \leq 2.5$  to 15 min, for  $2.5 < \text{TIB} \leq 3.0$  to 4 min, for  $3.0 < \text{TIB} \leq 4.0$  to 1 min and for  $4.0 < \text{TIB} \leq 5.0$  to 15 s. [Nelson states that for thermal indices in the range 2–6 time should be restricted to less than 30 min].
3. TI values greater than 5 [Nelson, >6] should be limited to scanning times less than 5 s [Nelson, 1 min].
4. For neonatal studies, one should consider further limiting exposure levels and durations as developmental processes are continuing.

It is emphasized that these are only suggested guidelines and not rules to be rigidly followed. This is due to the uncertainty regarding the relationship between acoustic output and the induction of biological effects. More importantly, it is understood that depending on the scanning conditions and diagnostic requirements of the study, these levels may be exceeded for limited periods to obtain diagnostically useful information and thus to ensure optimal patient care.

Output guidelines may be exceeded for a limited time if necessary to obtain diagnostically valuable information

## 4.10 Conclusions

Data from animal studies demonstrate that exposure for 0.5 min to a temperature increase of 4 °C above the normal body temperature is potentially hazardous to embryonic and foetal development; exposures longer than 5 min involve significant risk of harm. Temperature increases >4 °C have been measured at or near bone/soft tissue interfaces in the brains of animal foetuses during *in utero* exposure to conditions similar to those available with PD systems. The effects of elevated temperature may be minimized by keeping the time for which the beam passes through any point in tissue as short as possible. The central nervous system of the first-trimester embryo is particularly sensitive to damage and/or modification by heating. The absorption coefficient of embryonic tissue is lower than that of bone tissue and as the embryo contains no ossified bone, it has a lower risk of suffering bio-effects from ultrasound-induced heating. Adult tissue is less susceptible to damage from ultrasound-induced temperature rise.

There are few data on the biological effects of interaction of ultrasound with tissues that have a pre-existing temperature elevation. The results of specialized studies using rat embryo culture techniques imply that ultrasound-induced biological effects can be potentiated by an existing elevated core temperature; however, uncertainties remain about the possibility of synergistic effects from such ultrasound interactions. Epidemiology data provide little evidence of adverse effects following prenatal exposure to diagnostic ultrasound (see [Chapter 9](#)). However, there are no data on obstetric exposures with modern ultrasonographic equipment operating with a real-time output display, with which significant temperature increase can be produced.

## References

- Abbott JG. 1999. Rationale and derivation of the MI and TI: a review. *Ultrasound Med Biol*, 25, 431–441.
- Abramowicz JS, Barnett SB, Duck FA, Edmonds PD, Hynynen KH, Ziskin MC. 2008. Fetal thermal effects of diagnostic ultrasound. *J Ultrasound Med*, 27, 541–559.
- AIUM/NEMA. 1992. Standard for Real-time Display of Thermal and Mechanical Acoustic Output Indices on Diagnostic Ultrasound Equipment. Rockville, MD: American Institute of Ultrasound in Medicine.
- Angles JM, Walsh DA, Li K, Barnett SB, Edwards MJ. 1990. Effects of pulsed ultrasound and temperature on the development of rat embryos in culture. *Teratology*, 42, 285–293.
- Asakura N. 2004. Fetal and neonatal thermoregulation. *J Nippon Med Sch*, 71, 360–370.
- Barnett SB, Walsh DA, Angles JA. 1990. Novel approach to evaluate the interaction of pulsed ultrasound with embryonic development. *Ultrasonics*, 28, 166–170.
- Barnett SB, Edwards MJ, Martin P. 1991. Pulsed ultrasound induces temperature elevation and nuclear abnormalities in bone marrow cells of guinea-pig femurs. In Proceedings of the 6th WFUMB Congress in Ultrasound, Copenhagen, Denmark, #3405.
- Barnett SB, ter Haar GR, Ziskin MC, Nyborg WL, Maeda K, Bang J. 1994. Current status of research on biophysical effects of ultrasound. *Ultrasound Med Biol*, 20, 205–218.
- Barnett SB, Rott HD, ter Haar GR, Ziskin MC, Maeda K. 1997. The sensitivity of biological tissue to ultrasound. *Ultrasound Med Biol*, 23, 805–812.
- BMUS. 2000. The Safe Use of Ultrasound in Medical Diagnosis. 2nd Edition. London, UK: British Medical Ultrasound Society & The British Institute of Radiology.
- BMUS. 2010. Guidelines for the safe use of diagnostic ultrasound equipment. *Ultrasound*, 18, 52–59.
- Bell AW. 1987. Consequences of severe heat stress for fetal development. In Heat Stress: Physical Exertion and Environment, Hales JRS, Richards DAB (editors). Amsterdam, the Netherlands: Elsevier Science Publishers BV.
- Carstensen EL, Child SZ, Norton S, Nyborg WL. 1990. Ultrasonic heating of the skull. *J Acoust Soc Am*, 87, 1310–1317.
- Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. 1998. Maternal fever and birth outcome: a prospective study. *Teratology*, 58, 251–257.
- Church CC. 2007. A proposal to clarify the relationship between the thermal index and the corresponding risk to the patient. *Ultrasound Med Biol*, 33, 1489–1494.
- Church CC, Miller MW. 2007. Quantification of risk from fetal exposure to diagnostic ultrasound. *Prog Biophys Mol Biol*, 93, 331–353.
- Dewey WC. 1994. Arrhenius relationships from the molecule and cell to the clinic. *Int J Hyperthermia*, 10, 457–483.
- Dewey WC, Hopwood LE, Sapareto SA, Gerweck LE. 1977. Cellular responses to combinations of hyperthermia and radiation. *Radiology*, 123, 463–474.
- Duck FA. 1990. Physical Properties of Tissue. A Comprehensive Reference Book. London, UK: Academic Press.
- Duck FA, Henderson J. 1998. Acoustic output of modern ultrasound equipment: is it increasing? In Safety of Diagnostic Ultrasound, Barnett SB, Kossoff G (editors). New York, NY: Parthenon Publishing Group, pp. 15–25.

- Edwards MJ. 1967. Congenital defects in guinea pigs following induced hyperthermia during gestation. *Arch Pathol*, 84, 42–48.
- Edwards MJ. 1968. Congenital malformations in the rat following induced hyperthermia during gestation. *Teratology*, 1, 173–175.
- Edwards MJ. 1969a. Congenital defects in guinea pigs: fetal resorptions, abortions and malformations following induced hyperthermia during early gestation. *Teratology*, 2, 313–328.
- Edwards MJ. 1969b. Congenital defects in guinea pigs: prenatal retardation of brain growth of guinea pigs following hyperthermia during gestation. *Teratology*, 2, 329–336.
- Edwards MJ. 1986. Hyperthermia as a teratogen: a review of experimental studies and their clinical significance. *Teratog Carcinog Mutagen*, 6, 563–582.
- Edwards MJ. 1993. Hyperthermia and birth defects. *Cornell Vet*, 83, 1–7.
- Edwards MJ. 2006. Review: hyperthermia and fever during pregnancy. *Birth Defects Res A Clin Mol Teratol*, 76, 507–516.
- Edwards MJ, Penny RHC. 1985. Effects of hyperthermia on the myelograms of adult and fetal guinea-pigs. *Br J Radiol*, 59, 93–101.
- Edwards MJ, Mulley R, Ring S, Wanner RA. 1974. Mitotic cell death and delay in mitotic activity in guinea-pig embryos following brief maternal hyperthermia. *J Embryol Exp Morphol*, 32, 593–602.
- Edwards MJ, Shiota K, Smith MSR, Walsh DA. 1995. Hyperthermia and birth defects. *Reprod Toxicol*, 9, 411–425.
- Edwards MJ, Saunders RD, Shiota K. 2003. Effects of heat on embryos and fetuses. *Int J Hyperthermia*, 19, 295–324.
- Erickson JD. 1991. Risk factors for birth defects: data from the Atlanta birth defects case-control study. *Teratology*, 43, 41–51.
- FDA. 1997. Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers. Rockville, MD: Center for Devices and Radiological Health, US Food and Drug Administration.
- Fraser FC, Skelton J. 1978. Possible teratogenicity of maternal fever. *Lancet*, 2, 634.
- Germain MA, Webster WS, Edwards MJ. 1985. Hyperthermia as a teratogen: parameters determining hyperthermia-induced head defects in the rat. *Teratology*, 31, 265–272.
- Graham JM, Edwards MJ, Edwards MJ. 1998. Teratogen update: gestational effects of maternal hyperthermia due to febrile illness and resultant patterns of defects in humans. *Teratology*, 58, 209–221.
- Hardy JD. 1961. Physiology of temperature regulation. *Physiol Rev*, 41, 521–606.
- Henderson J, Whittingham TA, Dunn T. 1997. A review of the acoustic output of modern diagnostic ultrasound equipment. *BMUS Bull*, 3, 10–14.
- Henderson J, Willson K, Jago JR, Whittingham TA. 1995. A survey of the acoustic outputs of diagnostic ultrasound equipment in current clinical use. *Ultrasound Med Biol*, 21, 699–705.
- Hendrickx AG, Stone GW, Hendrickson RV, Matayoshi K. 1979. Teratogenic effects of hyperthermia in the bonnet monkey (*Macaca radiata*). *Teratology*, 19, 177–182.
- Herman BA, Harris GR. 2002. Models and regulatory considerations for transient temperature rise during diagnostic ultrasound pulses. *Ultrasound Med Biol*, 28, 1217–1224.
- Horder MM, Barnett SB, Vella GJ, Edwards MJ, Wood AKW. 1998a. Ultrasound-induced temperature increase in the guinea pig fetal brain *in utero*: third-trimester gestation. *Ultrasound Med Biol*, 24, 1501–1510.

- Horder MM, Barnett SB, Vella GJ, Edwards MJ, Wood AKW. 1998b. *In vivo* heating of the guinea-pig fetal brain by pulsed ultrasound and estimates of thermal index. *Ultrasound Med Biol*, 24, 1467–1474.
- Horder MM, Barnett SB, Edwards MJ. 1998c. Effects of pulsed ultrasound on sphenoid bone temperature and the heart rate in guinea-pig foetuses. *Early Hum Dev*, 52, 221–223.
- IEC. 2007. International Standard 60601-2-37 Medical Electrical Equipment – Part 2-37: Particular Requirements for the Basic Safety and Essential Performance of Ultrasonic Medical Diagnostic and Monitoring Equipment, Ed. 2.0. Geneva, Switzerland: International Electrotechnical Commission.
- IEC. 2010. International Standard 62359 Ultrasonics – Field Characterization – Test Methods for the Determination of Thermal and Mechanical Indices Related to Medical Diagnostic Ultrasonic Fields, Ed. 2.0. Geneva, Switzerland: International Electrotechnical Commission.
- Jago JR, Henderson J, Whittingham TA, Willson K. 1995. How reliable are manufacturers reported acoustic output data? *Ultrasound Med Biol*, 21, 135–136.
- Kimmel GL, Cuff JM, Kimmel CA, Heredia DJ, Tudor N, Silverman PM, *et al.* 1993. Skeletal development following heat exposure in the rat. *Teratology*, 47, 229–242.
- Kreshover SJ, Clough OW. 1953. Prenatal influences on tooth development. I. Artificially induced fever in rats. *J Dent Res*, 32, 565–577.
- Layde PM, Edmonds LD, Erickson JD. 1980. Maternal fever and neural tube defects. *Teratology*, 21, 105–108.
- Little BB, Ghali FE, Snell LM, Knoll KA, Johnston W, Gilstrap LC. 1991. Is hyperthermia teratogenic in humans? *Am J Perinatol*, 8, 185–189.
- Lubbers J, Hekkenberg RT, Bezemer RA. 2003. Time to threshold (TT), a safety parameter for heating by diagnostic ultrasound. *Ultrasound Med Biol*, 29, 755–764.
- Lyng H, Monge OR, Bohler PJ, Rofstad EK. 1991. Relationships between thermal dose and heat-induced tissue and vascular damage after thermoradiotherapy of locally advanced breast carcinoma. *Int J Hyperthermia*, 7, 403–415.
- Macauley JH, Randall NR, Bond K, Steer PJ. 1992. Continuous monitoring of fetal temperature by noninvasive probe and its relationship to maternal temperature, fetal heart rate, and cord arterial oxygen and pH. *Obstet Gynecol*, 79, 469–474.
- Mackowiak PA, Wasserman SS, Levine MM. 1992. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *J Am Med Assoc*, 268, 1578–1580.
- Martin K. 2010. The acoustic safety of new ultrasound technologies. *Ultrasound*, 18, 110–118.
- Mazza S, Battaglia LF, Miller MW, Dewey WC, Edwards MJ, Abramowicz JS. 2004. The  $\Delta T$  thermal dose concept 2: *in vitro* cellular effects. *J Therm Biol*, 29, 151–156.
- Mellette HC, Hutt BK, Askovitz SI, Horvath SM. 1951. Diurnal variations in body temperatures. *J Appl Physiol*, 3, 665–675.
- Miller MW, Ziskin MC. 1989. Biological consequences of hyperthermia. *Ultrasound Med Biol*, 15, 707–722.
- Miller MW, Nyborg WL, Dewey WC, Edwards MJ, Abramowicz JS, Brayman AA. 2002. Hyperthermic teratogenicity, thermal dose and diagnostic ultrasound during pregnancy: implications of new standards on tissue heating. *Int J Hyperthermia*, 18, 361–384.
- Moretti ME, Bar-Oz B, Fried S, Koren G. 2005. Maternal hyperthermia and the risk of neural tube defects in offspring. Systematic review and meta-analysis. *Epidemiology*, 16, 216–219.

- NA/NRC. 2006. Health Risks from Low Levels of Ionizing Radiation; BEIR VII Phase 2. Washington, DC: National Academy of Sciences/National Research Council.
- NCRP. 1990. Implementation of the Principle of as Low as Reasonably Achievable (ALARA) for Medical and Dental Personnel. Report no. 107. Bethesda, MD: National Council for Radiation Protection and Measurements.
- NCRP. 1992. Exposure Criteria for Medical Diagnostic Ultrasound: 1. Criteria Based on Thermal Mechanisms. Report no. 113. Bethesda, MD: National Council for Radiation Protection and Measurements.
- NCRP. 2002. Exposure Criteria for Medical Diagnostic Ultrasound: 1. Criteria Based on All Known Mechanisms. Report no. 140. Bethesda, MD: National Council for Radiation Protection and Measurements.
- Nelson TR, Fowlkes JB, Abramowicz JS, Church CC. 2009. Ultrasound biosafety considerations for the practicing sonographer/sonologist. *J Ultrasound Med*, 28, 139–150.
- Nielson NO. 1969. Teratogenic effects of hyperthermia. In *Teratology*, Bertelli A, Donati L (editors). Amsterdam, the Netherlands: Excerpta Medica Foundation.
- O'Brien WD, Deng CX, Harris GR, Herman BA, Merritt CR, Sanghvi N, *et al.* 2008. The risk of exposure to diagnostic ultrasound in postnatal subjects, thermal effects. *J Ultrasound Med*, 27, 517–535.
- Pennycuik PR. 1965. The effects of acute exposure to high temperatures on prenatal development in the mouse with particular reference to secondary vibrissae. *Aust J Biol Sci*, 18, 97–113.
- Pleet H, Graham JM, Smith DW. 1981. Central nervous system and facial defects associated with hyperthermia at four to 14 weeks gestation. *Paediatrics*, 67, 785–789.
- Poswillo D, Nunnerly H, Sopher D, Keith J. 1974. Hyperthermia as a teratogenic agent. *Ann R Coll Surg Engl*, 55, 171–174.
- Raaphorst GP, Romano SL, Mitchell JB, Bedford JS, Dewey WC. 1979. Intrinsic differences in heat and/or X-ray sensitivity of seven mammalian cell lines cultured and treated under identical conditions. *Cancer Res*, 39, 396–401.
- Sapareto SA, Dewey WC. 1984. Thermal dose determination in cancer therapy. *Int J Radiat Oncol*, 10, 787–800.
- Sarge KD, Bray AE, Goodson ML. 1995. Altered stress response in testis. *Nature*, 374, 126.
- Sasaki J, Yamaguchi A, Nabeshima Y, Shigemitsu S, Mesaki N, Kubo T. 1995. Exercise at high temperature causes maternal hyperthermia and fetal anomalies in rats. *Teratology*, 51, 233–236.
- Shaw A, Pay NM, Preston RC. 1998. Assessment of the Likely Thermal Index Values for Pulsed Doppler Ultrasonic Equipment Stages 2 & 3: Experimental Assessment of Scanner/Transducer Combinations. NPL Report CMAM 12. Teddington, UK: National Physical Laboratory.
- Shepard TH. 1982. Detection of human teratogenic agents. *J Paediatr*, 101, 810–815.
- Shepard TH. 1989. Catalogue of Teratogenic Agents. Baltimore, MD: John Hopkins University Press.
- Shiota K. 1982. Neural tube defects and maternal hyperthermia in early pregnancy: epidemiology in a human embryo population. *Am J Med Genet*, 12, 281–288.
- Shiota K. 1988. Induction of neural tube defects and skeletal malformations in mice following brief hyperthermia *in utero*. *Biol Neonate*, 53, 86–97.

- Skreb N, Frank A. 1963. Developmental abnormalities in the rat induced by heat-shock. *J Embryol Exp Morphol*, 5, 311–323.
- Smith DW, Clarren SK, Harvey MAS. 1978. Hyperthermia as a possible teratogenic agent. *J Pediatr*, 92, 878–883.
- Spraggett K, Fraser FC. 1982. Teratogenicity of maternal fever in women; a retrospective study. *Teratology*, 25, 75A.
- Suarez L, Felkner M, Hendricks K. 2004. The effect of fever, febrile illnesses, and heat exposures on the risk of neural tube defects in a Texas–Mexico border population. *Birth Defects Res A Clin Mol Teratol*, 70, 815–819.
- ter Haar G. 2010. The new British Medical Ultrasound Society Guidelines for the safe use of diagnostic ultrasound equipment. *Ultrasound*, 18, 50–51.
- Tikkanen J, Heinonen OP. 1991. Maternal hyperthermia during pregnancy and cardiovascular malformations in the offspring. *Eur J Epidemiol*, 7, 628–635.
- Upfold JB, Smith MSR, Edwards MJ. 1989. Quantitative study of the effects of maternal hyperthermia on cell death and proliferation in the guinea-pig brain on day 21 of pregnancy. *Teratology*, 39, 173–179.
- Walsh DA, Klein NW, Hightower LE, Edwards MJ. 1987. Heat shock and thermotolerance during early rat embryo development. *Teratology*, 36, 181–191.
- Webster WS, Edwards MJ. 1984. Hyperthermia and the induction of neural tube defects in mice. *Teratology*, 29, 417–425.
- WFUMB. 1992. World Federation for Ultrasound in Medicine and Biology Third Symposium in Medical Ultrasound. Issues and recommendations regarding thermal mechanisms for biological effects of ultrasound, Barnett SB, Kossoff G (editors). *Ultrasound Med Biol*, 18, 733–737.
- WFUMB. 1998. World Federation for Ultrasound in Medicine and Biology Symposium on Safety of Ultrasound in Medicine: conclusions and recommendations on thermal and non-thermal mechanisms for biological effects of ultrasound, Barnett SB (editor). *Ultrasound Med Biol*, 24(Special Issue)S1, 1–55.
- Whittingham TA. 2000. The acoustic output of diagnostic machines. In *The Safe Use of Ultrasound in Medical Diagnosis*, ter Haar G, Duck FA (editors). 2nd Edition. London, UK: British Medical Ultrasound Society & The British Institute of Radiology, pp. 16–31.
- Ziskin MC. 2010. The thermal dose index. *J Ultrasound Med*, 29, 1475–1479.

# Chapter 5

## Non-thermal effects of diagnostic ultrasound

J. Brian Fowlkes<sup>1,2</sup>

<sup>1</sup>Department of Radiology, University of Michigan, Ann Arbor, MI, USA

<sup>2</sup>Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

### Summary

- Mechanical effects, distinct from thermal effects, are those related to cavitation or other interactions of ultrasound with tissues not resulting in heating.
- Some ultrasound imaging modes, such as acoustic radiation force impulse (ARFI) and shear wave imaging, rely on mechanical effects as a source of contrast in images.
- Inertial cavitation can lead to high temperatures in and stresses around collapsing gas bubbles.
- A variety of locations in tissues have demonstrated effects of ultrasound in animal studies but the incidence and significance of such effects in humans has not been determined.
- Ultrasound contrast agents can provide significant diagnostic information and their safety profiles appear excellent based on clinical evidence although mechanisms for biological effects have been identified in animal studies.

### 5.1 Introduction

Diagnostic ultrasound has become one of the most widely used medical imaging modalities in the world. Its portability, relatively low cost and apparent lack of substantial biological effects have led to its use in a variety of medical disciplines. The benefits of ultrasound are well recognized, and its positive impact on healthcare is clear. Despite the large number of sonographic exams performed to date, there is no established casual relationship between clinical applications of diagnostic ultrasound and biologic effects on the patient or operator.

As ultrasound imaging becomes ubiquitously available, it is important to understand how ultrasound propagation can affect tissue. Here we will concentrate on effects not directly related to temperature increases in tissue, which will be termed “non-thermal”. While thermal effects can be readily understood as being associated with the absorption

Non-thermal effects arise from a number of mechanisms. Non-thermal effects may be cavitational or non-cavitational in origin

Cavitation is the activation of small gas bodies

Gas bodies in tissue may occur naturally, or may be exogenous, as, for example, injected contrast agent microbubbles

of ultrasound energy in tissue, non-thermal effects have a variety of source mechanisms, some of which will be discussed here.

The non-thermal effects of ultrasound can be divided into two groups, cavitational and non-cavitational. Cavitation is the activation of small pockets of gas or vapour, commonly called gas bodies. In the case of diagnostic ultrasound, it is the variation of pressure in the ultrasound wave that activates these gas bodies. The source of gas bodies can be naturally occurring within the tissue or be exogenous, such as injectable microbubbles used as ultrasound contrast agents. Because of the significant emphasis placed on effects ascribed to cavitation, the activation of gas bodies by ultrasound, more attention will be devoted to this subject in this chapter. However, that does not diminish the potential significance of the other non-cavital effects of ultrasound.

## 5.2 Mechanical effects

### 5.2.1 Radiation force

Radiation force is related to the amount of energy absorbed by tissue

The radiation force exerted on tissue is related to the amount of energy absorbed by the tissue.

(Note that this absorbed energy may be converted to heat and is a source for thermal effects as well.) The time-average value of this force per unit volume of tissue is given by:

$$F_v = \frac{2\alpha I}{c} \quad (5.1)$$

where  $\alpha$  is the absorption coefficient of the medium,  $I$  is the acoustic intensity and  $c$  is the sound speed. The total force exerted on the tissue can then be given in terms of the total power absorbed from the ultrasound beam  $W$  as:

$$F_T = \frac{W}{c} \quad (5.2)$$

Note that for totally reflecting interfaces the radiation force is due to the momentum transfer required for the wave reflection. This condition doubles the local radiation force. It is the acoustic radiation force that is generally examined as a means of producing biological effects in tissue.

Acoustic streaming results from radiation force in liquids

Given sufficient power and tissue absorption (or reflection), there are appreciable forces that occur with the potential for biological effects. Another effect related to radiation force is acoustic streaming. Liquids can be caused to flow as a result of radiation forces. This effect has been used in diagnostic application for identification of fluid-filled cysts and their distinction from solid lesions (Nightingale *et al.*, 1998).

Radiation force has a number of clinical applications, e.g. ARFI and SWEI

Overall, radiation force has seen a surge in medical application with the utilization of the wide dynamic range of the elastic modulus of tissues. Examples (with early references) of these methods include vibroacoustography (Fatemi and Greenleaf, 1998), shear wave elasticity imaging (SWEI) (Sarvazyan *et al.*, 1998), ARFI imaging (Nightingale *et al.*, 2000) and supersonic shear imaging (Bercoff *et al.*, 2004). A review of the topic provides a historic perspective and a more extensive collection of literature (Sarvazyan *et al.*, 2010). Given the actual use of radiation force in diagnostic procedures, the concept of

bio-effects needs to be defined more in terms of deleterious effects, given that by definition ultrasound fields interact with the tissues. The effects can be temporary and without adverse consequence.

Finally, the presence of bubbles can affect the local radiation force, increasing the effective absorption of the tissue and thereby increasing the radiation force. Radiation force will cause a bubble to move at speeds of  $\sim 10 \text{ m s}^{-1}$  in a cellular suspension and damage nearby cells by exposing them to high shear stresses near the bubble (Miller *et al.*, 1991).

### 5.2.2 Cavitation

Cavitation, the interaction of ultrasound with gas bodies, has been investigated for over a century now, and although we have much understanding of the physical phenomenon, we have less knowledge about its inception in, and interactions with, tissue. The initiation of cavitation is affected by a number of parameters including acoustic field parameters [such as centre frequency, pulse repetition frequency (PRF) and pulse duration for pulsed ultrasound], tissue properties (such as density, viscosity and elasticity) and the size of any initial gas bodies (often referred to as the cavitation nuclei). The number and size of these nuclei may be a principal factor in the likelihood of biologic effects. Cavitation bubbles may be found only in small numbers and only at selected sites, and the applied acoustic field parameters, particularly the acoustic pressure, will control which nuclei can undergo cavitation. Bubble formation in animals has been modelled (Harvey *et al.*, 1944a,b; Yount, 1979) with some models applied to predict cavitation thresholds.

Cavitation is often separated into types, with some confusion in the nomenclature (Church and Carstensen, 2001). However, inertial cavitation is one classification that is particularly useful and commonly used. Inertial cavitation occurs when the surrounding medium inertia controls the bubble motion (Flynn, 1975). When such cavitation occurs, the bubble collapse can be rapid, with large increases in the temperature inside and immediately surrounding the bubble, and causing significant mechanical stress to materials around the bubble. The prediction of conditions for inertial cavitation is the basis for the mechanical index (MI) (Holland and Apfel, 1989), to be discussed later, commonly used in the output display on diagnostic ultrasound systems. At very high acoustic pressures, beyond those used in diagnostic ultrasound, the bubbles can emulsify tissue (Parsons *et al.*, 2006; Khokhlova *et al.*, 2011). However, cavitation effects have also been observed with diagnostic pulses in fluids (Crum and Fowlkes, 1986; Holland *et al.*, 1992; Carmichael *et al.*, 1986).

Inertial cavitation can lead to high temperature increases and significant stresses in tissue

Cavitating bubbles can produce a variety of physical effects. As mentioned earlier, bubbles will affect the radiation force and will move in response to the field. Fluid flow immediately around the oscillating bubble, termed microstreaming, will subject cells to a high-velocity gradient as the fluid flow velocity will decrease away from the bubble. Shockwaves, produced by the bubble wall velocity exceeding the sound velocity in the gas and the tissue, will propagate through the tissue surrounding the bubble. Variations in tissue properties, and even within cells depending on the frequency components of the shockwave, will result in differential motion and, consequently, local stress (Lokhandwalla *et al.*, 2001; Lokhandwalla and Sturtevant, 2001). The temperature and

Mechanical index estimates the potential for inertial cavitation

pressure increases inside the bubble can produce free radicals, including the disassociation of water molecules from the water vapour in the collapsing bubble (Crum and Fowlkes, 1986; Carmichael *et al.*, 1986; Suslick and Flannigan, 2008; Flint and Suslick, 1991). Bubbles can collapse asymmetrically, resulting in microjets that have been observed in intravital microscopy in small vessels containing ultrasound contrast agent (Chen *et al.*, 2011).

### 5.3 Mechanical index

The mechanical index, or MI, was adopted by the US Food and Drug Administration (FDA), American Institute of Ultrasound in Medicine and NEMA as a real-time output display to estimate the potential for inertial cavitation *in vivo*. The MI is given by:

$$MI = p_{r,3} / \sqrt{f_c} \quad (5.3)$$

where  $p_{r,3}$  is the rarefactional pressure (in MPa) of the acoustic field derated at 0.3 dB (MHz cm)<sup>-1</sup> and  $f_c$  is the centre frequency (in MHz) of the field.

This index was based on a theoretical examination of the bubble collapse temperatures which could achieve 5000 K, a temperature at which free-radical generation can occur (Holland and Apfel, 1989). The MI is roughly proportional to the mechanical work that can be performed on a bubble in the rarefactional phase of the acoustic field.

The MI is valid under conditions for the onset of inertial cavitation. Below an MI of ~0.4, the physical conditions do not favour bubble growth even in the presence of a broad bubble nuclei distribution in the body, which is the assumption that is made for the MI formulation.

### 5.4 Observations of bio-effects

#### 5.4.1 Bone

Vascular damage has been seen near developing bone in small animal models

The effect of ultrasound on bone growth has been studied for therapeutic applications. Although this is not a diagnostic application, it does use pulsed ultrasound to elicit the response. Pulsed ultrasound (PRF of 100–1000 Hz) has shown efficacy in fracture healing (Dyson and Brookes, 1983; Wang *et al.*, 1994) and has accelerated the formation of the fracture callus in humans (Leung *et al.*, 2004). The stimulation appears mediated by intracellular calcium signalling (Parvizi *et al.*, 1999, 2002). It is not the megahertz carrier frequency commonly used in these experiments that is important since a 1 kHz squarewave signal produces similar chondrogenesis (Greenleaf *et al.*, 2006). In addition, shock wave devices similar to lithotripters used to disrupt kidney stones accelerate bone growth and healing (Schaden, 1997; Wang *et al.*, 2001). The pulsed nature of these devices makes it unlikely that heating is the mechanism for these effects. Vascular damage near developing bone has also been observed due to pulsed ultrasound (Dalecki *et al.*, 1997c) and appeared only at a gestational age after bone formation began. The effect has been seen in developing mouse (Dalecki *et al.*, 1999) and rat (Bigelow *et al.*, 2007) fetuses. The requisite acoustic amplitude is above current output limits of diagnostic imaging devices.

### 5.4.2 Lung

There are several reports which indicate that ultrasound exposure, using diagnostically relevant acoustic parameters, can produce localized lung haemorrhage in animal models, such as that seen in [Figure 5.1](#) ([Church \*et al.\*, 2008](#)). Results of these studies have previously been summarized ([Church \*et al.\*, 2008](#)). The effects can be confounded by experimental methods where it has been shown that the acoustic impedance condition of the lung is important ([O'Brien \*et al.\*, 2002](#); [Oelze \*et al.\*, 2008](#)). In fact, there is a suggestion for an alternative to the current MI for the case of the lung ([Church and O'Brien, 2007](#)). [Table 5.1](#) is a summary of experimental results involving lung effects in animal models ([Church \*et al.\*, 2008](#)). Although the acoustic parameters used to produce these pulmonary effects are similar to those used in humans, the effects are focal and may not manifest themselves as a significant effect in human subjects. It could be argued that subjects with compromised lungs might be at greater risk, but there are no data to address this question.

Lung haemorrhage in animal models has been observed as a result of ultrasound exposures

### 5.4.3 Intestine

Another location with naturally occurring gas bodies is the intestines. Although imaging through bowel gas is typically avoided, smaller gas bubbles contained within the intestine will not pose an imaging challenge but can still be activated by ultrasound. Using ultrasound near the current output limits as regulated by the FDA, effects have been seen in laboratory animals ([Dalecki \*et al.\*, 1995b](#); [Miller and Gies, 1998, 2000](#)).

Effects have been seen in small animal models when gas-containing bowel is exposed to ultrasound

### 5.4.4 Neurological development

[Marsal \(2010\)](#) provides an overview of potential neurological development effects that have been examined specifically in epidemiological studies. Along with the review by [Abramowicz \*et al.\* \(2008b\)](#), the indication is that with the possible exception of an increase



Figure 5.1. Appearance of subpleural haemorrhage (darker red area) in rat lung lobe following exposure to diagnostic ultrasound. Scale bar indicates 5.5mm. [Reproduced with permission from [Church \*et al.\* \(2008\)](#)].

## 5 Non-thermal effects of diagnostic ultrasound

Table 5.1. Summary of threshold data for lung haemorrhage. [Reproduced with permission from Church *et al.* (2008)].

Nature of study	Lung haemorrhage threshold results						
	Animal	Frequency (MHz)	Beamwidth ( $\mu\text{m}$ )	PRF (kHz)	Pulse duration ( $\mu\text{s}$ )	Exposure duration (s)	$p_{r,i}$ in situ (MPa)
Threshold (Zachary <i>et al.</i> , 2001)	Mouse	2.8	466	1.0	1.4	10	3.6
	Mouse	5.6	448	1.0	1.2	10	3.0
	Rat	2.8	466	1.0	1.4	10	2.3
	Rat	5.6	448	1.0	1.2	10	2.8
Beamwidth (O'Brien <i>et al.</i> , 2001)	Rat	2.8	470	1.0	1.1	10	3.6
	Rat	2.8	930	1.0	1.1	10	3.5
	Rat	5.6	310	1.0	1.1	10	3.5
	Rat	5.6	510	1.0	1.1	10	3.4
Age dependence (O'Brien <i>et al.</i> , 2003)	Pig, 5 d	3.1	610	1.0	1.2	10	3.6
	Pig, 39 d	3.1	610	1.0	1.2	10	5.8
	Pig, 58 d	3.1	610	1.0	1.2	10	2.9
Threshold (O'Brien <i>et al.</i> , 2006)	Rabbit	5.6	510	1.0	1.1	10	3.5
Frequency (Child <i>et al.</i> , 1990)	Mouse	3.7	NR	0.1	1.0	180	1.4
Threshold (Holland <i>et al.</i> , 1996)	Rat	4.0	NR	1.25	1.0	90	2.0
	Rat	4.0	NR	0.4	1.0	90	2.5
Pulse length (O'Brien <i>et al.</i> , 2003a,b)	Rat	2.8	470	1.0	1.3	10	3.1
	Rat	2.8	470	1.0	4.4	10	2.8
	Rat	2.8	470	1.0	8.2	10	2.3
	Rat	2.8	470	1.0	11.7	10	2.0
Frequency (Child <i>et al.</i> , 1990)	Mouse	1.1, U	NR	0.1	10.0	180	0.4
	Mouse	1.2	NR	0.1	10.0	180	0.7
	Mouse	2.3, U	NR	0.1	10.0	180	0.6
	Mouse	3.5, U	NR	0.1	10.0	180	1.3
	Mouse	3.7	NR	0.1	10.0	180	1.0
On time (Raeman <i>et al.</i> , 1993)	Mouse	1.2	3500	0.017	10.0	180	1.1
Threshold (Frizzell <i>et al.</i> , 1994)	Mouse	1.0	1000	0.1	10.0	180	0.4
	Mouse	1.0	1000	1.0	10.0	2.4	1.5
Exposure duration (Raeman <i>et al.</i> , 1996)	Mouse	2.3, U	NR	0.1	10.0	180	0.7
	Mouse	2.3, U	NR	0.1	10.0	20	0.8
Threshold (Baggs <i>et al.</i> , 1996)	Pig	2.3	3000	0.1	10.0	120	0.9
Threshold (Dalecki <i>et al.</i> , 1997a)	Pig	2.3	3000	0.1	10.0	120	0.7
Age dependence (Dalecki <i>et al.</i> , 1997b)	Mouse, N	1.15	NR	0.1	10.0	180	0.6
	Mouse, J	1.15	NR	0.1	10.0	180	0.9
	Mouse, A	1.15	NR	0.1	10.0	180	0.7

A indicates adult; J, juvenile; N, neonate; NR, not reported; and U, unfocused transducer.

incidence of non-right-handedness, there is insufficient evidence of an association. Marsal concluded that the epidemiological studies do not indicate abnormal neurological development as a consequence of ultrasound exposure. In the case of handedness, he pointed out some issues with the studies but indicated that they should not be disregarded.

Continuing the topic, Marsal went on to discuss an animal study in which changes in neuronal migration were suggested (Ang *et al.*, 2006). There has been some debate as to whether the experimental conditions can be related to those of human foetal exposure. While acoustic parameters used with the transvaginal probe selected for the study would be those of a commercial ultrasound system, the uninterrupted duration of the exposure, particularly with regard to the relative time for neuronal migration between species, and, importantly, the relative size of the brain to that of the ultrasound beam could lead to effects that might not manifest in clinical use. Nonetheless, the study points to the need for further investigation.

### 5.4.5 Heart

Application of ultrasound to the heart in an animal model has shown that radiation force can reduce the strength of contraction (Dalecki *et al.*, 1993). Ultrasound pulses coincident with cardiac contraction of the frog heart did show this effect but only for a minimum pulse duration of 5 ms. This duration is orders of magnitude longer than typical diagnostic pulses with the possible exception of those now being used with acoustic radiation force to measure tissue elastic properties. However, no specific evaluation has been performed to investigate this potential effect with respect to imaging modes using acoustic radiation force.

Evidence from small animals indicates that ultrasound can affect the strength of cardiac contractions

### 5.4.6 Human perception

Humans can perceive radiation force. For example, subjects were able to perceive 10 to 100 ms pulses of 2 MHz ultrasound applied to the forearm when the power was greater than 20 W (Dalecki *et al.*, 1995a). The foetus apparently will respond to the presence of ultrasound during a diagnostic examination (Saeian *et al.*, 1995). It is not clear if this is a response to the sound produced at the PRF (Fatemi *et al.*, 2001), which is in the audible range, or some other interaction with the foetus. It is expected that the sound pressure level is not substantial.

Humans can perceive radiation force

### 5.4.7 Contrast

There have been several reviews examining the safety of ultrasound contrast agents (ter Haar, 2009; Miller *et al.*, 2008a). Microbubble contrast agents provide an obvious source of cavitation nuclei that would not normally be found in tissue. Based on animal studies, ultrasound exposure of tissues containing microbubble contrast agents can result in bio-effects, including haemolysis (Dalecki *et al.*, 1997d), capillary rupture (Miller and Quddus, 2000; Wible *et al.*, 2002), endothelial damage (Kobayashi *et al.*, 2002, 2003), cardiac arrhythmias (van der Wouw, 2000; Li *et al.*, 2003, 2004; Dalecki *et al.*, 2005) and effects in the kidney (Miller *et al.*, 2007a,b, 2008b, 2009, 2010a,b; Williams *et al.*, 2007) and the pancreas (Miller *et al.*, 2011). In a review of this research (Miller *et al.*, 2008a), the conclusion drawn was that “the use of high MI values ( $>0.8$ ) involves rapid gas-body destruction with a potential for bio-effects (*e.g.*, PVCs), whereas bio-effects have not been observed at low values of  $(p/\sqrt{f} < 0.2)$ , which involve minimal gas-body destruction”.

The safety and efficacy of ultrasound microbubble contrast agents is under continuous review

Certainly, this is consistent with the common practice of low-MI imaging where the output is maintained below levels expected to produce significant contrast disruption as this would eliminate the signal needed for imaging. The exception would be the use of contrast replenishment where the agent is purposely disrupted to monitor its return to the tissue. There are specific uses for such imaging, and it will be important to consider the benefit of the procedure against any potential risk. Recently, there has been a concerted effort to summarize and add to the evidence on the safety of ultrasound contrast agents in echocardiology. The FDA issued a “black box” warning for contrast agent use. This precipitated a considerable response from the scientific community investigating ultrasound contrast safety. Main *et al.* (Main, 2009; Main *et al.*, 2009) summarized the results of these studies and concluded that there is substantial evidence to support the safe and effective use of ultrasound contrast for the current indicated clinical uses in echocardiology.

### 5.5 Conclusions

Given the considerations indicated here and the literature on the topic of non-thermal effects of ultrasound similar to that used in diagnostic ultrasound, effects have been observed in animal models, although the significance of these and the relationship to the clinical application of ultrasound is unclear. Certainly, there is not sufficient epidemiologic evidence to conclude a causal relationship between diagnostic ultrasound and adverse bio-effects in patients. This is the same conclusion drawn in other reviews (Abramowicz *et al.*, 2008a,b). However, there are reasons why we may actually need to increase acoustic output to achieve diagnostic information that is of value to the patient. For example, acoustic radiation force used to evaluate tissue elasticity may require outputs exceeding those currently regulated by the FDA to be able to perform the procedure in deeper tissues. It is important that we consider this objectively from the standpoint of the benefit to the patient versus the risk, if any, that exists. We should be addressing these questions out of an obligation to do what is correct for the patient and should even accept some additional risk if necessary. It can be argued that the bigger risk to the patient may reside in the decision to obtain the information by some other imaging modality or to not perform any imaging procedure. This could subject the patient to much greater risks.

### References

- Abramowicz JS, Barnett SB, Duck FA, Edmonds PD, Hynynen K, Ziskin MC. 2008a. Fetal thermal effects of diagnostic ultrasound. *J Ultrasound Med*, 27, 541–559.
- Abramowicz JS, Fowlkes JB, Skelly AC, Stratmeyer ME, Ziskin MC. 2008b. Conclusions regarding epidemiology for obstetric ultrasound. *J Ultrasound Med*, 27, 637–644.
- Ang Jr ES, Gluncic V, Duque A, Schafer ME, Rakic P. 2006. Prenatal exposure to ultrasound waves impacts neuronal migration in mice. *Proc Natl Acad Sci USA*, 103, 12903–12910.
- Baggs R, Penney DP, Cox C, Child SZ, Raeman CH, Dalecki D, *et al.* 1996. Thresholds for ultrasonically induced lung hemorrhage in neonatal swine. *Ultrasound Med Biol*, 22, 119–128.
- Bercoff J, Tanter M, Fink M. 2004. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. *IEEE Trans Ultrason Ferroelectr Freq Control*, 51, 396–409.
- Bigelow TA, Miller RJ, Blue JPJ. 2007. Hemorrhage near fetal rat bone exposed to pulsed ultrasound. *Ultrasound Med Biol*, 33, 311–317.

- Carmichael AJ, Mossoba MM, Riesz P, Christman CL. 1986. Free radical production in aqueous solutions exposed to simulated ultrasonic diagnostic conditions. *IEEE Trans Ultrason Ferroelectr Freq Control*, UFFC 33, 148–155.
- Chen H, Brayman AA, Kreider W, Bailey MR, Matula TJ. 2011. Observations of translation and jetting of ultrasound-activated microbubbles in mesenteric microvessels. *Ultrasound Med Biol*, 37, 2139–2148.
- Child SZ, Hartman CL, Schery LA, Carstensen EL. 1990. Lung damage from exposure to pulsed ultrasound. *Ultrasound Med Biol*, 16, 817–825.
- Church CC, Carstensen EL. 2001. “Stable” inertial cavitation. *Ultrasound Med Biol*, 27, 1435–1437.
- Church CC, Carstensen EL, Nyborg WL, Carson PL, Frizzell LA, Bailey MR. 2008. The risk of exposure to diagnostic ultrasound in postnatal subjects – nonthermal mechanisms. *J Ultrasound Med*, 27, 565–592.
- Church CC, O’Brien Jr WD. 2007. Evaluation of the threshold for lung hemorrhage by diagnostic ultrasound and a proposed new safety index. *Ultrasound Med Biol*, 33, 810–818.
- Crum LA, Fowlkes JB. 1986. Acoustic cavitation generated by microsecond pulses of ultrasound. *Nature*, 319, 52–54.
- Dalecki D, Child SZ, Raeman CH, Carstensen EL. 1995a. Tactile perception of ultrasound. *J Acoust Soc Am*, 97, 3165–3170.
- Dalecki D, Child SZ, Raeman CH, Cox C. 1999. Hemorrhage in murine fetuses exposed to pulsed ultrasound. *Ultrasound Med Biol*, 25, 1139–1144.
- Dalecki D, Child SZ, Raeman CH, Cox C, Carstensen EL. 1997a. Ultrasonically induced lung hemorrhage in young swine. *Ultrasound Med Biol*, 23, 777–781.
- Dalecki D, Child SZ, Raeman CH, Cox C, Penney DP, Carstensen EL. 1997b. Age dependence of ultrasonically induced lung hemorrhage in mice. *Ultrasound Med Biol*, 23, 767–776.
- Dalecki D, Child SZ, Raeman CH, Penney DP, Mayer R, Cox C, *et al.* 1997c. Thresholds for fetal hemorrhages produced by a piezoelectric lithotripter. *Ultrasound Med Biol*, 23, 287–297.
- Dalecki D, Keller BB, Raeman CH, Carstensen EL. 1993. Effects of ultrasound on the frog heart. I: thresholds for changes in cardiac rhythm and aortic pressure. *Ultrasound Med Biol*, 19, 385–390.
- Dalecki D, Raeman CH, Child SZ, Carstensen EL. 1995b. Intestinal hemorrhage from exposure to pulsed ultrasound. *Ultrasound Med Biol*, 21, 1067–1072.
- Dalecki D, Raeman CH, Child SZ, Cox C, Francis CW, Meltzer RS, *et al.* 1997d. Hemolysis *in vivo* from exposure to pulsed ultrasound. *Ultrasound Med Biol*, 23, 307–313.
- Dalecki D, Rota C, Raeman CH, Child SZ. 2005. Premature cardiac contractions produced by ultrasound and microbubble contrast agents in mice. *Acoust Res Lett Online*, 6, 221–226.
- Dyson M, Brookes M. 1983. Stimulation of bone repair by ultrasound. *Ultrasound Med Biol*, 9(Suppl. 2), 61–66.
- Fatemi M, Greenleaf JF. 1998. Ultrasound-stimulated vibro-acoustic spectrography. *Science*, 280, 82–85.
- Fatemi M, Ogburn PL, Greenleaf JF. 2001. Fetal stimulation by pulsed diagnostic ultrasound. *J Ultrasound Med*, 20, 883–889.
- Flint EB, Suslick KS. 1991. The temperature of cavitation. *Science*, 253, 1397–1399.
- Flynn HG. 1975. Cavitation dynamics. I. A mathematical formulation. *J Acoust Soc Am*, 57, 1379–1396.
- Frizzell LA, Chen E, Lee C. 1994. Effects of pulsed ultrasound on the mouse neonate: hind limb paralysis and lung hemorrhage. *Ultrasound Med Biol*, 20, 53–63.

- Greenleaf JF, Argadine HM, Bolander ME. 2006. 1 kHz vibration stimulates ATDC5 chondrocytes. In Fifth International Symposium on Therapeutic Ultrasound, Clement GT, McDannold NJ, Hynynen K (editors). New York, NY: American Institute of Physics, pp. 49–53.
- Harvey EN, Barnes KK, McElroy WD, Whitely AH, Pease DC, Cooper KWJ. 1944a. Bubble formation in animals. I. Physical factors. *J Cell Comp Physiol*, 24, 1–22.
- Harvey E, Barnes K, McElroy W, Whitely A, Pease D, Cooper K. 1944b. Bubble formation in animals. II. Gas nuclei and their distribution in blood and tissues. *J Cell Comp Physiol*, 24, 23–34.
- Holland CK, Apfel RE. 1989. An improved theory for the prediction of microcavitation due to pulsed ultrasound. *IEEE Trans Ultrason Ferroelectr Freq Control*, 36, 204–208.
- Holland CK, Deng CX, Apfel RE, Alderman JL, Fernandez LA, Taylor KJ. 1996. Direct evidence of cavitation *in vivo* from diagnostic ultrasound. *Ultrasound Med Biol*, 22, 917–925.
- Holland CK, Roy RA, Apfel RE, Crum LA. 1992. *In vitro* detection of cavitation induced by a diagnostic ultrasound system. *IEEE Trans Ultrason Ferroelectr Freq Control*, 39, 95–101.
- Khokhlova TD, Canney MS, Khokhlova VA, Sapozhnikov OA, Crum LA, Bailey MR. 2011. Controlled tissue emulsification produced by high intensity focused ultrasound shock waves and millisecond boiling. *J Acoust Soc Am*, 130, 3498–3510.
- Kobayashi N, Yasu T, Yamada S, Kudo N, Kuroki M, Kawakami M, *et al.* 2002. Endothelial cell injury in venule and capillary induced by contrast ultrasonography. *Ultrasound Med Biol*, 28, 949–956.
- Kobayashi N, Yasu T, Yamada S, Kudo N, Kuroki M, Miyatake K, *et al.* 2003. Influence of contrast ultrasonography with perflutren lipid microspheres on microvessel injury. *Circ J*, 67, 630–636.
- Leung K-S, Lee W-S, Tsui H-F, Liu P-L, Cheung W-H. 2004. Complex tibial fracture outcomes following treatment with low-intensity pulsed ultrasound. *Ultrasound Med Biol*, 30, 389–395.
- Li P, Armstrong WF, Miller DL. 2004. Impact of myocardial contrast echocardiography on vascular permeability: comparison of three different contrast agents. *Ultrasound Med Biol*, 30, 83–91.
- Li P, Cao LQ, Dou CY, Armstrong WF, Miller DL. 2003. Impact of myocardial contrast echocardiography on vascular permeability: an *in vivo* dose response study of delivery mode, pressure amplitude and contrast dose. *Ultrasound Med Biol*, 29, 1341–1349.
- Lokhandwalla M, McAteer JA, Williams Jr JC, Sturtevant B. 2001. Mechanical haemolysis in shock wave lithotripsy (SWL): II. *In vitro* cell lysis due to shear. *Phys Med Biol*, 46, 1245–1264.
- Lokhandwalla M, Sturtevant B. 2001. Mechanical haemolysis in shock wave lithotripsy (SWL): I. Analysis of cell deformation due to SWL flow-fields. *Phys Med Biol*, 46, 413–437.
- Main ML. 2009. Ultrasound contrast agent safety: from anecdote to evidence. *JACC Cardiovasc Imaging*, 2, 1057–1059.
- Main ML, Goldman JH, Grayburn PA. 2009. Ultrasound contrast agents: balancing safety versus efficacy. *Expert Opin Drug Saf*, 8, 49–56.
- Marsal K. 2010. Exposure to ultrasound *in utero*: epidemiology and relevance of neuronal migration studies. *Ultrasound Med Biol*, 36, 1221–1223.
- Miller DL, Averkiou MA, Brayman AA, Everbach EC, Holland CK, Wible Jr JH, *et al.* 2008a. Bioeffects considerations for diagnostic ultrasound contrast agents. *J Ultrasound Med*, 27, 611–632.
- Miller DL, Dou C, Sorenson D, Liu M. 2011. Histological observation of islet hemorrhage induced by diagnostic ultrasound with contrast agent in rat pancreas. *PLoS One*, 6, e21617.
- Miller DL, Dou C, Wiggins RC. 2008b. Frequency dependence of kidney injury induced by contrast-aided diagnostic ultrasound in rats. *Ultrasound Med Biol*, 34, 1678–1687.

- Miller DL, Dou C, Wiggins RC. 2007a. Doppler mode pulse sequences mitigate glomerular capillary hemorrhage in contrast-aided diagnostic ultrasound of rat kidney. *IEEE Trans Ultrason Ferroelectr Freq Control*, 54, 1802–1810.
- Miller DL, Dou C, Wiggins RC, Wharram BL, Goyal M, Williams AR. 2007b. An *in vivo* rat model simulating imaging of human kidney by diagnostic ultrasound with gas-body contrast agent. *Ultrasound Med Biol*, 33, 129–135.
- Miller DL, Dou C, Wiggins RC. 2009. Glomerular capillary hemorrhage induced in rats by diagnostic ultrasound with gas-body contrast agent produces intratubular obstruction. *Ultrasound Med Biol*, 35, 869–877.
- Miller DL, Dou CY, Wiggins RC. 2010a. Contrast-enhanced diagnostic ultrasound causes renal tissue damage in a porcine model. *J Ultrasound Med*, 29, 1391–1401.
- Miller DL, Dou CY, Wiggins RC. 2010b. Gas body efficacy for glomerular capillary hemorrhage induced by diagnostic ultrasound in rats. *IEEE Trans Biomed Eng*, 57, 167–174.
- Miller DL, Gies RA. 1998. Gas-body-based contrast agent enhances vascular bioeffects of 1.09 MHz ultrasound on mouse intestine. *Ultrasound Med Biol*, 24, 1201–1208.
- Miller DL, Gies RA. 2000. The influence of ultrasound frequency and gas-body composition on the contrast agent-mediated enhancement of vascular bioeffects in mouse intestine. *Ultrasound Med Biol*, 26, 307–313.
- Miller DL, Quddus J. 2000. Diagnostic ultrasound activation of contrast agent gas bodies induces capillary rupture in mice. *Proc Natl Acad Sci USA*, 97, 10179–10184.
- Miller DL, Thomas RM, Williams AR. 1991. Mechanisms for hemolysis by ultrasonic cavitation in the rotating exposure system. *Ultrasound Med Biol*, 17, 171–178.
- Nightingale KR, Kornguth PJ, Trahey GE. 1998. The use of acoustic streaming in breast lesion diagnosis: a clinical study. *Ultrasound Med Biol*, 25, 75–87.
- Nightingale KR, Nightingale RW, Palmeri ML, Trahey GE. 2000. A finite element model of remote palpation of breast lesions using radiation force: factors affecting tissue displacement. *Ultrason Imaging*, 22, 35–54.
- O'Brien WD Jr, Kramer JM, Waldrop TG, Frizzell LA, Miller RJ, Blue JP, *et al.* 2002. Ultrasound-induced lung hemorrhage: role of acoustic boundary conditions at the pleural surface. *J Acoust Soc Am*, 111, 1102–1109.
- O'Brien WDJ, Simpson DG, Frizzell LA, Zachary JF. 2001. Superthreshold behavior and threshold estimation of ultrasound-induced lung hemorrhage in adult rats: role of beamwidth. *IEEE Trans Ultrason Ferroelectr Freq Control*, 48, 1695–1705.
- O'Brien WDJ, Simpson DG, Frizzell LA, Zachary JF. 2003a. Threshold estimates and superthreshold behavior of ultrasound-induced lung hemorrhage in adult rats: role of pulse duration. *Ultrasound Med Biol*, 29, 1625–1634.
- O'Brien WDJ, Simpson DG, Ho MH, Miller RJ, Frizzell LA, Zachary JF. 2003b. Superthreshold behavior and threshold estimation of ultrasound-induced lung hemorrhage in pigs: role of age dependency. *IEEE Trans Ultrason Ferroelectr Freq Control*, 50, 153–169.
- O'Brien Jr WD, Yang Y, Simpson DG, Frizzell LA, Miller RJ, Blue Jr JP, *et al.* 2006. Threshold estimation of ultrasound-induced lung hemorrhage in adult rabbits, and comparison of thresholds in rabbits, rats and mice. *Ultrasound Med Biol*, 32, 1793–1804.
- Oelze ML, Miller RJ, Blue Jr JP, Zachary JF, O'Brien Jr WD. 2008. Estimation of the acoustic impedance of lung versus level of inflation for different species and ages of animals. *J Acoust Soc Am*, 124, 2340–2352.

- Parsons JE, Cain CA, Abrams GD, Fowlkes JB. 2006. Pulsed cavitational ultrasound therapy for controlled tissue homogenization. *Ultrasound Med Biol*, 32, 115–129.
- Parvizi J, Parpura JF, Greenleaf JF, Bolander ME. 2002. Calcium signaling is necessary for ultrasound-stimulated aggrecan synthesis by rat chondrocytes. *J Orthop Res*, 20, 51–57.
- Parvizi J, Wu CC, Lewallen DG, Greenleaf JF, Bolander ME. 1999. Low-intensity ultrasound stimulates proteoglycan synthesis in rat chondrocytes by increasing aggrecan gene expression. *J Orthop Res*, 17, 488–494.
- Raeman CH, Child SZ, Carstensen EL. 1993. Timing of exposures in ultrasonic hemorrhage of murine lung. *Ultrasound Med Biol*, 19, 507–512.
- Raeman CH, Child SZ, Dalecki D, Cox C, Carstensen EL. 1996. Exposure-time dependence of the threshold for ultrasonically induced murine lung hemorrhage. *Ultrasound Med Biol*, 22, 139–141.
- Saeian K, Weintraub R, Hagen-Ansert S, Sahn C, Shiota T, Kenny A, *et al.* 1995. Increased fetal activity and heart rate during and immediately after pulsed Doppler echocardiography. *Echocardiography*, 12, 71–77.
- Sarvazyan AP, Rudenko OV, Nyborg WL. 2010. Biomedical applications of radiation force of ultrasound: historical roots and physical basis. *Ultrasound Med Biol*, 36, 1379–1394.
- Sarvazyan AP, Rudenko OV, Swanson SD, Fowlkes JB, Emelianov SY. 1998. Shear wave elasticity imaging: a new ultrasonic technology of medical diagnostics. *Ultrasound Med Biol*, 24, 1419–1435.
- Schaden W. 1997. Clinical experience with shock wave therapy of pseudarthrosis, delayed fracture healing, and cement-free endoprosthesis loosening. In *Extracorporeal Shock Waves in Orthopaedics*, Siebert W, Buch M (editors). Heidelberg, Germany: Springer-Verlag, pp. 137–148.
- Suslick KS, Flannigan DJ. 2008. Inside a collapsing bubble: sonoluminescence and the conditions during cavitation. *Annu Rev Phys Chem*, 59, 659–683.
- ter Haar G. 2009. Safety and bio-effects of ultrasound contrast agents. *Med Biol Eng Comput*, 47, 893–900.
- van der Wouw PA. 2000. Premature ventricular contractions during triggered imaging with ultrasound contrast. *J Am Soc Echocardiogr*, 13, 288–294.
- Wang C, Chen H, Yang K. 2001. Treatment of nonunions of long bone fractures with shock waves. *Clin Orthop Relat Res*, 387, 95–101.
- Wang SJ, Lewallen DG, Bolander ME, Chao EYS, Illstrup DM. 1994. Low-intensity ultrasound treatment increases strength in a rat femoral fracture model. *J Orthop Res*, 12, 40–47.
- Wible JH, Galen KP, Wojdyla JK, Hughes MS, Klibanov AL, Brandenburger GH. 2002. Microbubbles induce renal hemorrhage when exposed to diagnostic ultrasound in anesthetized rats. *Ultrasound Med Biol*, 28, 1535–1546.
- Williams AR, Wiggins RC, Wharram BL, Goyal M, Dou C, Johnson KJ, *et al.* 2007. Nephron injury induced by diagnostic ultrasound imaging at high mechanical index with gas body contrast agent. *Ultrasound Med Biol*, 33, 1336–1344.
- Yount DE. 1979. Skins of varying permeability: a stabilization mechanism for gas cavitation nuclei. *J Acoust Soc Am*, 65, 1429–1439.
- Zachary JF, Frizzell LA, Norrell KS, Blue JP, Miller RJ, O'Brien WDJ. 2001. Temporal and spatial evaluation of lesion reparative responses following superthreshold exposure of rat lung to pulsed ultrasound. *Ultrasound Med Biol*, 27, 829–839.

# Chapter 6

## Radiation force and its possible biological effects

Hazel C. Starritt

*Royal United Hospital, Bath, UK*

### Summary

- Radiation force is generated within a material in an acoustic field.
- Bio-effects attributed to radiation forces have been observed experimentally in tissue; these include physical effects and sensory effects.
- The volume force generated in diagnostic fields causes biological fluids to stream.
- Any radiation force effects produced at diagnostic exposure levels are transitory.
- Only under extreme conditions has permanent damage to cells been observed.
- Accelerated tissue repair resulting from ultrasound exposure has been attributed to radiation force.

### 6.1 Introduction

Traditionally the mechanisms producing ultrasound bio-effects have been classed as either thermal or cavitational. However, there are reports in the literature of bio-effects occurring in situations where heating and cavitation are unlikely to be contributing factors. Radiation force is the most probable mechanism occurring in these circumstances, since low-level radiation forces are exerted whenever an ultrasound beam passes through tissue. Useful reviews can be found in the literature ([Duck, 1998](#); [Barnett, 1998](#); [Sarvazyan et al., 2010](#)). This chapter examines aspects of radiation force effects in the context of ultrasound safety. Although the forces resulting from ultrasound propagation are very small indeed, nevertheless some of the effects that they produce can be easily observed under appropriate conditions. One example is acoustic streaming and another is the force exerted on the target of a radiation force balance.

## 6.2 Radiation force

### 6.2.1 Radiation force at a boundary

An ultrasound beam generates a force at an interface

Before considering the radiation forces experienced throughout a three-dimensional volume of fluid or tissue, a simpler situation will be discussed: that of an ultrasound beam passing through a fluid and reaching a solid surface. The surface could, for example, be a target in a radiation force balance, or in the body it could be an interface between soft tissue and bone, or tissue and air in the lungs. A force is generated at the surface. This tends to push it away from the source of ultrasound. The strength of this push will depend on the details of the surface and of the beam. The shape of the surface, its size in comparison with the acoustic beam, the angle of incidence and the extent to which it absorbs or reflects the ultrasound beam will influence the magnitude and direction of the force. In addition, the intensity or power in the ultrasound beam is a determining factor. So long as the surface extends outside the ultrasound beam, the total radiation force exerted on the surface is proportional to the total acoustic power in the beam. Measurement of this force is a standard method of determining acoustic power.

Spatial variations in the radiation pressure at a surface result in shear forces in an absorber

The force is the integral of the radiation pressure across the surface. At each point the radiation pressure depends on the ratio of the intensity in the beam to the velocity of sound in the fluid. For a totally absorbing surface perpendicular to the beam, the local radiation pressure is explicitly the local acoustic intensity divided by the speed of sound. Hence the radiation pressure will be greatest on the axis of the beam where the intensity is greatest, and will decrease towards the edges of the beam as the intensity falls off. The radiation pressure profile does, in fact, vary across the beam in the same manner as the intensity profile. As a result of this variation in radiation pressure at the surface, shear stress will be generated within an absorber.

### 6.2.2 Radiation forces in a volume

A volumetric force is established by energy absorption in an ultrasound field

The next stage is to consider the more complicated situation of what happens within a volume of tissue or fluid when an ultrasound beam passes through it. An ultrasound beam passing through a material such as soft tissue will lose energy to the material by a process of absorption. As a result, a volumetric internal force that acts in the direction of wave propagation is generated in the material. For a plane wave, the force per unit volume is given by  $2\alpha I/c$ , where  $c$  is the speed of sound,  $I$  is the local intensity and  $\alpha$  is the attenuation coefficient. It varies throughout the field as the intensity varies. So, for an unscanned beam (Doppler and M-mode) the volume force is greater at the focus and on the axis of the beam than elsewhere. In addition, because of its dependence on the absorption coefficient, the radiation force is greater at higher acoustic frequencies, and varies because of tissue inhomogeneity and non-linear enhancement (see [Chapter 2](#)). The situation is very complex, and this makes it difficult to carry out a complete theoretical analysis of the forces that are likely to be generated.

The universal presence of radiation force in all ultrasonic fields has led to its exploitation in new methods for elastography. For example, acoustic radiation force impulse imaging

uses short-duration (typically less than 1ms) acoustic radiation forces to generate localized displacements in tissue, which are detected and used as the basis for the image (Nightingale *et al.*, 2001, 2002). Shear wave elasticity imaging characterizes the shear modulus of the medium by mapping the velocity of shear waves generated by a short-duration acoustic radiation force (Bercoff *et al.*, 2002). These and other similar methods all derive information on the elastic properties of tissue from the detection of small displacements caused by radiation force, whilst still operating at low enough spatial average intensities to lie within international safety constraints for diagnostic ultrasound.

Radiation force elastography exploits the universal presence of radiation force in all ultrasound fields

Radiation force is experienced only during the passage of an acoustic pulse. Between pulses no force is generated. For pulsed Doppler and pulse-echo applications the magnitude of the force depends on the pulse-average intensity and not on the time-average intensity. For continuous wave ultrasound systems such as physiotherapy units and foetal heart monitors, the force is proportional to the time-average intensity.

Radiation force is experienced only during the passage of an acoustic pulse

## 6.3 Acoustic streaming

### 6.3.1 Introduction

Acoustic streaming results from the generation of a force field in a liquid in the direction of wave propagation. It is a directly observable, bulk movement of liquid away from a transducer that occurs as a result of the absorption of acoustic energy from an ultrasound beam. All absorption processes contribute to this effect, including shear and bulk viscosity, relaxation and excess absorption due to non-linear propagation. There have been a number of attempts to predict streaming in plane, progressive waves (Eckart, 1948; Nyborg, 1998) under bounded and free-field conditions although none have modelled the situation in diagnostic ultrasound fully (Kamakura *et al.*, 1995; Mitome *et al.*, 1995). Nevertheless, generalized expressions derived from theoretical models give a good indication of the way in which the velocity of a stream depends upon the characteristics of the acoustic beam and the propagation fluid. In particular, the flow velocity is proportional to the acoustic intensity, the radius of the acoustic beam and the amplitude attenuation coefficient associated with all processes of acoustic loss. The maximum velocity reached in a fluid is limited by viscous forces and by the geometric boundaries of the fluid space.

Acoustic streaming can be generated in fluids by an ultrasound beam

### 6.3.2 Investigation of acoustic streaming *in vitro*

Acoustic streaming can easily be demonstrated using most diagnostic ultrasound scanners. Measurements of streaming induced using commercial equipment reported by Starritt *et al.* (1989) yielded a maximum streaming velocity in water of  $14\text{ cm s}^{-1}$  in the field of a diagnostic scanner operated in pulsed Doppler mode. Figure 6.1 shows a stream produced in water using a single element 3.5MHz diagnostic transducer operating in pulsed Doppler mode. In imaging fields the streaming velocities reported were lower, of the order of  $1\text{ cm s}^{-1}$ . Streaming has also been observed *in vitro* in human blood and in human serum albumin solution. Zauhar *et al.* (2006) compared acoustic streaming in amniotic fluid with that in water. They demonstrated that the speed was greater in

Streaming occurs in diagnostic ultrasound beams

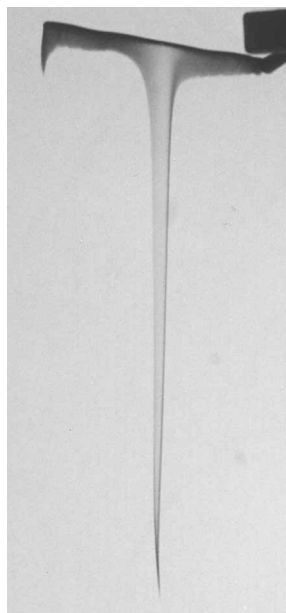


Figure 6.1. Picture of a stream produced in water in the field of a 3.5 MHz transducer operating in pulsed Doppler mode. (Reproduced from [Starritt \*et al.\*, 1991](#), with permission).

amniotic fluid than in water, because of the difference in absorption coefficient. However, when using high-amplitude ultrasound pulses, the speeds were very similar, the force being dominated by non-linear absorption effects (see [Chapter 2](#)).

Streaming can be generated at powers as low as 1mW

More sensitive means, such as magnetic resonance imaging, have been used to investigate streaming at low acoustic powers and within restricted spaces ([Starritt \*et al.\*, 2000](#)). In water, streaming velocities as low as  $0.1 \text{ mm s}^{-1}$  were measured, generated by acoustic powers as low as 1mW. This is at the lower end of the power levels available from commercial ultrasound equipment operating in Doppler mode ([Duck and Henderson, 1998](#); [Martin, 2010](#)). Streaming was also detected within the pores of a coarse sponge. These results imply that streaming is probably occurring within fluid spaces *in vivo* during diagnostic ultrasound examinations more frequently than may be appreciated in practice. It is not normally detected, because of the low velocities involved.

Streaming has been observed *in vivo*

Although not often reported in the literature, streaming in fluid spaces *in vivo* may be easily observed during scanning when operating at higher intensities. Fluid movement has been reported in breast cysts by [Nightingale \*et al.\* \(1995\)](#) and proposed as a diagnostic tool for distinguishing solid from fluid-filled cysts.

It is very unlikely indeed that acoustic streaming occurs in cells and extracellular spaces

It has been postulated that fluids may be caused to stream within the extracellular spaces and even within cells themselves. There is no experimental evidence to suggest that this happens, and it seems to be extremely unlikely to occur. The creation of a stream requires a finite fluid volume, and it is strongly inhibited by the cohesive forces from the volume boundary, and the viscous forces of the fluid. The physical environment of cellular fluids is such that these cohesive forces will be sufficient to prevent fluid movement caused by radiation force.

### 6.3.3 Non-linear propagation

The propagation of high-amplitude pulses, such as those used for diagnostic ultrasound, is accompanied by losses that result in extra absorption of ultrasound energy (see [Chapter 2](#)). This in turn increases the effective attenuation coefficient, altering the volumetric force and any fluid streaming arising from it. If tissue lies behind a fluid path, radiation forces on this tissue can be enhanced. This arises because a shocked wave, carrying harmonic components generated during propagation through a fluid, impinges on tissue and results in enhancement of the absorption. Similarly enhanced forces may also operate on tissue in the absence of such a fluid path, but such effects are much weaker.

Non-linearity can lead to enhanced absorption resulting in increased radiation force and streaming

One factor in any consideration of the significance of acoustic streaming in clinical situations is the time period over which a stream develops. [Starritt \*et al.\* \(1991\)](#) found that in water the shortest rise times to establish the stream were of the order of a few hundred milliseconds for unscanned pulsed beams and up to a few seconds for imaging beams. [Hartley \(1997\)](#) reported rise times in water and blood of 200 ms and 80 ms, respectively. It is clear that acoustic streaming becomes established very quickly when an ultrasound beam is applied to a fluid.

Streaming can become established in under a second

## 6.4 Radiation force in fluids and tissues

Streaming is just one potential outcome of the generation of internal stresses in a material caused by the passage of an ultrasound beam. The forces causing fluids to stream will also be present in soft tissue, but tissue is not free to move in the same way as a fluid. Some of the effects on tissues and fluids that may arise from these forces are discussed below.

The forces causing streaming in fluids are also present within tissue

### 6.4.1 Effects of radiation force on fluids and cell suspensions

In all bulk fluids and cell suspensions, the fluid will move as a result of acoustic streaming. However, it is unlikely that the process of gentle stirring, for example of amniotic fluid or urine *in vivo*, will present a biological hazard. Shear forces will occur at the boundary of a stream, but these are unlikely to cause damage to cells in suspension. A simple calculation shows that for a streaming velocity of  $10 \text{ cm s}^{-1}$  the shear is about 10 Pa at the boundary of a 2 mm stream, which is well below the threshold of 150 kPa for lysis of erythrocytes.

Shear forces arising from streaming are unlikely to damage cells

Acoustic streaming has been suggested as the mechanism responsible for observed changes in diffusion across a planar lipid bilayer membrane ([Pohl \*et al.\*, 1993](#)). The thickness of the unstirred layer near the membrane was reduced in the presence of ultrasound, particularly on the side nearest to the transducer. This is a significant finding because unstirred boundary layers have an essential role to play in transport across biological membranes. The phenomenon of phonophoresis, that is, the enhancement of diffusion rates caused by ultrasound, is best explained by the effect that ultrasound has on the boundary fluid layers. These effects may be further enhanced in the presence of bubbles. In addition, [Pohl \*et al.\* \(1995\)](#), suggest that acoustic streaming may explain an observed effect of ultrasound on the ability of red blood cells to form aggregates.

Streaming can alter the thickness of unstirred boundary layers

### 6.4.2 Effects of radiation force on soft tissue

A number of papers report observations of radiation force effects on soft tissues. These may be grouped into two categories, as either physical effects or sensory effects.

#### 6.4.2.1 Physical effects on tissue

Radiation force has been associated with some physical effects in tissue

Several papers in the literature report physical effects on tissue which the authors believe may be better explained as radiation force effects than thermal or cavitation effects. [Lizzi \*et al.\* \(1981\)](#) have reported blanching of the choroid of the eye prior to the onset of thermal damage. It has been suggested that this occurred due to radiation force causing compression of the blood vessels. [Dalecki \*et al.\* \(1997a\)](#) used an experimental lithotripter to deliver ultrasound pulses to the abdomen of pregnant mice. Pulse amplitudes were in the diagnostic range, but the pulse powers used were higher. The foetal tissue showed evidence of haemorrhage, but only where the soft tissue was near to developing bone or cartilage. The authors suggest that this could result from the relative motion between ossified bone and surrounding soft tissue, caused by radiation force on the bone.

The accelerated tissue repair observed in an acoustic field is probably due to mechanical forces

There have been a number of reports of accelerated healing of bone fractures *in vivo* using low intensity pulsed ultrasound ([Kristiansen \*et al.\*, 1997](#); [Heckman \*et al.\*, 1994](#)). Although the precise biophysical mechanism is unknown, it has been suggested that it arises from the application of mechanical force to the cellular system. An associated alteration in gene expression has been reported ([Yang \*et al.\*, 1996](#); [Parvisi \*et al.\*, 1999](#); see also [Chapter 7](#)). Enhancement of soft-tissue regeneration has also been reported using low intensity therapeutic ultrasound ([Dyson \*et al.\*, 1968, 1970](#)). The effect, which is greatest during the early stages of regeneration, was not attributed to heating due to the low intensities employed.

#### 6.4.2.2 Sensory effects on tissue

Radiation forces can alter neurosensory responses

Several papers have suggested radiation force as the biophysical mechanism for neurosensory responses. [Dalecki \*et al.\* \(1995\)](#) have demonstrated that it is possible to feel the radiation forces that are exerted on the skin by an ultrasound beam. Also reported by [Dalecki \*et al.\* \(1997b\)](#) was a decrease in aortic pressure caused by ultrasound insonation of frog hearts. The authors demonstrated that radiation force was responsible by showing an equivalent effect when the beam was incident on a total absorber in contact with the surface of the heart. A number of papers have reported that the auditory nerve may be directly stimulated by ultrasound ([Magee and Davies, 1993](#)). The mechanism is unknown but we can speculate that it is the direct effect of the varying force field across the neural structures.

#### 6.4.2.3 Developmental effects

Preliminary observations of altered neuronal migration have been attributed to radiation force

[Ang \*et al.\* \(2006\)](#) reported evidence that exposure to ultrasound from a clinical scanner caused partial inhibition of neural migration in the embryonic cerebral cortex of mice. In the absence of evidence suggesting heating or cavitation as the cause, radiation force was proposed as being the most likely mechanism.

## 6.5 Pulsed radiation force as a bio-effects mechanism

Radiation force is experienced only during the time a pulse is passing through tissue and there is no force between pulses. The magnitude of the force in modes such as pulse echo and pulsed Doppler depends on the pulse-average intensity rather than the time-average intensity. In continuous wave applications such as physiotherapy or foetal heart monitoring the tissue experiences a steady force dependent on the time-averaged intensity.

Traditionally, biological effects that show a dependence on time-average intensity are interpreted as being thermal in origin and those that depend on pulse-average intensity or pulse amplitude are explained in terms of cavitation. Once we start to consider radiation force as a possible mechanism it becomes more difficult to separate the dependence on exposure factors. Although radiation force effects are experienced only during a pulse, and are therefore dependent on pulse amplitude or pulse-average intensity, some of the outcomes, like streaming and some of the sensory effects, rely on an integration of the force over time. In this respect they resemble thermal effects. However, the time scales can be very different. Acoustic streaming for example is established almost instantaneously, in time scales of less than a second, whereas tissue temperature takes tens of seconds to increase.

Table 6.1 shows the minimum pulse lengths and number of pulses required in order to produce the radiation force effects described in the papers reviewed above. It shows that some effects can be produced and observed following only a single pulse of ultrasound, while others require the force to be repeated over a number of pulses.

From this table it can be seen that, for example, 200 pulses of about 10  $\mu$ s duration were required to produce haemorrhage in foetal mouse tissue. Choroid blanching, however, occurred with a single pulse about 100  $\mu$ s in duration and the cardiac response in frogs was also seen with a single long pulse, 5 ms in duration. In order to sense ultrasound on the skin a repetitive stress is required and similarly, whilst local fluid movement must be induced by a single pulse, there needs to be a repeated effect before it manifests itself as bulk streaming.

Table 6.1. Minimum ultrasonic pulse duration and number of pulses for radiation force-induced effects.

Effect	Pulse length	Number of pulses
Haemorrhage at bone/soft tissue interface in mice	$\approx 10 \mu$ s	200
Choroid blanching	100 $\mu$ s	1
Tactile sensation	1 ms	Repetitive
Cardiac response in frog	5 ms	1
Fluid movement	0.5 $\mu$ s	1

In pulsed ultrasound fields the radiation force depends on the pulse-average intensity

Radiation force effects occur over a shorter time scale than thermal effects

Some radiation force effects are manifest in a single acoustic pulse

Cellular mechano-transduction pathways will respond to radiation force in ways that are yet to be understood

## 6.6 Cellular mechano-transduction

Cells sense and respond to external forces, by a wide range of mechanisms, yet to be fully understood (Huang *et al.*, 2003). They do so in order to protect themselves from shear, probably the most threatening force, and to adapt their function to altered mechanical environments. It is believed that the cell membrane can sense mechanical forces by means of the molecular agents integrins. This mechano-sensing links extracellular forces to the cytoskeleton, and thus can initiate a cellular response both by gene expression and biochemical change. A broadly homogeneous force may be amplified as a result of local cell–matrix or cell–cell adhesions, with amplification factors of 100 being suggested. The effect of haemodynamic shear on the vascular endothelium is the mechanical effect subject to the most detailed study (Van Bavel, 2007; Davies, 1995). The critical level of fluid shear stress for a variety of biological responses is about 1Pa. Force thresholds associated with other experiments suggest a response threshold of about 1nN. It may be expected, therefore, that cells can detect, and may respond to, radiation force during many ultrasound diagnostic procedures.

## 6.7 Conclusion

Radiation force effects provide a possible explanation for ultrasound bio-effects which appear to be non-thermal and non-cavitation in nature. In adult tissue these forces are highly unlikely to be significant compared with the tensile strength of tissue, even that of weak adult tissue. However, in the embryonic stage tissue does not have the structural strength that develops in later foetal and adult life since the intercellular matrix has yet to develop. The period of organogenesis, between 3.5 weeks and 8 weeks gestation in humans, is a period during which cell differentiation and migration is occurring, and it is possible that the developing foetus may be more vulnerable to mechanical stress at this time. However, there is insufficient evidence to know whether or not the passage of an ultrasound beam could exert sufficient radiation force to cause permanent displacement of cells. The effect of these known radiation forces on cellular mechano-transduction is likewise very unclear. It is therefore important to keep the potential for bio-effects arising from radiation forces in mind, particularly when ultrasound scanning is carried out during the first trimester. As previously recommended, it is prudent to reduce the exposure whenever this can be done without compromising diagnostic information.

## References

- Ang E, Gluncic V, Duque A, Schafer M, Rakic P. 2006. Prenatal exposure to ultrasound waves impacts neuronal migration in mice. *PNAS*, 103, 12903–12910.
- Barnett S (editor). 1998. Other non-thermal mechanisms: acoustic radiation force and streaming. In *Conclusions and Recommendations on Thermal and Non-thermal Mechanisms for Biological Effects of Ultrasound*. Proceedings of the World Federation for Ultrasound in Medicine and Biology Symposium on Safety of Ultrasound in Medicine. *Ultrasound Med Biol*, 24(Suppl. 1), S23–S28.

- Bercoff J, Chaffai S, Tanter M, Fink M. 2002. Ultrafast imaging of beamformed shear waves induced by the acoustic radiation force in soft tissue: application to transient elastography. In Proc 2002 IEEE Ultrasonics Symposium, Yuhas DE, Schneider SC (editors). New York, NY: IEEE, pp. 1899–1902.
- Daleki D, Raeman CR, Child SZ, Carstensen EL. 1997a. Effects of pulsed ultrasound on the frog heart: III. The radiation force mechanism. *Ultrasound Med Biol*, 23, 275–285.
- Daleki D, Child SZ, Raeman CR, Penney DP, Meyer R, Cox C, *et al.* 1997b. Thresholds for fetal haemorrhages produced by a piezoelectric lithotripter. *Ultrasound Med Biol*, 23, 287–297.
- Daleki D, Child SZ, Raeman CH, Carstensen EL. 1995. Tactile perception of ultrasound. *J Acoust Soc Am*, 97, 3165–3170.
- Davies PF. 1995. Flow-mediated endothelial mechanotransduction. *Physiol Rev*, 75, 519–556.
- Duck FA. 1998. Acoustic streaming and radiation pressure in diagnostic applications. In Safety of Diagnostic Ultrasound, Barnett SB, Kossoff G (editors). Carnforth, UK: Parthenon, pp. 87–98.
- Duck FA, Henderson J. 1998. Acoustic output of modern ultrasound equipment: is it increasing? In Safety of Diagnostic Ultrasound, Barnett SB, Kossoff G (editors). Carnforth, UK: Parthenon, pp. 15–25.
- Dyson M, Pond JB, Joseph J, Warwick R. 1968. The stimulation of tissue regeneration by means of ultrasound. *Clin Sci*, 35, 273–285.
- Dyson M, Pond JB, Joseph J, Warwick R. 1970. Stimulation of tissue regeneration by pulsed plane-wave ultrasound. *IEEE Trans Sonics Ultrason*, SU 17, 133–139.
- Eckart C. 1948. Vortices and streams caused by sound waves. *Physiol Rev*, 73, 68–76.
- Hartley CJ. 1997. Characteristics of acoustic streaming created and measured by pulsed Doppler ultrasound. *IEEE Trans Ultrason Ferroelectr Freq Control*, 44, 1278–1285.
- Heckman JD, Ryaby JP, McCabe J, Frey J, Kilcoyne RF. 1994. Acceleration of tibial fracture-healing by non-invasive low-intensity pulsed ultrasound. *J Bone Joint Surg*, 76, 6–43.
- Huang H, Kamm RD, Lee RT. 2003. Cell mechanics and mechanotransduction: pathways, probes and physiology. *Am J Cell Physiol*, 287, C1–C11.
- Kamakura T, Matsuda K, Kumamoto Y. 1995. Acoustic streaming induced in focused Gaussian beams. *J Acoust Soc Am*, 97, 2740–2746.
- Kristiansen TK, Ryaby JP, Frey JJ, Roe LR. 1997. Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound. A multicenter, prospective, randomized, double-blind, placebo-controlled study. *J Bone Joint Surg Am*, 79, 961–973.
- Lizzi FL, Coleman DJ, Driller J, Franzen LA, Leopold M. 1981. Effects of pulsed ultrasound on ocular tissue. *Ultrasound Med Biol*, 7, 245–252.
- Magee TR, Davies AH. 1993. Auditory phenomena during transcranial Doppler insonation of the basilar artery. *J Ultrasound Med*, 12, 747–750.
- Martin K. 2010. The acoustic safety of new ultrasound technologies. *Ultrasound*, 18, 110–118.
- Mitome H, Kozuka T, Tuziuti T. 1995. Effects of nonlinearity in development of acoustic streaming. *Jpn J Appl Phys*, 34, 2584–2589.
- Nightingale KR, Kornguth PJ, Walker WF, McDermott BA, Trahey GE. 1995. A novel ultrasonic technique for differentiating cysts from solid lesions: preliminary results in the breast. *Ultrasound Med Biol*, 21, 745–751.

- Nightingale KR, Palmeri ML, Nightingale R, Trahey G. 2001. On the feasibility of remote palpation using acoustic radiation force. *J Acoust Soc Am*, 110, 625–634.
- Nightingale KR, Soo MS, Nightingale R, Trahey G. 2002. Acoustic radiation force impulse imaging: *in vivo* demonstration of clinical feasibility. *Ultrasound Med Biol*, 28, 227–235.
- Nyborg N. 1998. Acoustic streaming. In *Non-linear Acoustics*, Hamilton MF, Blackstock DT (editors). New York, NY: Academic Press, pp. 207–231.
- Parvisi JP, Wu CC, Lewallen DG, Greenleaf JF, Bolander ME. 1999. Low-intensity ultrasound stimulates proteoglycan synthesis in rat chondrocytes by increasing aggrecan gene expression. *J Orthop Res*, 17, 488–494.
- Pohl P, Antonenko YN, Rosenfeld E. 1993. Effect of ultrasound on the pH profiles in the unstirred layers near planar bilayer lipid membranes measured by microelectrodes. *Biochim Biophys Acta*, 1152, 155–160.
- Pohl EE, Rosenfeld EH, Pohl P, Millner R. 1995. Effects of ultrasound on agglutination and aggregation of human erythrocytes *in vitro*. *Ultrasound Med Biol*, 21, 711–719.
- Sarvazyan AP, Rudenko OV, Nyborg WL. 2010. Biomedical applications of radiation force of ultrasound: historical roots and physical basis. *Ultrasound Med Biol*, 36, 1379–1394.
- Starritt HC, Duck FA, Humphrey VF. 1989. An experimental investigation of streaming in pulsed diagnostic ultrasound beams. *Ultrasound Med Biol*, 15, 363–373.
- Starritt HC, Duck FA, Humphrey VF. 1991. Forces acting in the direction of propagation in pulsed ultrasound fields. *Phys Med Biol*, 36, 1465–1474.
- Starritt HC, Hoal CL, Duck FA, Nassiri DK, Summers IR, Vennart W. 2000. Measurement of acoustic streaming using magnetic resonance. *Ultrasound Med Biol*, 26, 321–333.
- Van Bavel E. 2007. Effects of shear stress on endothelial cells: possible relevance for ultrasound applications. *Prog Biophys Mol Biol*, 93, 374–383.
- Yang KH, Parvizi J, Wang SJ, Lewallen DG, Kinnick RR, Greenleaf JF, *et al.* 1996. Exposure to low intensity ultrasound increases the aggrecan gene expression in a rat femur fracture model. *J Orthop Res*, 14, 802–809.
- Zauhar G, Duck FA, Starritt HC. 2006. Comparison of the acoustic streaming in amniotic fluid and water in medical ultrasonic beams. *Ultraschall Med/Eur J Ultrasound*, 14, 152–158.

# Chapter 7

## Bio-effects—cells and tissues

Gail ter Haar

*Institute of Cancer Research, Sutton, UK*

### Summary

Laboratory experiments carried out *in vivo* and *in vitro* allow the following conclusions to be drawn:

- In the absence of acoustic cavitation, no cell lysis or loss of reproductive integrity has been seen.
- No effects have been seen when embryos or foetuses are exposed to ultrasound *in utero* if the temperature is kept below 41.5°C.
- Observed reduction in birth weight following ultrasound exposure is probably due to changes in maternal physiology.
- Mechanisms which lead to effects observed *in vitro* may not occur in the same way *in vivo*.
- Unless an ultrasonic beam is scaled appropriately, a significantly larger fraction of an experimental animal is exposed than would be the case for a human foetus.

### 7.1 Introduction

The interaction of an ultrasonic beam with the tissues through which it passes is an essential prerequisite for production of a diagnostic ultrasound scan. It is, after all, the scattered beam that is used to form an image. It has long been known that ultrasound can induce change in biological tissues, and this is the basis for physiotherapy applications where beneficial changes (which may often be reversible) in cellular function are sought, and in surgery, where cell killing is required. The requirement for the safe use diagnostic ultrasound is that any cellular changes that may occur are reversible and do not constitute a hazard to the individual being scanned. In the quest for information about safety, a number of different experimental models and ultrasonic exposures have been investigated. The resulting literature is somewhat confusing, but a number of conclusions may be drawn, as outlined in this chapter. For a fuller treatment of this topic, the reader is directed to fuller reviews such as those published by [NCRP \(2002\)](#), [Miller \(2007\)](#), [ter Haar \(2007\)](#) or [AGNIR \(2010\)](#).

The relative importance of physical damage mechanisms is different when cells are held *in vitro* or are in intact tissues *in vivo*

## 7.2 Studies of isolated cells

Experiments conducted with single cells can yield useful information about ultrasonically induced changes produced under closely defined exposure conditions, in well controlled physiological environments. A number of endpoints have been used. These include “gross” effects such as lysis, loss of reproductive ability and damage to cellular ultrastructure, and more subtle effects such as altered growth patterns, chromosomal and functional changes. Care must be taken, however, in extrapolating from results seen with cells exposed to ultrasound *in vitro* to effects that might be expected when cells are subjected to ultrasound *in vivo*. The aqueous nutrient media required for these cell experiments have a lower threshold for acoustic cavitation induction, and a lower acoustic absorption coefficient than would be expected *in vivo*. Cavitation is therefore more likely, and thermal damage less likely, to occur under these circumstances. The presence of liquid in close contact with the cells may also enhance any effects due to acoustic streaming. Thus, the relative importance of physical mechanisms that may result in damage are different when cells are held *in vitro* from when they exist in intact tissues *in vivo*. Provided this is realized, useful results may be obtained from such models.

### 7.2.1 Cell lysis

Cavitation can lead to cell lysis

There is no doubt that ultrasound exposures can lyse cells. Cavitation has been shown by a number of people to be the major mechanism in producing complete cellular destruction (see, for example, Kaufman *et al.*, 1977; Morton *et al.*, 1982; Hallow *et al.*, 2006; Lai *et al.*, 2007). It is not clear that ultrasound can produce cell lysis in the absence of cavitation. It has been shown that the proportion of cells lysed depends on the cellular concentration, high cellular concentrations exhibiting a lower proportion of cells disrupted than low ones (see for example Elwart *et al.*, 1988; Brayman *et al.*, 1996a). This cell density effect may be due in part to the higher respiratory consumption of dissolved oxygen, with its concomitant release of CO<sub>2</sub> into the suspension medium, thus reducing the probability of cavitation effects (Brayman *et al.*, 1992; Carstensen *et al.*, 1993). Lysis appears to be an immediate consequence of ultrasonic exposure, rather than a delayed effect. Cells actively undergoing division (in mitosis) are more susceptible to being lysed by a given ultrasonic exposure than those at other stages in the cell cycle (Clarke and Hill, 1969).

### 7.2.2 Loss of reproductive integrity

Cells subjected to simultaneous heat and ultrasound exposure may lose their ability to divide

The clonogenic assay is a commonly-used measure of toxicity in radiobiology. It is used to assess the ability of a cell to divide and produce viable progeny following an insult. In general, it appears that cells which are not lysed by an ultrasound exposure go on to divide in the same way as their untreated counterparts (Bleaney *et al.*, 1972; Morton *et al.*, 1982). The exception to this appears to lie with cells that are heated (41–45 °C) while being exposed to ultrasound (Li *et al.*, 1977; ter Haar *et al.*, 1980; Feril and Kondo, 2004). These exhibit a loss in reproductive ability that is greater than if the cells were subjected to heat alone. The mechanism for this is not fully understood, but is thought to be non-thermal and non-cavitational in origin (Morton *et al.*, 1983).

### 7.2.3 Ultrastructural changes

There is a wealth of literature concerned with the effects of ultrasound on cellular ultrastructure. A variety of changes have been reported, many of them sublethal or reversible.

The extracellular membrane is an obvious target for study. Ultrasonically induced effects have usually manifested themselves as changes in permeability to ion transport. There are several examples of this, including the sublethal alteration in the thymocyte plasma membrane that leads to a decrease in potassium concentration following  $1 \text{ W cm}^{-2}$  irradiation *in vitro* at 1.8 MHz (Chapman, 1974) and the reversible increase in calcium uptake in fibroblasts shown by Mortimer and Dyson (1988) [ $1 \text{ MHz}$ ,  $0.5\text{--}1.0 \text{ W cm}^{-2} I_{\text{spta}}$ ]. These effects have been under extensive investigation more recently with an upsurge of interest in ultrasound enhancement of drug and gene delivery (ter Haar, 2007; Deckers and Moonen, 2010).

Ultrasound can affect extracellular membrane permeability

Organelle damage following ultrasound exposure has been demonstrated using electron microscopy. Mitochondria are the most frequently affected. Lysosomal damage has been demonstrated following exposure to intact tissues, with the consequent release of lysosomal enzymes. However, it is not clear whether this is a direct or indirect effect of the ultrasound on the lysosomes (Dvorak and Hrazdira, 1966; Hrazdira, 1970; Taylor and Pond, 1972). Dilated rough endoplasmic reticulum (RER) and some irregular intracellular lesions in addition to membrane and mitochondrial effects have been observed in exposures at intensities lying above the cavitation threshold (Harvey *et al.*, 1975).

Ultrasound affects mitochondria and lysosomes, but not the cell nucleus

In general, in the absence of cavitation, the cell nucleus appears to be unaffected by ultrasonic exposures. The only lesions that have been reported are slit-like vacuoles at the nuclear membrane (ter Haar *et al.*, 1979).

### 7.2.4 DNA and chromosomal effects

Ultrasound can degrade DNA in solution. It appears that cavitation is necessary to achieve this, and that the damage is due to the hydrodynamic shear stresses, free-radical formation or excessive heating that may accompany cavitation events (Thacker, 1973; Miller and Thomas, 1995, 1996). As discussed in Chapter 5, such cavitation activity is unlikely to occur during diagnostic ultrasound exposures.

DNA damage can only be induced by ultrasound in the presence of acoustic cavitation

Considerable effort has been expended in looking for ultrasonically induced chromosomal aberrations and for sister chromatid exchange (SCE). The evidence is strong that even up to quite high intensities ( $100 \text{ W cm}^{-2}$ ) ultrasound does not produce chromosomal damage (see Rott, 1981; EFSUMB, 1994 for comprehensive reviews). Although there have been occasional reports that ultrasound may induce chromosomal effects, these have never been independently substantiated by a second investigation, and the vast majority of the literature has yielded negative results. There may, however, be some synergistic effect when an ultrasound exposure follows X-irradiation, but not when it precedes it ( $810 \text{ kHz}$ ,  $3 \text{ W cm}^{-2}$ ; Kunze-Muhl, 1981).

Ultrasound does not produce chromosome damage

There are conflicting reports about SCE increase

SCE analysis is a frequently used assay for the effect of potentially mutagenic agents on mammalian cells (Latt and Schreck, 1980; Gebhart, 1981). Liebeskind *et al.* (1979) reported that diagnostic ultrasound might be capable of inducing SCEs *in vitro*. This stimulated a considerable amount of work, with the majority of investigators reporting negative findings even for intensities up to  $3.0 \text{ W cm}^{-2}$  (3.15 MHz cw). The significance of an increase in SCEs for the cell or whole organism is not properly understood.

## 7.2.5 Functional changes

Ultrasound enhances collagen synthesis

Ultrasound exposures may act either to stimulate or inhibit cellular function. For example, ultrasound irradiation of human fibroblasts *in vitro* may act to increase protein synthesis. Ultrasound has been shown to have considerable effect on the synthesis of collagen by fibroblasts both *in vitro* and *in vivo* (Dyson and Smalley, 1983; Webster *et al.*, 1979). Harvey *et al.* (1975) have demonstrated that when primary diploid human fibroblasts were irradiated with 3 MHz ultrasound at an intensity of  $0.5 \text{ W cm}^{-2}$  *in vitro*, the amount of protein synthesized was increased. Electron microscopic examination of irradiated cells revealed that, in comparison with control cells, there were more free ribosomes, more dilatation of RER, more cytoplasmic vacuolation, more autophagic vacuoles and more damage to lysosomal membranes and mitochondria. Subsequent work from the same group (Webster *et al.*, 1978, 1980) has shown that cavitation may be involved in producing this stimulation of collagen synthesis. It has also been shown that ultrasound can stimulate the release of histamine by mast cell degranulation (Fyfe and Chahl, 1982), possibly by an increase of calcium ion transport across their membranes (Mortimer and Dyson, 1988).

Ultrasound affects cellular movement and mobility

Other observed functional changes have been associated with cellular motion. In time lapse photomicrography studies, ultrasonically induced changes in cellular movement that lasted for several generations were reported (Liebeskind *et al.*, 1982). The electrophoretic mobility of cells may be affected by ultrasound (Taylor and Newman, 1972) although this reflects a change in surface cell density arising from an increase in cellular volume. This appears only to occur *in vitro* in association with cavitation events (Mummery, 1978; Joshi *et al.*, 1973).

## 7.3 Studies of multicellular organisms

A wide range of tissue models has been used for the study of the effects of ultrasound on multicellular structures. These include plants, insects, fish, small and large animals and man. Only mammalian studies will be highlighted here, although useful information has also been derived from the other models.

### 7.3.1 Bone effects

The principle cause for concern when bone lies in an ultrasonic beam lies with periosteal heating since attenuation of energy by bone is too high to allow significant

penetration at diagnostic frequencies. This heating is likely to provide the limiting factor in physiotherapy or hyperthermia treatments as the periosteum is rich in nerve endings. There is also the possibility of significant bone heating with pulsed Doppler examinations at the maximum available output levels. In the aware human, with normal pain sensitivity, excessive periosteal heating is likely to lead to pain. If the treatment is stopped when pain is felt, then it is probable that damage will be avoided. Of potential pulsed Doppler examinations, those in obstetrics give the most grounds for concern on these thermal grounds as proliferating tissue has been shown to be especially susceptible to thermal injury. In laboratory animals there have been measurements of biological significant temperature rises ( $>2^{\circ}\text{C}$ ) close to the skull bone as a result of ultrasonic exposures (Carstensen *et al.*, 1990; Duggan *et al.*, 1995; Bosward *et al.*, 1993; Horder *et al.*, 1998; see Chapter 4).

Bone may be heated by ultrasound

There are some reports that ultrasound can accelerate bone healing (Claes and Willie, 2007, Chang *et al.*, 2002, Duarte, 1983). The mechanism for this is not clear. Experimental studies of fracture in rat fibulae indicate that ultrasonic irradiation during the inflammatory and early proliferative phases of repair accelerates and enhances healing. Direct ossification, with little cartilage production, is seen. Treatment in the late proliferative phase, however, was found to be disadvantageous, cartilage growth being stimulated, with delay to bony union (Dyson and Brookes, 1983). In their study, it was found that 1.5 MHz was more effective than 3.0 MHz ( $I_{\text{satp}} 0.5 \text{ W cm}^{-2}$ , 2 ms:8 ms, 5 min), and so a non-thermal effect is suggested. This finding has been repeated by a number of authors. Pilla *et al.* (1990) showed that the strength of that of intact bone was reached in ultrasonically treated rabbit fibulae 17 days after osteotomy as compared to 28 days for control animals (1.5 MHz,  $I_{\text{sata}} 0.03 \text{ W cm}^{-2}$ , 200  $\mu\text{s}$ :800  $\mu\text{s}$ , 20 min daily). Heckman *et al.* (1994) demonstrated similar acceleration of healing in a human clinical trial. They treated open fractures of the tibial shaft, and found a significant reduction in the time needed to achieve clinical and radiographic healing ( $96 \pm 4.9$  days for the ultrasonically treated group,  $154 \pm 13.7$  days for the control group) (1.5 MHz,  $I_{\text{sata}} 0.03 \text{ W cm}^{-2}$ , 200  $\mu\text{s}$ :800  $\mu\text{s}$ , daily, starting within 7 days of fracture). There appears to be evidence that it is not only the time at which treatment is started that is important, but also the dose level. Too high an intensity can lead to inhibition of protein synthesis, or, at worst to deleterious effects. Tsai *et al.* (1992) found that whereas  $0.5 \text{ W cm}^{-2}$  ( $I_{\text{sata}}$ ) significantly accelerated bone repair,  $1.0 \text{ W cm}^{-2}$  ( $I_{\text{sata}}$ ) suppressed the repair process (1.5 MHz, 200  $\mu\text{s}$ , 5–20 min daily). Reher *et al.* (1997) found in an *in vitro* study of the effect of ultrasound exposure on mouse calvaria bone, that whereas  $0.1 \text{ W cm}^{-2}$  (3 MHz, 2 ms:8 ms, 5 min) stimulated collagen and non-collagenous protein synthesis, intensities of  $0.5\text{--}2 \text{ W cm}^{-2}$  inhibited these. The observed protein synthesis stimulation was attributed to osteoblastic activity. Yang *et al.* (1996) found a statistically significant increase in mechanical strength in fractured rat femurs at  $0.05 \text{ W cm}^{-2}$  ( $I_{\text{sata}} 0.5 \text{ MHz}$ ) but not at  $0.1 \text{ W cm}^{-2}$ . They noted a shift in the expression of genes associated with cartilage formation in the treated bones. Aggrecan gene expression was higher than control values on Day 7, but lower than control on Day 21. Wang *et al.* (1994) found ultrasonically accelerated fracture repair at 21 days in a rat femoral model, but only at 1.5 MHz ( $I_{\text{sata}} 0.03 \text{ W cm}^{-2}$ , 200  $\mu\text{s}$ : 800  $\mu\text{s}$ ) and not at 0.5 MHz.

Ultrasound can accelerate bone repair

### 7.3.2 Effects on soft tissues

Ultrastructural changes resulting from ultrasonic exposure of intact soft tissues have been described above. Extracellular membranes, lysosomes and mitochondria are the cellular sites most readily affected. Ultrasonic exposure of soft-tissue wounds can accelerate healing (Dyson *et al.*, 1968; Dyson, 1990; Young and Dyson, 1990; De Deyne and Kirsch-Volders, 1995). This is probably due to the stimulation of protein synthesis.

Ultrasound may stimulate wound healing

Intensities above  $1 \text{ W cm}^{-2}$  have been shown to produce a variety of effects in smooth muscle. These include alteration of contractile activity (Talbert, 1975; ter Haar *et al.*, 1978) and inhibition of action potentials (Hu *et al.*, 1978). These effects are thought to be due to acoustic streaming mediated alteration of ion transport across cell membranes.

### 7.3.3 Effects on blood components and vasculature

Ultrasound may damage platelets

The most fragile component of the vasculature is the platelet population. Damage to platelets is important because it carries with it the associated risk of thrombus formation. Williams (1974) and Miller *et al.* (1979) have shown that platelet damage may be induced *in vitro* by the shear stresses associated with an ultrasonic exposure, at levels lower than those needed to produce damage to erythrocytes. In the presence of stable bubbles, platelets in suspension *in vitro* may be damaged at spatial average intensities as low as  $0.8 \text{ W cm}^{-2}$  (Miller *et al.*, 1979).

Erythrocytes are resistant to ultrasound damage

In contrast, it appears that erythrocytes are resistant to ultrasonically induced damage. In the presence of collapse (inertial cavitation) haemolysis has been observed (Rooney, 1970; Williams *et al.*, 1970; Wong and Watmough, 1980). ATP may be released at lower spatial average intensities in the presence of non-inertial cavitation (Williams and Miller, 1980).

It is difficult to produce cavitation in whole blood

Whole blood *in vivo* is continuously filtered of impurities, and so is not rich in potential cavitation nuclei. It is therefore very difficult to induce cavitation in whole blood. However, Brayman *et al.* (1996a,b) have demonstrated that it may occur if the acoustic pressure is sufficiently high ( $\sim 17 \text{ MPa}$ ). The addition of gas-filled contrast agents to whole or diluted blood may reduce the acoustic pressure thresholds for the production of cavitation to as low as  $11 \text{ MPa}$  (Miller and Thomas, 1995; 1996; Brayman *et al.*, 1995; Ivey *et al.*, 1995). However, this is still significantly higher than the pressures found in commercial diagnostic scanners.

*In vivo* attempts to detect damage to blood components has largely proved negative (Williams *et al.*, 1977; Deng *et al.*, 1996; Dalecki *et al.*, 1997; Poliachik *et al.*, 1999). This is perhaps unsurprising since it is to be expected that only a small volume of cells is likely to be affected, and any that were would rapidly become diluted by normal cells flowing into the area. Dalecki *et al.* (1997) were able to detect a clinically insignificant level of haemolysis ( $<4\%$ ) following exposure of mouse blood through the chest wall. At  $2.35 \text{ MHz}$  only  $0.46\%$  haemolysis was detected for a pressure amplitude of  $10 \text{ MPa}$ .

Erythrocyte extravasation has been observed following ultrasound exposure of mammalian lungs. This is the subject of extensive review in [Chapter 5](#).

Haemorrhage has been observed close to foetal bone (1.2 MHz; peak positive pressure 4 MPa, peak rarefactional pressure 2.5 MPa) ([Dalecki et al., 1999](#)). This has been attributed to the relative motion between partially ossified bones and surrounding tissues, which may result in damage to the fragile foetal blood vessels. A thermal mechanism has also been suggested ([Bigelow et al., 2007](#)).

Damage to the plasma membrane of the luminal aspect of endothelial cells of the blood vessels in the chick embryo and in mouse uterus have been seen following exposure to ultrasonic standing waves *in vivo* ([Dyson et al., 1974](#); [ter Haar et al., 1979](#)).

### 7.3.4 Consequences of ultrasonic exposure of embryos *in utero*

The most important question to be considered when the safety of obstetric ultrasound is under consideration is whether ultrasound has any deleterious effect on the embryo when irradiated *in utero*. The literature on this topic has been extensively reviewed ([Church and Miller, 2007](#); [NCRP, 2002](#); [Miller et al., 2002](#); [AGNIR, 2010](#)). This question has been addressed through studies into gross teratogenic effects, developmental changes and genetic effects. The majority of these studies have been carried out in rats and mice. While these yield some interesting results, there are a number of limitations to these studies. In particular, the acoustic field is difficult to quantify in these small animals, and in most cases, the beam may have exposed a large fraction of the animal, with the consequent possibility of whole-body heating ([Miller et al., 2002](#); [Edwards et al., 2003](#)).

Raised maternal or foetal temperatures can result in a spectrum of adverse outcomes that affect many developing tissues, but especially the developing brain and nervous system. While the likelihood is low, it is possible that pulsed ultrasound could affect the integrity of maternal and developing tissues through non-thermal interactions, and especially by cavitation mechanisms when ultrasound contrast agents are present ([Abramowicz, 2005](#)).

Whole embryo culture is sometimes used as a model system for the study of external influences on embryonic development. [Ramnarine et al. \(1998\)](#) exposed rat embryos in culture to ultrasound with a range of intensity levels at frequencies between 1 MHz and 4 MHz for 30 min. No significant effects were found for spatial-peak temporal-average intensities below  $4 \text{ W cm}^{-2}$  or negative pressures below 1.9 MPa. These levels are higher than used in diagnostic ultrasound machines (see [Chapter 3](#)). At higher exposure levels some gross morphological abnormalities such as cephalocaudal flexion and abnormal head development were observed. Both thermal and cavitation mechanisms were implicated in these findings. A maximum temperature rise of  $3.5^\circ\text{C}$  was observed within the sample holder. Bubbles were produced during the higher ultrasound exposures, indicating that cavitation had occurred. There is no good evidence that cavitation occurs *in vivo* at diagnostic ultrasound exposure levels. Moreover, 30 min is a longer exposure time than would be expected during clinical examinations ([ter Haar, 2008](#)).

Ultrasound effects have been reported in embryo culture

No effects have been seen in embryos or fetuses of experimental animals exposed to ultrasound *in utero*

There have been a large number of studies of the effect of ultrasound on embryonic and foetal development following exposure *in utero*. In general, no abnormalities have been observed in the absence of a temperature rise to levels above 41.5°C (Shoji *et al.*, 1975; Hara *et al.*, 1977; Hara, 1980). Lele (1979), Edwards (1986, 1993) and Abramowicz *et al.* (2008) have shown that uterine hyperthermia can lead to a number of teratological effects, foetal resorption and growth retardation.

The effect of *in utero* ultrasound exposure on neuronal migration in mice on day 16 of gestation has been studied (Ang *et al.*, 2006). There was no difference in brain size or gross cortical architecture when studied 10 days after birth, but there was a statistically significant dose dependent difference in neuronal dispersion in animals that had been exposed to ultrasound for 30 min or more, with ~4% more neurons in the experimental group of animals remaining in the deeper neuronal layers after 60 min of exposure. In control animals all neurons had reached the superficial layers. A number of important factors must be considered when extrapolating these results to the human. For experimental reasons, the pregnant females required restraint during exposure. This, alone, influences neuronal migration, as was shown by the increased dispersion in the sham control animals. There was very little ultrasound attenuation in the tissue path overlying the foetal mice, leading to much higher intensities than might be experienced by the human foetus. The whole foetal mouse was exposed, whereas only a small proportion of the human foetus would be using these probes. It is therefore difficult to extrapolate these results to human exposures, and their functional significance is difficult to judge, since the neurons involved may not persist.

There have been reports that ultrasound exposures may lead to reduced birth weight

A number of reports have suggested that ultrasonic irradiation *in utero* may result in foetal weight reduction (O'Brien, 1976; Stolzenberg *et al.*, 1980; Tachibana *et al.*, 1977). Barnett and Williams (1990) concluded that the adverse effects seen were caused by changes in maternal physiology produced largely by heating of maternal organs such as the bladder and spine.

The majority of the studies reported in the literature have been conducted at the potentially most sensitive stage of organogenesis (about 8 days in the mouse, 9 days in the rat). Despite this, no adverse effects have been seen at exposure levels used diagnostically. It therefore seems unlikely that current obstetric diagnostic ultrasound practice will lead to teratogenic or developmental changes. Available human epidemiological studies reinforce this finding (see Chapter 9).

## 7.4 Conclusion

While a number of ultrasonically induced changes in biological systems have been reported, it is important that they be assessed in an informed manner. It must be remembered that the mechanisms by which effects may be produced *in vitro* may not carry the same weight as those that operate *in vivo*. In addition, the difficulties in scaling ultrasonic beams to an appropriate size for small animal exposures mean that a proportionately much larger fraction of, for example, a rat uterus, is exposed by a stationary beam than is the case for a human foetus.

Nevertheless, useful information can be gleaned from the existing literature, and while there is currently no good biological evidence which suggests that ultrasound for obstetric examinations should be withheld, constant vigilance and continued, targeted research is essential.

## Acknowledgement

This chapter is a revised version of [Chapter 7](#) in the second edition. The contribution of Stan Barnett to that chapter is acknowledged.

## References

- Abramowicz JS. 2005. Ultrasonographic contrast media: has the time come in obstetrics and gynecology? *J Ultrasound Med*, 24, 517–531.
- Abramowicz JS, Barnett SB, Duck FA, Edmonds PD, Hynynen KH, Ziskin MC. 2008. Fetal thermal effects of diagnostic ultrasound. *J Ultrasound Med*, 27, 541–559.
- AGNIR. 2010. Health Effects of Exposure to Ultrasound & Infrasound Advisory Group on Non-ionising Radiation. London, UK: Health Protection Agency.
- Ang Jr ES, Gluncic V, Duque A, Schafer ME, Rakic P. 2006. Prenatal exposure to ultrasound waves impacts neuronal migration in mice. *Proc Natl Acad Sci USA*, 103, 12903–12910.
- Barnett SB, Williams AR. 1990. Identification of possible mechanisms responsible for fetal weight reduction in mice following exposure. *Ultrasonics*, 28, 159–165.
- Bigelow TA, Miller RJ, Blue JP, O'Brien Jr WD. 2007. Haemorrhage near fetal rat bone exposed to pulsed ultrasound. *Ultrasound Med Biol*, 33, 311–317.
- Bleaney BI, Blackbourne P, Kirkley J. 1972. Resistance of CHLF hamster cells to ultrasonic radiation of 1.5 MHz frequency. *Br J Radiol*, 45, 354–357.
- Bosward KL, Barnett SB, Wood AKW, Edwards MJ, Kossoff G. 1993. Heating of guinea-pig fetal brain during exposure to pulsed ultrasound. *Ultrasound Med Biol*, 19, 415–424.
- Brayman AA, Doida Y, Miller MW. 1992. Apparent contribution of respiratory gas exchange to the *in vitro* “cell density effect” in ultrasonic cell lysis. *Ultrasound Med Biol*, 18, 701–714.
- Brayman AA, Azadniv M, Makin IRS, Miller MW, Carstensen EL, Child SZ, *et al.* 1995. Effect of a stabilised microbubble contrast agent on haemolysis of human erythrocytes exposed to high intensity pulsed ultrasound. *Echocardiography*, 12, 13–21.
- Brayman AA, Azadniv M, Cox C, Miller MW. 1996a. Haemolysis of Albunex-supplemented, 40% haematocrit human erythrocytes *in vitro* by 1 MHz pulsed ultrasound: acoustic pressure and pulse length dependence. *Ultrasound Med Biol*, 22, 927–938.
- Brayman AA, Church CC, Miller MW. 1996b. Re-evaluation of the concept that high cell concentrations “protect” cells *in vitro* from ultrasonically induced lysis. *Ultrasound Med Biol*, 22, 497–514.
- Carstensen EL, Child SZ, Norton S, Nyborg WL. 1990. Ultrasonic heating of the skull. *J Acoust Soc Am*, 87, 1310–1317.
- Carstensen EL, Kelly P, Church CC, Brayman AA, Child SZ, Raeman CH, *et al.* 1993. Lysis of erythrocytes by exposure to CW ultrasound. *Ultrasound Med Biol*, 19, 147–165.
- Chang WH, Sun JS, Chang SP, Lin JC. 2002. Study of thermal effects of ultrasound stimulation on fracture healing. *Bioelectromagnetics*, 23, 256–263.

- Chapman IV. 1974. The effect of ultrasound on the potassium contents of rat thymocytes *in vitro*. *Br J Radiol*, 47, 411–415.
- Church CC, Miller MW. 2007. Quantification of risk from fetal exposure to diagnostic ultrasound. *Prog Biophys Mol Biol*, 93, 331–353.
- Claes L, Willie B. 2007. The enhancement of bone regeneration by ultrasound. *Prog Biophys Mol Biol*, 93, 384–398.
- Clarke PR, Hill CR. 1969. Biological action of ultrasound in relation to the cell cycle. *Exp Cell Res*, 58, 443.
- Dalecki D, Raeman CH, Child SZ, Cox C, Francis CW, Meltzer RS, *et al.* 1997. Haemolysis *in vivo* from exposure to pulsed ultrasound. *Ultrasound Med Biol*, 23, 307–313.
- Dalecki D, Child SZ, Raeman CH, Cox C. 1999. Haemorrhage in murine fetuses exposed to pulsed ultrasound. *Ultrasound Med Biol*, 25, 1139–1144.
- De Deyne PG, Kirsch-Volders M. 1995. *In vitro* effects of therapeutic ultrasound on the nucleus of human fibroblasts. *Phys Ther*, 75, 629–634.
- Deckers R, Moonen C. 2010. Ultrasound triggered, image guided, local drug delivery. *J Control Release*, 148, 25–33.
- Deng CX, Xu Q, Apfel RE, Holland CK. 1996. *In vitro* measurements of inertial cavitation thresholds in human blood. *Ultrasound Med Biol*, 22, 939–948.
- Duarte LR. 1983. The stimulation of bone growth by ultrasound. *Arch Orthop Trauma Surg*, 101, 153–159.
- Dyson M. 1990. Role of ultrasound in wound healing. In *Wound Healing: Alternatives in Management*, Kloth LC, McCulloch JM, Feedar JA (editors). Philadelphia, PA: FA Davis, pp. 259–285.
- Dyson M, Brookes M. 1983. Stimulation of bone repair by ultrasound. In *Ultrasound '82*, Lerski RA, Morley P (editors). Oxford, UK: Pergamon Press, pp. 61–66.
- Dyson M, Pond JB, Joseph J, Warwick R. 1968. The stimulation of tissue regeneration by means of ultrasound. *Clin Sci*, 35, 273–295.
- Dyson M, Pond JB, Woodward B, Broadbent J. 1974. The production of blood cell stasis and endothelial damage in the blood vessels of chick embryos treated with ultrasound in a stationary wave field. *Ultrasound Med Biol*, 1, 133–148.
- Dyson M, Smalley D. 1983. Effects of ultrasound on wound contraction. In *Ultrasound Interactions in Biology and Medicine*, Millner R, Corbet U (editors). New York, NY: Plenum Press, p. 151.
- Duggan PM, Liggins GC, Barnett SB. 1995. Ultrasonic heating of the brain of the fetal sheep *in utero*. *Ultrasound Med Biol*, 21, 553–560.
- Dvorak M, Hrazdira I. 1966. Changes in the ultrastructure of bone marrow cells in rats following exposure to ultrasound. *Z Mikrosk Anat Forsch*, 4, 451–460.
- Edwards MJ. 1986. Hyperthermia as a teratogen: a review of experimental studies and their clinical significance. *Teratog Carcinog Mutagen*, 6, 563–582.
- Edwards MJ. 1993. Hyperthermia and birth defects. *Cornell Vet*, 83, 1–7.
- Edwards MJ, Saunders RD, Shiota K. 2003. Effects of heat on embryos and foetuses. *Int J Hyperthermia*, 19, 295–324.
- EFSUMB. 1994. European Federation of Societies for *Ultrasound in Medicine & Biology*. Tutorial paper: genetic effects. *Eur J Ultrasound*, 1, 91–92.
- Ellwart JW, Brettel H, Kober LO. 1988. Cell membrane damage by ultrasound at different cell concentrations. *Ultrasound Med Biol*, 14, 43–50.

- Feril Jr LB, Kondo T. 2004. Biological effects of low intensity therapeutic ultrasound *in vitro*: the potentials for therapy and the implications on safety of diagnostic ultrasound. *Int Congress Ser*, 1274, 133–140.
- Fyfe M, Chahl LA. 1982. Mast cell degranulation: a possible mechanism of action of therapeutic ultrasound. *Ultrasound Med Biol*, 8(Suppl. 1), 62.
- Gebhart E. 1981. Sister chromatid exchange (SCE) and structural chromosome aberration in mutagenicity testing. *Hum Genet*, 58, 235–254.
- ter Haar G. 2007. Therapeutic applications of ultrasound. *Prog Biophys Mol Biol*, 93, 111–129.
- ter Haar GR. 2008. Results of a survey of exposure conditions used in ultrasound scans in the UK, February 2007. *Ultrasound*, 16, 110–113.
- ter Haar GR, Dyson M, Talbert D. 1978. Ultrasonically induced contractions in mouse uterine smooth muscle *in vivo*. *Ultrasonics*, 16, 275–276.
- ter Haar GR, Dyson M, Smith SP. 1979. Ultrastructure changes in the mouse uterus brought about by ultrasonic irradiation at therapeutic intensities in standing wave fields. *Ultrasound Med Biol*, 5, 167–179.
- ter Haar GR, Stratford LJ, Hill CR. 1980. Ultrasonic irradiation of mammalian cells *in vitro* at hyperthermic temperatures. *Br J Radiol*, 53, 784–789.
- Hallow DM, Mahajan AD, McCutchen TE, Prausnitz MR. 2006. Measurement and correlation of acoustic cavitation with cellular bioeffects. *Ultrasound Med Biol*, 32, 1111–1122.
- Hara K, Minoura S, Okai T, Sakamoto S. 1977. Symposium on recent studies in the safety of diagnostic ultrasound, safety of ultrasonics on organism. *Jpn J Med Ultrason*, 4, 256–258.
- Hara K. 1980. Effect of ultrasonic irradiation on chromosomes, cell division and developing embryos. *Acta Obstet Gynecol Jpn*, 32, 6148.
- Harvey W, Dyson M, Pond JB, Grahame R. 1975. The *in vitro* stimulation of protein synthesis in human fibroblasts by therapeutic levels of ultrasound. In *Ultrasonics in Medicine*, Kazner E, de Vlieger M, Muller HR, McCready VR (editors). Excerpta Medica, International Congress, Series No. 363. Amsterdam, the Netherlands: Excerpta Medica, pp. 10–21.
- Heckman JD, Ryaby JP, McCabe J, Frey JF, Kilcoyne RF. 1994. Acceleration of tibial fracture healing by non-invasive, low intensity pulsed ultrasound. *J Bone Joint Surg*, 76, 26–34.
- Horder MM, Barnett SB, Vella GJ, Edwards MJ, Wood AKW. 1998. *In vivo* heating of the guinea-pig fetal brain by pulsed ultrasound and estimates of thermal index. *Ultrasound Med Biol*, 24, 1467–1474.
- Hrazdira L. 1970. Changes in cell ultrastructure under direct and indirect action of ultrasound. In *Ultrasonographia Medica*, Bock J, Ossoinig K (editors). Vienna, Austria: Vienna Academy of Medicine, pp. 457–463.
- Hu JH, Taylor JD, Press HC, White JE. 1978. Ultrasonic effects on mammalian interstitial muscle membrane. *Aviat Space Environ Med*, 49, 607–609.
- Ivey JA, Gardner EA, Fowlkes JB, Rubin JM, Carson PL. 1995. Acoustic generation of intra-arterial contrast boluses. *Ultrasound Med Biol*, 21, 757–767.
- Joshi GP, Hill CR, Forrester JA. 1973. Mode of action of ultrasound on the surface charge of mammalian cells. *Ultrasound Med Biol*, 1, 45–48.
- Kaufman GE, Miller MW, Griffiths TD, Ciaravino V. 1977. Lysis and viability of cultured mammalian cells exposed to 1 MHz ultrasound. *Ultrasound Med Biol*, 3, 21–25.

- Kunze-Muhl E. 1981. Observations on the effect of X-ray alone and in combination with ultrasound on human chromosomes. *Hum Genet*, 57, 257–260.
- Lai CY, Wu CH, Chen CC, Li PC. 2007. Quantitative relations of acoustic inertial cavitation with sonoporation and cell viability. *Ultrasound Med Biol*, 32, 1931–1941.
- Latt SA, Schreck RR. 1980. Sister chromatid exchange analysis. *Am J Hum Genet*, 32, 297.
- Li GC, Hahn GM, Tolmach LJ. 1977. Cellular inactivation by ultrasound. *Nature*, 267, 163–165.
- Liebeskind D, Bases R, Mendez F, Elequin F, Koenigsberg M. 1979. Sister chromatid exchanges in human lymphocytes after exposure to diagnostic ultrasound. *Science*, 205, 1274–1275.
- Liebeskind D, Padawer J, Wolley R, Bases R. 1982. Diagnostic ultrasound: time lapse and transmission electron microscopic studies of cells insonated *in vitro*. *Br J Cancer Suppl*, 45(Suppl. V), 176–186.
- Lele PP. 1979. Safety and potential hazards in the current applications of ultrasound in obstetrics and gynaecology. *Ultrasound Med Biol*, 5, 307–320.
- Miller DL, Thomas RM. 1995. Ultrasound contrast agents nucleate inertial cavitation *in vitro*. *Ultrasound Med Biol*, 21, 1059–1065.
- Miller DL, Thomas RM. 1996. Contrast agent gas bodies enhance haemolysis induced by lithotripter shock waves and high intensity focused ultrasound in whole blood. *Ultrasound Med Biol*, 22, 1089–1095.
- Miller MW, Nyborg WL, Dewey WC, Edwards MJ, Abramowicz JS, Brayman AA. 2002. Hyperthermic teratogenicity, thermal dose and diagnostic ultrasound during pregnancy: implications of new standards on tissue heating. *Int J Hyperther*, 8, 361–384.
- Mortimer AJ, Dyson M. 1988. The effect of therapeutic ultrasound on calcium uptake in fibroblasts. *Ultrasound Med Biol*, 14, 499–506.
- Morton KI, ter Haar GR, Stratford LJ, Hill CR. 1982. The role of cavitation in the interaction of ultrasound with V79 Chinese Hamster cells *in vitro*. *Br J Cancer*, 45, 147–150.
- Morton KI, ter Haar GR, Stratford LJ, Hill CR. 1983. Subharmonic emission as an indicator of ultrasonically induced biological damage. *Ultrasound Med Biol*, 9, 629–633.
- Miller DL. 2007. Overview of experimental studies of biological effects of medial ultrasound caused by gas body activation and inertial cavitation. *Prog Biophys Mol Biol*, 93, 414–430.
- Miller DL, Nyberg WL, Whitcomb CC. 1979. Platelet aggregation induced by ultrasound under specialized conditions *in vitro*. *Science*, 205, 505–507.
- Mummery CL. 1978. Effect of ultrasound on fibroblasts *in vitro*. Ph.D. thesis, University of London.
- NCRP. 2002. Exposure Criteria for Medical Diagnostic Ultrasound: II Criteria Based on all Known Mechanisms. NCRP Report no. 140. Bethesda, MD: National Council on Radiation Protection and Measurements.
- O'Brien WD. 1976. Ultrasonically induced fetal weight reduction in mice. In *Ultrasound in Medicine*, White DN (editor). New York, NY: Plenum Press, pp. 531–532.
- Pilla AA, Mont MA, Nasser PR, Khan SA, Figueiredo M, Kaufman JJ, *et al.* 1990. Non-invasive low intensity pulsed ultrasound accelerates bone healing in the rabbit. *J Orthop Trauma*, 4, 246–253.
- Poliachik SL, Chandler WL, Mourad PD, Bailey MR, Bloch S, Cleveland RO, *et al.* 1999. Effect of high intensity focused ultrasound on whole blood with and without microbubble contrast agent. *Ultrasound Med Biol*, 25, 991–998.

- Ramnarine KV, Nassiri DK, McCarthy A, Brown NA. 1998. Effects of pulsed ultrasound on embryonic development: an *in vitro* study. *Ultrasound Med Biol*, 24, 575–585.
- Reher P, Elbeshir E-NI, Harvey W, Meghji S, Harris M. 1997. The stimulation of bone formation *in vitro* by therapeutic ultrasound. *Ultrasound Med Biol*, 23, 1251–1258.
- Rooney JA. 1970. Hemolysis near an ultrasonically pulsating gas bubble. *Science*, 169, 869–871.
- Rott H-D. 1981. Zur Frage der Schädigungsmöglichkeit durch diagnostischen Ultraschall. *Ultraschall Med*, 2, 56.
- Shoji R, Murackami U, Shimizu T. 1975. Influence of low intensity ultrasonic irradiation on prenatal development of two inbred mouse strains. *Teratology*, 12, 227–232.
- Stolzenberg SJ, Torbit CA, Pryor GT, Edmonds PD. 1980. Toxicity of ultrasound in mice: neonatal studies. *Radiat Environ Biophys*, 18, 37–44.
- Tachibana M, Tachibana Y, Suzuki M. 1977. The present status of the safety of ultrasonic diagnosis in the area of obstetrics — the effect of ultrasound irradiation on pregnant mice as indicated in their fetuses. *Jpn J Med Ultrason*, 4, 279–283.
- Talbert DG. 1975. Spontaneous smooth muscle activity as a means of detecting biological effects of ultrasound. In *Proceedings of Ultrasonics International*. Guildford, UK: IPC Science & Technology Press, pp. 279–284.
- Taylor KJW, Newman DL. 1972. Electrophoretic mobility of Ehrlich suspensions exposed to ultrasound of varying parameters. *Phys Med Biol*, 17, 270–276.
- Taylor KJW, Pond JB. 1972. Primary sites of ultrasonic damage on cell systems. In *Interaction of Ultrasound and Biological Tissues*, Reid M, Sikov MR (editors). Washington, DC: DHEW Publication No. (FDA)73-8008.
- Thacker J. 1973. The possibility of genetic hazard from ultrasonic radiation. *Curr Top Radiat Res Q*, 8, 235–258.
- Tsai C-L, Chang WH, Liu T-K. 1992. Preliminary studies of duration and intensity of ultrasonic treatments on fracture repair. *Chin J Physiol*, 35, 21–26.
- Wang SJ, Lewallen DG, Bolander ME, Chao EYS, Ilstrup DM, Greenleaf JF. 1994. Low intensity ultrasound treatment increases strength in a rat femoral fracture model. *J Orthop Res*, 12, 40–47.
- Webster DF, Dyson M, Harvey W. 1979. Ultrasonically induced stimulation of collagen synthesis *in vivo*. In *Proceedings of the 4th European Symposium on Ultrasound in Biology and Medicine*, 1, pp. 135–140.
- Webster DF, Harvey W, Dyson M, Pond JB. 1980. The role of ultrasound-induced cavitation in the *in vitro* stimulation of collagen synthesis in human fibroblasts. *Ultrasonics*, 18, 33–37.
- Webster DF, Pond JB, Dyson M, Harvey W. 1978. The role of cavitation in the *in vitro* stimulation of protein synthesis in human fibroblasts by ultrasound. *Ultrasound Med Biol*, 4, 343–351.
- Williams AR, Hughes DE, Nyborg WL. 1970. Hemolysis near a transversely oscillating wire. *Science*, 169, 871–873.
- Williams AR. 1974. Release of serotonin from human platelets by acoustic microstreaming. *J Acoust Soc Am*, 56, 1640–1643.
- Williams AR, Chater BV, Sanderson JH, Taberner DA, May SJ, Allen KA, *et al.* 1977. Beta-thromboglobulin release from human platelets after *in vivo* ultrasound irradiation. *Lancet*, 2, 931–932.

Williams AR, Miller DL. 1980. Photometric detection of ATP release from human erythrocytes exposed to ultrasonically activated gas-filled pores. *Ultrasound Med Biol*, 6, 251–256.

Wong YS, Watmough DJ. 1980. Hemolysis of red blood cells *in vitro* and *in vivo* caused by therapeutic ultrasound at 0.75 MHz. In *Proceedings of Ultrasound Interaction in Biology and Medicine Symposium*, Reinhardtbrunn, GDR, 10–14 November. Paper C-14.

Yang KH, Parvizi J, Wang SJ, Lewallen DG, Kinnick RR, Greenleaf JF, *et al.* 1996. Exposure to low intensity ultrasound increases the aggrecan gene expression in a rat femur fracture model. *J Orthop Res*, 14, 802–809.

Young SR, Dyson M. 1990. Effect of therapeutic ultrasound on the healing of full-thickness excised skin lesions. *Ultrasonics*, 28, 175–180.

# Chapter 8

## The safe use of contrast-enhanced diagnostic ultrasound

**Douglas L. Miller**

*Department of Radiology, University of Michigan, Ann Arbor, MI, USA*

### Summary

- Ultrasound contrast agents are complex drugs consisting of suspended gas bodies.
- Post-marketing surveillance has identified adverse events, which led to the inclusion of new warnings and contraindications in package inserts.
- Ultrasonic activation of the gas bodies produces strong echoes, and concentrates mechanical activity in their vicinity, which can lead to localized biological effects.
- Reported bio-effects include subcellular lesions, cell lysis, capillary leakage and haemorrhage, lethal injury of cardiomyocytes, cardiac arrhythmia, renal tubular obstruction and haematuria.
- The current mechanical index does not provide actual dosimetric information for biological effects when gas-body based contrast agents are used in diagnostic ultrasound.
- The optimum risk-to-benefit ratio may be obtained for the patient through the diligent application of the contraindications, warnings and usage instructions for ultrasound contrast agents.

### 8.1 Introduction

The concept of contrast enhancement by an external agent originated early in the evolution of diagnostic imaging by ultrasound. Blood-filled regions often appear empty in an ultrasound image, and provision of material (contrast agent), which brings the image brightness above the normal background of blood or tissue, can yield new diagnostic information. Beginning with observations of contrast from saline injections ([Gramiak, 1997](#)), the development of ultrasound contrast agents has progressed to an expanding list of commercially-developed agents which are approved for clinical use. Ultrasound contrast agents are unique in several ways. Since ultrasound images involve echoes, a passive absorptive agent (analogous to the iodinated agents used in X-ray angiography) would be of little value. The ideal contrast agents for ultrasound are suspensions of

Modern ultrasound contrast agents consist of suspensions of stabilized microbubbles engineered to persist when in the circulation

Safety issues for the clinical use of ultrasound contrast materials include adverse reactions to the drugs and biological effects associated with ultrasonic cavitation

microbubbles that can circulate through the body and provide strong pulse echoes. Contrast echocardiography has been shown to be useful in cardiology both for left ventricular boarder delineation and for assessing perfusion of the myocardium (Porter and Xie, 2010). In addition, contrast-enhanced diagnostic ultrasound (CEDUS) is utilized in abdominal organs, particularly for evaluation of liver masses (Cosgrove, 2006; Wilson and Burns, 2010). In this review of safety issues, the advantages and benefits of CEDUS will not be described in detail; the reader is referred to several comprehensive books (Nanda *et al.*, 1997; Thomsen *et al.*, 1999; Goldberg *et al.*, 2001) and numerous reviews on specific applications.

Since the first review of the safe use of ultrasound contrast agents (Miller, 2000), the progress and adoption of CEDUS has been negatively impacted by safety issues, which are the topic of this update. Ultrasound contrast agents present two distinct types of risks. First, these agents have many of the same potential risk factors as other injectable agents, such as adverse reactions, which have been of concern for regulatory agencies. Second, diagnostic ultrasound pulses not only activate the gas bodies, producing strong and unique echoes for imaging, but can also nucleate ultrasonic cavitation, a potential mechanism for bio-effects. Without the addition of such exogenous cavitation nuclei, cavitation thresholds are expected to be high (Church, 2002; Carstensen *et al.*, 2000). Thus, the injection of gas-body based contrast agents into the circulation introduces an entirely novel risk of bio-effects for diagnostic ultrasound. Several authoritative reviews of bio-effects considerations for CEDUS have been conducted by the National Council on Radiation Protection (NCRP, 2002), the World Federation of Ultrasound in Medicine and Biology (Barnett *et al.*, 2007) and the American Institute of Ultrasound in Medicine (Miller *et al.*, 2008a) among others. Unfortunately, the research has not been exhaustive or conclusive, leaving many uncertainties. The purpose of this update is to review recent developments in ultrasound contrast agents, their ultrasonic behaviour, pharmacological safety issues, bio-effects research and guidance for the safe use of CEDUS.

## 8.2 Ultrasound contrast agents and how they work

### 8.2.1 Gas-body design

Advanced contrast agents use low solubility gases and a stabilizing skin to extend lifetime

Some popular commercial agents, which have been approved for clinical use, are listed in Table 8.1. In addition, other agents are under development and in clinical trails, which may be approved in the near future. The two agents Echovist and Levovist (Schering AG, Berlin) consist of dry galactose particles which are manually reconstituted for use (Schlief *et al.*, 1993). The ultrasonic attenuation produced by Levovist peaks at about 2–3 MHz, indicating a typical bubble size of 2.7  $\mu\text{m}$ . Albunex (Molecular Biosystems, Inc. or Mallinckrodt, Inc.) was created by sonication of a solution of human serum albumin, which produced numerous gas bodies with stable shells of denatured albumin about 15 nm in thickness (Christiansen *et al.*, 1994). Advanced agents have been invented to improve persistence in the circulation. Optison (GE Healthcare, Princeton, NJ, USA) is related to the earlier product Albunex, but contains perflutren, a gas which is much less soluble in aqueous media than air (Killam and Dittrich, 1997). The product contains about  $5\text{--}8 \times 10^8$  per ml of gas bodies with a mean diameter range of 3.0–4.5  $\mu\text{m}$ , which

Table 8.1. A partial listing of ultrasound contrast agents, which have been approved for clinical use.

Agent designation	Stabilization	Gas	Associated company	Exemplary citation
Echovist	Galactose	Air	Schering AG	Schlieff <i>et al.</i> , 1993
Albunex	Albumin	Air	Mallinckrodt	Bleeker <i>et al.</i> , 1990
Levovist	Galactose	Air	Schering AG	Schlieff <i>et al.</i> , 1993
Optison	Albumin	Perflutren	Mallinckrodt	Killam and Dittich, 1997
Definity	Lipids	Octafluoropropane	ImaRx Pharm.	Unger <i>et al.</i> , 1997
Sonovue	Lipids	Sulphur hexafluoride	Bracco Diagnostics	Schneider <i>et al.</i> , 1995
Imagent US	Surfactants	Perflexane	Alliance Pharm.	Mattrey and Pelura, 1997

are stable under refrigeration for several years. Definity (Lantheus Medical Imaging, N Billerica, MA, USA) is prepared by shaking a 2ml vial containing clear liquid and octafluoropropane gas, which produces a creamy suspension containing  $1.2 \times 10^{10}$  lipid-stabilized microbubbles per ml with a 1.1–3.3  $\mu\text{m}$  mean diameter range. Imagent (Perflexane Lipid Microsphere, Alliance Pharmaceutical, San Diego, CA, USA) is reconstituted with 10ml of water, which results in about  $10^9$  per ml of lipid-stabilized microbubbles of 6  $\mu\text{m}$  volume-weighted mean diameter. Sonovue (Bracco International, Amsterdam, The Netherlands) is reconstituted from a dry powder with 5ml of saline, which yields a suspension of  $2\text{--}5 \times 10^8$  lipid-stabilized microbubbles per ml of 1–10  $\mu\text{m}$  diameter with sulphur hexafluoride gas.

### 8.2.2 Physics of ultrasound contrast agents

Commercial ultrasound contrast agents consist of gas bodies in a carrier medium. Gas bodies interact with a low-amplitude acoustic pressure wave by pulsating, much like a simple resonant oscillator. The size range required for passage through the circulation, less than about 4  $\mu\text{m}$  radius, fortuitously coincides with the range of strongly responding sizes of bubbles in the MHz frequency range of diagnostic ultrasound. Although the stabilizing shells or skins reduce the pulsation relative to free gaseous microbubbles, measurements of scattering have shown that these gas bodies are more effective, by orders of magnitude, in producing echoes than are cells of the blood.

At amplitudes relevant to diagnostic imaging, the scattered ultrasound includes the second harmonic, which can be exploited in harmonic imaging modes of ultrasound scanners to produce stronger contrast between the agents and tissue (Krishna and Newhouse, 1997). Another useful non-linear signal is the subharmonic, which may have

Contrast gas bodies less than about 4  $\mu\text{m}$  radius can pass through the capillary bed: they also provide strong echoes at diagnostic ultrasound frequencies

Microbubble pulsation is non-linear, which allows special contrast-specific imaging modes in CEDUS

advantages over the second harmonic for imaging (Forsberg *et al.*, 2000). The non-linear behaviour can be exploited by using special imaging modes designed to separate the gas-body echoes from normal tissue echoes (Averkiou *et al.*, 2003). These modes can utilize relatively low power to image tissue perfusion with contrast agent in real-time (Cosgrove and Blomley, 2004). The actual tissue blood supply at the capillary level is revealed, which is not possible for non-contrast diagnostic ultrasound imaging.

Contrast agents are easily destroyed by diagnostic ultrasound, eliminating the contrast-enhancement phenomenon

### 8.2.3 Gas-body stability and nucleation of inertial cavitation

Although the commercial gas-body contrast agents are stable in storage for extended periods, most are unstable during handling and use. The gas bodies are also susceptible to destruction by ultrasound, because the stabilizing films or shells are fragile (Stride and Saffari, 2003). At low pulse rarefactional pressure amplitudes (RPAs), the shells can effectively prevent expansion, resulting in a one-sided oscillation (Marmottant *et al.*, 2005). However, at higher amplitudes the gas bodies become unstable, and are effectively destroyed by the diagnostic ultrasound. The destruction of the gas bodies can be complex and depends strongly on the ultrasonic RPAs (Shi *et al.*, 2000; Chomas *et al.*, 2001). Basically, however, at modest RPAs the stabilization is lost, which leads to release of free gaseous microbubbles, followed by dissolution at the conclusion of the pulse (Porter *et al.*, 2006).

Released microbubbles may act as nuclei for inertial cavitation, an important potential mechanism for biological effects

At the time of destabilization, the liberated microbubble can exhibit a greatly increased echo amplitude. This process can also be viewed as the nucleation of cavitation activity. The possible initiation of inertial cavitation during CEDUS is important because cavitation is a well-known potential mechanism for biological effects of ultrasound (see Chapter 5). Secondary mechanisms for bio-effects arising from the cavity dynamics may include: volume pulsation, fragmentation, mechanical displacement and tearing of structures, capillary circumferential stress, formation of destructive liquid jets, acoustic microstreaming, transient hot-spots and creation of free radicals by the extreme temperatures achieved inside microbubbles upon inertial collapse (NCRP, 2002).

Early in the consideration of diagnostic ultrasound safety, Apfel (1982) and Flynn (1982) showed that cavitation was theoretically possible for diagnostic ultrasound. The thresholds for nucleation of cavitation in blood when ideal nuclei were present was analysed by Apfel and Holland (1991). The threshold ranged from about 0.4MPa at 1MHz to 1.1MPa at 10MHz, which are well within the capabilities of diagnostic ultrasound machines.

## 8.3 Pharmaceutical considerations and post-marketing surveillance

### 8.3.1 Drug approval and regulation

The clinical safety and efficacy of ultrasound contrast agents are evaluated by regulatory agencies before approval for use. These agents carry the general risks of bleeding and infection that pertain to any injection procedure. The agents are approved as injectable

Potential adverse drug reactions to ultrasound contrast agents have been detected in the sensitive porcine model of human imaging

drugs, but are not intended to be pharmacologically active. After intravenous injection, most agents are depleted from the circulation by the lungs or by the reticuloendothelial system, with a potential for adverse reactions. In research, anaphylactoid reactions are rare in rats, but are frequent and severe in swine, which makes this animal a sensitive test subject for drug reactions (e.g. [Szebeni et al., 2007](#)). Such reactions are known to occur from ultrasound contrast agents, including Definity ([Grauer et al., 1996](#)), Albunex ([Ostensen et al., 1992](#)) and Sonovue ([Bramos et al., 2008](#)). In a recent study of renal bio-effects in swine ([Miller et al., 2010a](#), see below), the reactions to contrast agent infusion complicated the experiments with 4 of 48 (8.3%) swine having life-threatening reactions. These reactions occurred even after brief pre-treatment with Diphenhydramine and Dexamethasone as a preventative measure.

The gases used in advanced ultrasound contrast agents can be of concern under some conditions, due to their relatively slow dissolution. In rodents, injection of gas-carrier contrast agents can induce intestinal and hepatic lesions due to the growth of relatively large gas bubbles ([Rasmussen et al., 2003](#); [Dirven et al., 2003](#)). In addition, intra-arterial injection of a contrast agent can lead to local blood–brain barrier disruption, without any ultrasound exposure ([Mychaskiw et al., 2000](#)). The mechanism of this effect is uncertain, but may be related to relatively large gas bodies containing perflutren gas, which can enter the brain directly by intra-arterial injection without the filtering effect of lung passage.

Optison and Definity were approved for patients with suboptimal echocardiograms in 1997 and 2001, respectively. In post-marketing surveillance, serious adverse events were reported, prompting a re-evaluation of the labelling for these agents in 2007. A “black box” warning of serious cardiopulmonary reactions and contraindications were added to the package inserts. The contraindications were later relaxed, but warnings remain for serious cardiopulmonary reactions, anaphylactoid reactions, systemic embolization in patients with cardiac shunts, high ultrasound mechanical index (MI) (greater than 0.8) and QTc prolongation in the electrocardiogram (ECG). These are noteworthy warnings for clinical diagnostic ultrasound. For example, QTc prolongation has recently become an important factor for drug safety evaluation ([Shah, 2005](#); [Whellan et al., 2009](#)). The guideline used by the FDA Center for Drug Evaluation and Research is that a QTc prolongation >20ms may be of concern ([CDER, 2005](#)). The package insert for Definity lists a warning that in a preclinical study, a QTc prolongation >30ms was noted in 29% of subjects (64/221). The revised package inserts are available on line at [FDA \(2008a\)](#) for Optison and [FDA \(2008b\)](#) for Definity. Sonovue was approved by the European Medicines Agency in 2001. A post-marketing review in 2004 resulted in an Urgent Safety Restriction issued in 2004, including suppression of the echocardiography indication. A scientific discussion is available on line at [EMA \(2004\)](#). The restrictions were later relaxed, and a new European Public Assessment Report issued ([EMA, 2008](#)).

Intra-arterial injection of contrast agents is not recommended for CEDUS examinations

Advanced ultrasound contrast agents have been the subject of regulatory review for serious adverse events reported in post-marketing surveillance

### 8.3.2 Recent epidemiological studies

The restrictions placed in the labelling of contrast agents have been controversial, and have stimulated several retrospective epidemiological studies of possible adverse effects. A study was conducted using records of 23,188 investigations using Sonovue

Recent epidemiological studies are reassuring that the 24 h mortality rates were similar for patients receiving contrast or non-contrast ultrasound examinations

in abdominal applications (Piscaglia *et al.*, 2006). Adverse events were reported in only 29 cases. No information was available on the prevalence of cardiac disease, the reasons for the examinations, the dose or ultrasound imaging utilized. No comparison was made with non-contrast patients. Kusnetzky *et al.* (2008) investigated the incidence of death within 24h of echocardiography examination in records of 12,475 patients without contrast and 6,196 with Definity. The death rate was 0.37% without contrast and 0.42% with contrast, which was not a statistically significant increase. Little patient information, such as the reason for the examinations, was available. A large database was used to examine 24h mortality after echocardiography in a study supported by Lantheus Medical Imaging (Main *et al.*, 2008). Echocardiography was performed during hospitalization in 4,242,712 patients without contrast enhancement and 58,254 (1.4% of the total) with Definity enhancement. The contrast dosage or ultrasound examination methods were not specified. The 24h mortality rates were 1.08% and 1.06% for non-contrast and contrast echocardiography patients, respectively. Multivariate logistic regression analysis indicated that contrast echocardiography patients were 24% less likely to die than patients not receiving a contrast agent (adjusted odds ratio 0.76, 95% confidence interval 0.70–0.82). However, only crude mortality data (not cause of death) were available for the patients, and the vast majority of patients did not receive ultrasound contrast agent due to clinical contraindications. Records of 5,250 consecutive adult patients were evaluated prospectively for adverse events after dobutamine–atropine stress echocardiography and myocardial contrast echocardiography (MCE) with Sonovue (Aggeli *et al.*, 2008). Patients with unstable angina, acute coronary syndrome in the previous 30 days and other similar criteria were excluded. An average of 2.5ml of Sonovue was given within 1min, and 1.7MHz real-time MCE [mechanical index (MI)=0.1–0.2] was used with intermittent agent-destructive scans (MI=1.7). There were no reported deaths. A variety of adverse events was reported, with the most prevalent event being dry-mouth (19.8%). The total of cardiac arrhythmia events was 6.3%, including 4% incidence of premature ventricular contractions. There was no comparison with non-contrast patient groups.

## 8.4 Research on biological effects induced by CEDUS

### 8.4.1 Bio-effects *in vitro*

The thresholds for membrane injury and lysis in monolayer cells have been shown to be very low and proportional to diagnostic ultrasonic frequency

Many *in vitro* studies of cavitation bio-effects have taken advantage of the nucleation ability of ultrasound contrast agents to improve and enhance results (Miller, 2007). These studies reveal the range of potential cellular bio-effects with contrast agents, but results are not necessarily directly applicable to *in vivo* conditions. Only a few studies have employed actual clinical ultrasound machines. Miller and Quddus (2000a) studied cell membrane bio-effects in epidermoid cell monolayers scanned using Optison and 3.5MHz diagnostic ultrasound. The monolayer was located at the top of the vessel during exposure so that the gas bodies would rise to become adjacent to the monolayer. Sonoporation (transient membrane permeabilization) was detected at RPAs as low as 0.23MPa in pulsed Doppler mode and 0.39MPa in B-mode. Phagocytic cells grown in monolayers and pre-incubated with Optison to attach the gas bodies to the cells were lysed by exposure to ultrasound produced by a diagnostic ultrasound machine operated

in spectral Doppler mode, with an RPA threshold of  $\sim 0.2$  MPa (Miller and Quddus 2001). In similar experiments using 2-cycle ultrasound pulses, the RPA thresholds for killing phagocytic cells pre-loaded with Optison showed a linear correlation ( $r^2=0.982$ ) with frequency over the 1–10 MHz range, increasing with a slope of  $\sim 0.06$  MPa/MHz (Miller and Dou 2004a). These data are plotted in Figure 8.1. These pressure thresholds were lower than those for nucleation of inertial cavitation and were proportional to the frequency (not its square root, as expected from the MI, see Figure 8.1). The frequency dependence of gas-body destabilization and cellular bio-effects observed for this *in vitro* system can be modelled by theory for shell stresses and acoustic microstreaming shear stress on cells (Miller and Dou, 2004b). The theory substantiated the observed linear dependence of thresholds on frequency. Owing to the design of this model monolayer system for maximum sensitivity to cellular bio-effects, the thresholds observed may approximate the lowest RPAs for which biologically significant bio-effects (*i.e.* cell killing) can be expected for CEDUS.

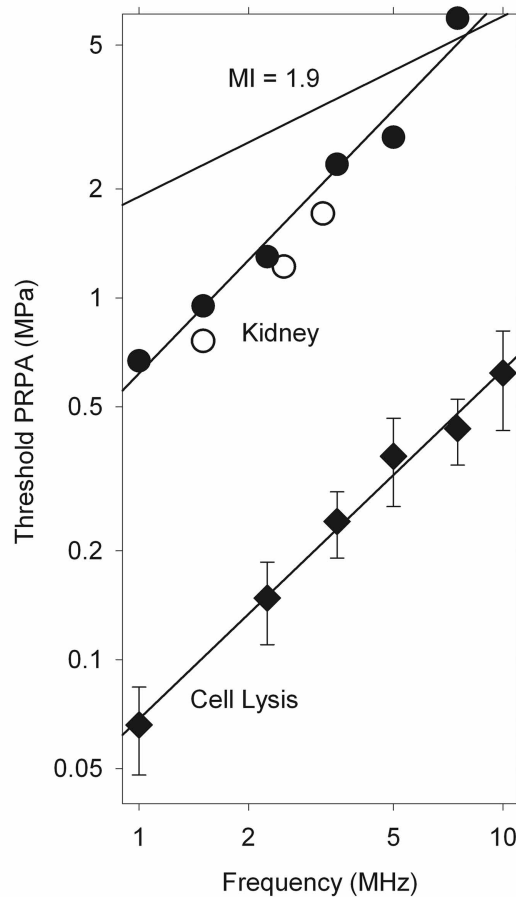


Figure 8.1. The frequency dependence of *in vitro* lysis of monolayer cells (diamonds) with contrast agent gas bodies in contact with the cells, determined using simulated diagnostic exposure. Thresholds for glomerular capillary haemorrhage in rat kidney are also plotted for diagnostic ultrasound exposure (open circles) and simulated diagnostic ultrasound (filled circles). The straight lines were fitted to the data by the least-squares method and indicate a strong dependence of CEDUS bio-effects thresholds (approximate proportionality to frequency). For comparison, the US-FDA maximum value of the on-screen mechanical index (MI=1.9) for diagnostic scanners is also plotted.

Capillary leakage and rupture in intestine and skeletal muscle has been shown to occur in mice for CEDUS, even for single image frames

### 8.4.2 Early research on CEDUS induced bio-effects *in vivo*

For pulsed ultrasound, the presence of Albunex gas bodies in the circulation enhanced the induction of petechiae in mouse intestine (Miller and Gies, 1998). The occurrence of microvascular injury to rat mesentery was examined by Kobayashi *et al.* (2002, 2003) using diagnostic ultrasound in an intra-vital preparation. A phased array probe was used at 1.8MHz RPAs of 0.14MPa (equivalent mechanical index, eMI ~0.10) or 0.82MPa (eMI ~0.61) with Levovist or Definity. Capillary ruptures and endothelial cell killing were observed in capillaries and venules (but not arterioles) for real-time imaging even for the low-MI setting. Micro-vessel rupture was observed to occur with intra-vital microscopy in rat spinotrapezius muscle (Skyba *et al.*, 1998). Optison gas bodies were injected and exposed with a 2.3MHz diagnostic ultrasound scanner in the harmonic imaging mode resulted in capillary rupture and non-viable cells for eMI values above 0.4. The induction of petechiae and capillary leakage by CEDUS was found in skeletal muscle *in vivo* by Miller and Quddus (2000b). The beam from a 2.5MHz diagnostic probe was aimed at the abdomens of anesthetized mice mounted in a water bath to provide conditions simulating human exposure. Muscle petechiae were significantly elevated relative to shams at RPAs above 0.64MPa (eMI=0.4). A single image frame was sufficient to produce petechiae and capillary rupture was also seen in fat, small intestine and Peyers' patches (intestinal lymph nodes).

### 8.4.3 Bio-effects in contrast-enhanced echocardiography

MCE with intermittent contrast destruction can induce ECG premature complexes in animals and humans

Ultrasound contrast agents were initially applied in echocardiography to opacify the left ventricular chamber and improve endocardial border delineation, which remains, at this time, the only indication approved in the USA. In addition, MCE can be used to image perfusion, which includes intermittent scans to destroy gas bodies in the myocardial microcirculation (Porter and Xie, 2010). During MCE, increased numbers of premature complexes (PCs) in the ECG were reported in humans with an experimental contrast agent by van der Wouw *et al.* (2000). Intermittent imaging was conducted at 1.66 MHz with a significant increase in PCs to about 1 per minute seen for end-systolic triggering at MI = 1.5, but not at MI = 1.1. Subsequently, this PC-effect of MCE has been reported independently (confirming the observation) in humans using experimental contrast agents (Chapman *et al.*, 2005), in dogs using a commercial agent (Okazaki *et al.*, 2004; Miller *et al.*, 2006), and also in rats with various agents (*e.g.* Li *et al.*, 2003, 2004; Vancraeynest *et al.*, 2009). The PCs from MCE are important because these provide a clinically observable indication of myocardial perturbation.

MCE can induce microvascular bio-effects including capillary leakage, capillary haemorrhage, release of cardiac injury biomarkers, and transient arrhythmia

The microvascular effects of MCE have been examined in several different animal models. Chen *et al.* (2002) imaged rat hearts at 1.3MHz with ECG triggering each 4 cardiac cycles with Optison or Definity, and found elevations of Troponin T in blood plasma, indicating myocardial damage, after 30min for MIs of 1.2 and 1.6. Clinical studies of MCE were conducted with Optison and power Doppler imaging at 1.7–1.9MHz each 1–3 heartbeats at end systole with no consistent changes in cardiac injury markers (Borges *et al.*, 2002; Knebel *et al.*, 2005). However, Vancraeynest *et al.* (2007) detected a significant release of cardiac

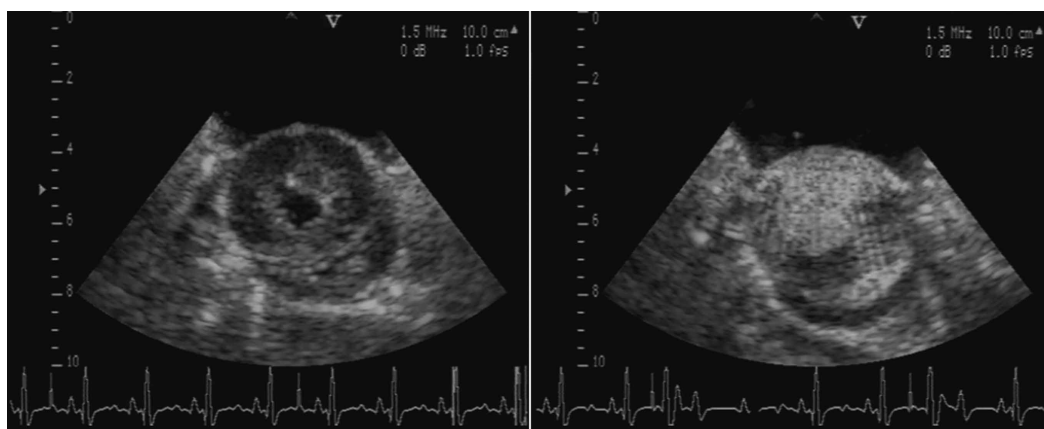


Figure 8.2. Ultrasound images for an open-chest canine model of MCE with intermittent imaging each 4 beats at end systole. The image on the left shows the normal B-mode image. The image on the right shows the same view after contrast-agent infusion and the accompanying ECG trace shows two PCs occurring just after the image triggers (vertical spikes).

injury biomarkers in humans, including troponin I in a group with 1.3 MHz MCE at an MI of 1.5. In rats, MCE at 1.7 MHz with Optison, Definity or Imagent was reported to induce microvascular permeabilization and PCs (Li *et al.*, 2003, 2004). Threshold RPAs above which effects were significant were about the same for all three agents, and were 1.0 MPa (eMI=0.8) for PCs and 0.54 MPa (eMI=0.41) for capillary haemorrhage. Similar bio-effects were seen in a canine model of MCE (Miller *et al.*, 2006), as shown for open-chest imaging in Figure 8.2. The resulting leakage of blue dye and petechiae is shown in Figure 8.3a. Vancraeynest *et al.* (2009) reported that triggered imaging at high MI with multiple doses of contrast agent over periods up to 30 min resulted in left ventricular dysfunction, ST-segment elevation and even the death of some rats (up to 5 of 6 rats at the longest duration).

Histologically defined microlesions with inflammatory cell infiltration induced by MCE were reported by Miller *et al.* (2005a). MCE with 1:4 end-systolic triggering was performed in rats at 1.5 MHz and 2 MPa (eMI=1.7) with Optison, which induced microvascular leakage, petechiae and cardiomyocytes with contraction band necrosis. Similar bio-effects were found histologically by Vancraeynest *et al.* (2006). The lethal cardiomyocyte injury could be characterized through use of Evans blue dye as a vital stain, as shown in Figure 8.3b (Miller *et al.*, 2005b). The thresholds and exposure response trends were found to be quite similar for PCs and cardiomyocyte death, as shown in Figure 8.4, with a good correlation between these bio-effects over a wide range of experimental conditions (Miller *et al.*, 2011). This result was consistent with the hypothesis that the PCs were a physiological response to the lethal cardiomyocyte injury.

PCs induced by MCE were associated with lethal cardiomyocyte injury and microlesion formation within the myocardium

#### 8.4.4 Bio-effects of CEDUS in kidney

The kidney appears to be an organ which is especially sensitive to CEDUS associated bio-effects, owing to the unique structure of the glomerular capillaries which filter liquid into the urinary space and tubules. Wible *et al.* (2002) found that glomerular

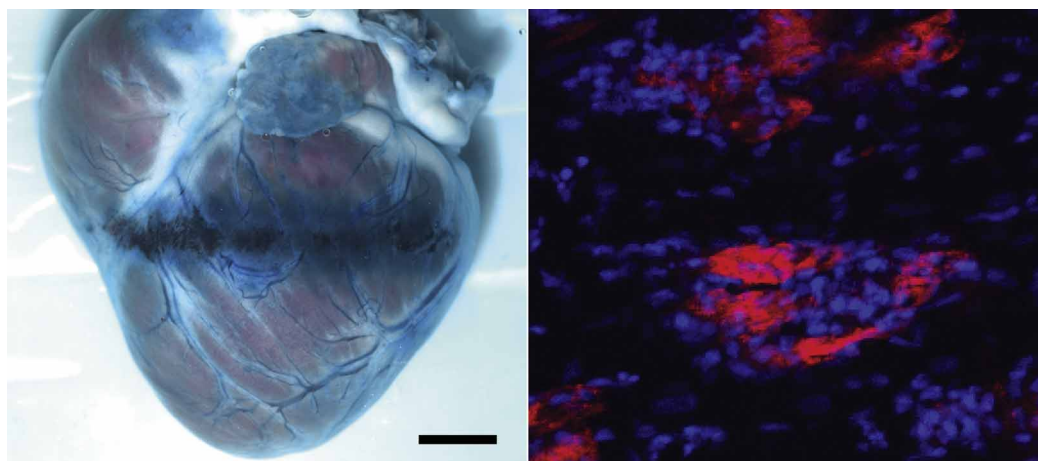


Figure 8.3. A canine heart (left) after exposure in an open-chest canine model of MCE showed petechial haemorrhages and leakage of Evans blue dye in the scan plane (scale bar 5 mm). MCE at relatively high RPAs induced lethal cardiomyocyte injury (right) indicated by the fluorescent red staining in a rat heart after 1 day. The nuclei of all cells present are indicated by the fluorescent blue staining.

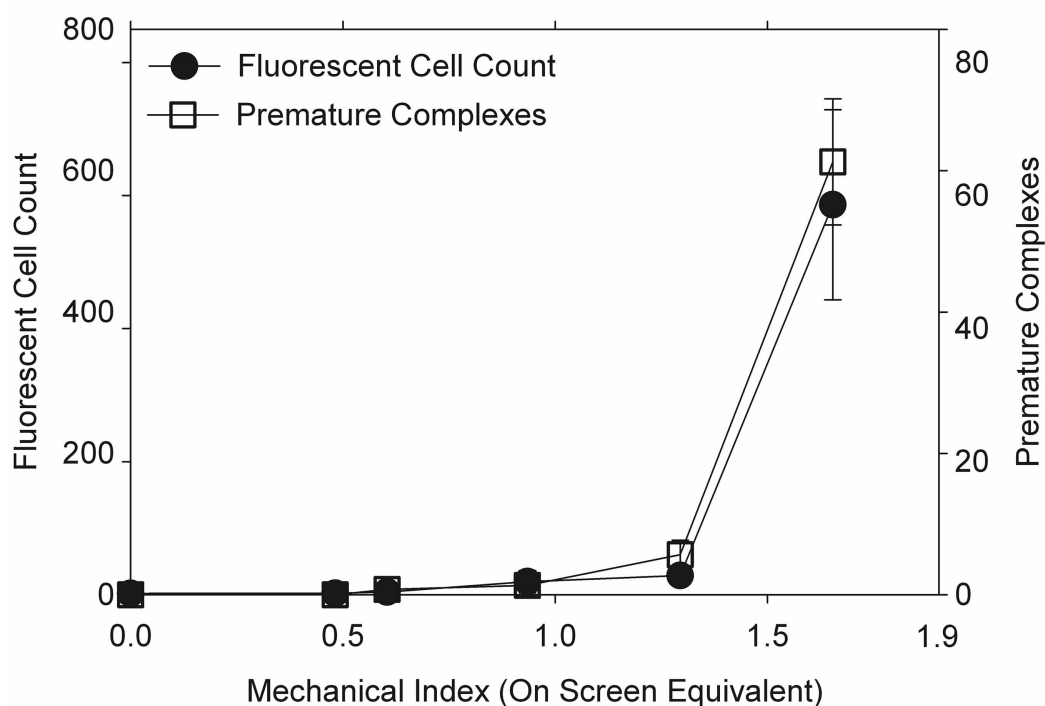


Figure 8.4. The fluorescent-cell counts and PCs found for MCE of rat hearts, plotted against the eMI.

GCH induced by CEDUS can obstruct and injure the tubules, and produce clinically detectable haematuria

capillary haemorrhage (GCH) was induced by CEDUS in rats. Ultrasound contrast agents including Optison were used with intermittent imaging. GCH into the proximal convoluted tubules was visible on the kidney surface within the scanned plane, and was statistically significant for an RPA of 1.26 (eMI = 0.94) at 1.8 MHz. A 1.5 MHz diagnostic exposure system was designed to simulate human clinical exposure in rats ([Miller et al., 2007a](#)). Exposure at 1.8 MPa with a 1 s trigger interval for 1 min during infusion of Definity

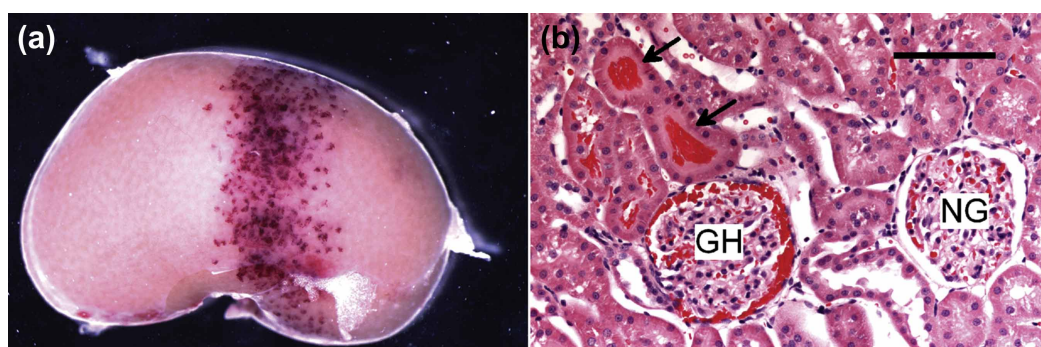


Figure 8.5. (a) A rat kidney after contrast-enhanced diagnostic ultrasound showing the pattern of petechia within the scan plane, which were visible on the surface of the kidney. (b) A histological section with a Bowman's space and proximal tubule (arrows) positive for glomerular capillary haemorrhage (GH) and a normal glomerulus (NG) (scale bar 0.1 mm).

produced of  $37\% \pm 5.0\%$  of the glomeruli in histology at the scan plane, which decreased to an apparent threshold of 0.73 MPa ( $eMI = 0.6$ ). Examples of the visible haemorrhage on the kidney surface, and of the histological appearance of the GCH are shown in Figure 8.5. The agent dosage used for this study in rats followed the human recommendation in the package insert, but the circulating gas-body dose may have been much less than that which would be delivered in humans, owing to substantial gas-body loss in the small animals (Miller *et al.*, 2010b). The kidney CEDUS in rats produced readily detectable haematuria, which paralleled the incidence of GCH as shown in Figure 8.6 (Williams *et al.*, 2007). In addition, many of the injured nephrons remained filled with tightly packed erythrocytes 24 h after imaging, with the degeneration seen in acute tubular necrosis. Histological observation of Bowman's space showed enlargement and clots, which were indicative of tubular obstruction (Miller *et al.*, 2009). For kidney CEDUS in swine, Jimenez *et al.* (2008) reported that GCH did not occur with Sonovue; however, the ultrasound probe was placed directly on the kidney, which located the cortex in the near-field of the probe with very low RPAs. In contrast, a study in swine showed that CEDUS using Definity did produce GCH in the focal zone, which was comparable to that seen in rats (Miller *et al.*, 2010a).

The frequency dependence of thresholds for GCH induced by CEDUS was examined in rats (Miller *et al.*, 2008b). Diagnostic ultrasound scanners were used for exposure at 1.5, 2.5, 3.2, 5.0 and 7.4 MHz and a laboratory exposure system was used at 1.0, 1.5, 2.25, 3.5, 5.0 and 7.5 MHz. The RPA thresholds for GCH were proportional to the ultrasound frequency (not its square root) at 0.5 MPa/MHz for diagnostic ultrasound and 0.6 MPa/MHz for the laboratory system, as shown in Figure 8.1. These results show that the frequency dependence of the on-screen MI does not have the correct frequency dependence for anticipating the GCH bio-effect.

The influence of imaging mode on GCH was investigated in rat kidney (Miller *et al.*, 2007b). B-mode flash echo imaging (FEI), colour Doppler (CD) FEI and real-time Doppler imaging at 1 frame per second were compared for 2.5 MHz and 2.6 MPa with Definity. B-mode induced  $38.6\% \pm 17.1\%$  GCH, while the CD mode gave  $19.6\% \pm 7.4\%$  GCH

Thresholds for GCH have a different frequency dependence than the MI

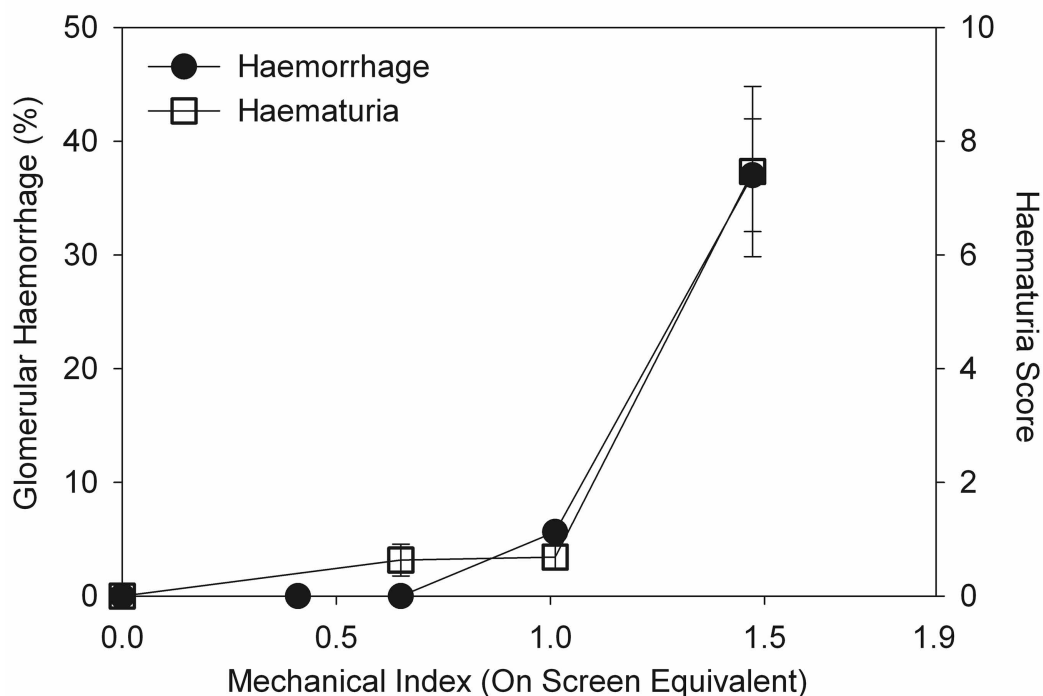


Figure 8.6. The percentage of glomeruli in the scan plane with evidence of capillary haemorrhage and the relative haematuria score after CEDUS in rats, plotted against the eMI.

The GCH bio-effect can be reduced by using special pulse sequences for contrast destruction

( $P < 0.02$ ) and the Doppler mode gave  $5.3\% \pm 3.8\%$  GCH ( $P < 0.001$ ), respectively. This result was surprising, because the Doppler mode delivered pulses for about 83.5 ms per image, compared to 15.8 ms and 0.53 ms for CD and B-modes, respectively. This finding of reduced GCH for slow frame rates suggests that GCH could be minimized in CEDUS examinations by using specially designed pulse-amplitude sequences for agent destruction scans.

#### 8.4.5 Bio-effects of CEDUS in tumours, liver and brain

Contrast-enhanced ultrasound scanning of various tissues can assist in the identification of malignant tumours but might also cause microvascular perturbations. Subcutaneous melanoma tumours in mice, which have an enhanced potential for lung metastasis, were scanned intermittently with 1.5 MHz diagnostic ultrasound during or after Definity injection (Miller and Dou, 2005). For ultrasound plus contrast agent, observation of a brightening of the tumour image confirmed the interaction of ultrasound with the contrast agent within the tumour. One day after scanning, the primary tumour was surgically removed, and the possible lung metastasis allowed to develop for 28 days. No significant increase in metastases was seen in the lungs.

The liver is often the subject of ultrasound examinations, and these can be improved by CEDUS. Effects of Levovist-aided ultrasound on rat liver was investigated by Shigeta *et al.* (2004). The on-screen MI values were 1.8 at 8 MHz and 0.7 at 12 MHz, and both were used

CEDUS did not increase metastasis in subcutaneous mouse tumours

CEDUS may induce platelet, hepatic or endothelial cell perturbation in liver

on each rat. The transducers were moved to expose the entire liver, which was examined by electron microscopy. Qualitative observation of the specimens revealed increased platelet aggregation and endothelial cell damage in the sinusoids for ultrasound plus contrast agent groups. Levovist was compared to an experimental agent by [Shigeta \*et al.\* \(2005\)](#). The gas bodies appeared to be taken up by some Kupffer (phagocytic liver cells) cells. In addition, the hepatic cells had distinct vascularization not seen in the sham or contrast only groups.

The possible alteration of the blood–brain barrier by contrast aided ultrasound was investigated by [Schlachetzki \*et al.\* \(2002\)](#) using Levovist and Optison and by using Sonovue. Transcranial colour coded sonography was performed on human volunteers using a 2–3.5 MHz phased array probe with maximal output settings. The contrast agent Magnevist was also injected intravenously, and evidence of microvascular leakage was sought using magnetic resonance imaging of the brain. There were no indications of focal signal enhancement attributable to extravasation of the Magnevist. Similar clinical research was conducted using Sonovue in patients with small vessel disease using intermittent 2.5 MHz imaging with a mean MI of 0.7, and no blood–brain barrier changes were detectable with contrast magnetic resonance imaging ([Jungehulsing \*et al.\*, 2008](#)).

CEDUS induced bio-effects may present opportunities for therapeutic benefits under special circumstances. Pulsed Doppler ultrasound is used in diagnosis of stroke patients. In patients with occluded middle cerebral artery being treated with tPA, continuous transcranial Doppler monitoring has been shown to improve the outcome of the treatment relative to placebo monitoring ([Alexandrov \*et al.\*, 2004](#)). This suggests that the ultrasound accelerated the thrombolysis. Ultrasound contrast agents may be used to improve transcranial signals, and addition of contrast agent has been tested for the continuous monitoring treatment with encouraging results ([Molina \*et al.\*, 2006](#); [Perren \*et al.\*, 2008](#)). For example, 2 h of 2 MHz continuous Doppler monitoring during tPA infusion was augmented by Levovist injection in three doses at 2, 20 and 40 min. The 2 h complete recanalization rate was statistically significantly higher in the CEDUS group (54.5%) relative to non-contrast Doppler (40.8%) and to tPA alone (23.9%), with no trend in observed intracranial haemorrhage. The future development of these intriguing stroke treatment methods are presently uncertain, owing to many possible variations in ultrasound application, contrast agent, thrombolytic drug and side effects ([Rubiera and Alexandrov, 2010](#)).

## 8.5 Discussion

Ultrasound contrast agents are suspensions of gas bodies prepared as an injectable drug. The gas bodies are engineered with stabilizing shells or lipid skins and contain slowly dissolving gasses such as perfluoropropane or sulphur hexafluoride. This design provides useful persistence times for the micron-sized gas bodies after intravenous injection, and strong echoes for imaging. CEDUS is valuable for echocardiography and abdominal imaging particularly of the liver and kidneys. CEDUS is primarily used to improve diagnostic value after sub optimal examinations. In addition, these agents also

Transcranial CEDUS does not appear to induce microvascular bio-effects in brain

CEDUS-enhanced thrombolysis may find beneficial application in stroke treatment

Contrast enhancement brings completely new imaging capabilities to diagnostic ultrasound

Ultrasound contrast agents can induce adverse patient reactions and cavitation activity generated by diagnostic ultrasound pulses can induce a range of harmful microscale bio-effects

The on-screen MI provides little dosimetric guidance for the safe use of CEDUS aside from a general indication of exposure within a specific examination

With training and attention to safety issues, the benefits of CEDUS can be delivered with a minimum of patient risk

bring a new dimension to diagnostic ultrasound by allowing the imaging of blood flow and tissue perfusion without ionizing radiation.

CEDUS also brings completely new patient risks to diagnostic ultrasound. In post-marketing surveillance, contrast agents have been associated with adverse patient reactions. These findings have led to new contraindications and warnings in package inserts. Worrisome concerns include cardiac arrhythmia and anaphylactoid reactions. Recent epidemiology studies have been reassuring in regard to possible fatal reactions within one day, but no information is available from large randomized controlled trials. In addition, destabilization of the gas bodies effectively nucleates ultrasonic cavitation from liberated microbubbles, which provides a potent mechanism for biological effects not normally associated with diagnostic ultrasound. For low pulse-pressure amplitudes, cellular injury and capillary leakage may occur. With intermittent imaging at high diagnostic pressure amplitudes, lethal injury of cardiomyocytes can occur with accompanying PCs in the ECG. In kidney, glomerular capillary rupture can occur leading to tubular obstruction and haematuria. Further research into the possible medical significance of these microscale bio-effects would be valuable for patient risk assessment.

The dosimetric characterization of CEDUS examinations has proven to be complex. The theoretical MI and its upper limit for diagnostic ultrasound were established without regard for any bio-effects. This exposure index does not relate to the destabilization of the microbubbles (Forsberg *et al.*, 2005) or the frequency dependence of microlesions, which occur well below the upper limit for diagnostic ultrasound, see Figure 8.1 (Miller *et al.*, 2008a,b). Bio-effects depend on RPA, agent dose, agent delivery, image mode and tissue properties. Low-MI imaging modes can lead to tissue injury through the use of high RPAs in agent clearance scans. Further consideration of CEDUS by regulatory agencies to develop better dosimetric parameters, to recommend specific agent-destructive scans that minimize bio-effects risk and to provide specific guidance on microscale bio-effects all would be of value for the advancement of CEDUS.

## 8.6 Conclusion

Physicians and sonographers should possess a general knowledge of CEDUS safety issues in order to maximize the risk-to-benefit ratio in medical imaging. Specifically, safety issues should be covered in training or certification for CEDUS. Guidance for the performance of CEDUS is available in recent publications from the American Society of Echocardiography (Mulvagh *et al.*, 2008) and the European Federation of Societies for Ultrasound in Medicine and Biology (Claudon *et al.*, 2008). Strategies for reducing possible ultrasound-induced bio-effects may be found in recent safety reviews (Barnett *et al.*, 2007; Miller *et al.*, 2008a; ter Haar, 2009). For a specific CEDUS examination the bio-effects risk may be minimized generally by keeping the MI for both imaging and contrast destruction less than 0.4, above which level bio-effects have been observed (AIUM, 2008). Finally, the contraindications, warnings and usage instructions found in package inserts of ultrasound contrast agents should be followed diligently to minimize patient risks.

## References

- AIUM. 2008. Bioeffects of Diagnostic Ultrasound with Gas Body Contrast Agents. Laurel, MD: American Institute of Ultrasound in Medicine. Available online at: <http://www.aium.org/publications/statements.aspx>.
- Aggeli C, Giannopoulos G, Roussakis G, Christoforatu E, Marinos G, Toli C, *et al.* 2008. Safety of myocardial flash-contrast echocardiography in combination with dobutamine stress testing for the detection of ischaemia in 5250 studies. *Heart*, 94, 1571–1577.
- Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, *et al.* 2004. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. *N Engl J Med*, 351, 2170–2178.
- Apfel RE. 1982. Acoustic cavitation: a possible consequence of biomedical uses of ultrasound. *Br J Cancer Suppl*, 45, 140–146.
- Apfel RE, Holland CK. 1991. Gauging the likelihood of cavitation from short-pulse, low-duty cycle diagnostic ultrasound. *Ultrasound Med Biol*, 17, 179–185.
- Averkiou M, Powers J, Skyba D, Bruce M, Jensen S. 2003. Ultrasound contrast imaging research. *Ultrasound Q*, 19, 27–37.
- Barnett SB, Duck F, Ziskin M. 2007. Recommendations on the safe use of ultrasound contrast agents. *Ultrasound Med Biol*, 33, 173–174.
- Bleeker HJ, Shung KK, Barnhart JL. 1990. Ultrasonic characterization of Albunex, a new contrast agent. *J Acoust Soc Am*, 87, 1792–1797.
- Borges AC, Walde T, Reibis RK, Grohmann A, Ziebig R, Rutsch W, *et al.* 2002. Does contrast echocardiography with Optison induce myocardial necrosis in humans? *J Am Soc Echocardiogr*, 10, 1080–1086.
- Bramos D, Tsirikos N, Kottis G, Pamboucas C, Kostopoulou V, Trika C. 2008. The acute effect of an echo-contrast agent on right ventricular dimensions and contractility in pigs. *J Cardiovasc Pharmacol*, 51, 86–91.
- Carstensen EL, Gracewski S, Dalecki D. 2000. The search for cavitation *in vivo*. *Ultrasound Med Biol*, 26, 1377–1385.
- CDER. 2005. Guidance for Industry. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs. Center for Drug Evaluation and Research. Rockville, MD: Food and Drug Administration. Available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf>.
- Chapman S, Windle J, Xie F, McGrain A, Porter TR. 2005. Incidence of cardiac arrhythmias with therapeutic versus diagnostic ultrasound and intravenous microbubbles. *J Ultrasound Med*, 24, 1099–1107.
- Chen S, Kroll MH, Shohet RV, Frenkel P, Mayer SA, Grayburn PA. 2002. Bioeffects of myocardial contrast microbubble destruction by echocardiography. *Echocardiography*, 19, 495–500.
- Chomas JE, Dayton P, May D, Ferrara K. 2001. Threshold of fragmentation for ultrasonic contrast agents. *J Biomed Optics*, 6, 141–150.
- Christiansen C, Kryvi H, Sontum PC, Skotland T. 1994. Physical and biochemical characterization of Albunex™, a new ultrasound contrast agent consisting of air-filled albumin microspheres suspended in a solution of human albumin. *Biotechnol Appl Biochem*, 19, 307–320.

- Church CC. 2002. Spontaneous homogeneous nucleation, inertial cavitation and the safety of diagnostic ultrasound. *Ultrasound Med Biol*, 28, 1349–1364.
- Claudon M, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, *et al.* 2008. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) – update 2008. *Ultraschall Med*, 29, 28–44.
- Cosgrove D, Blomley M. 2004. Liver tumors: evaluation with contrast-enhanced ultrasound. *Abdom Imaging*, 29, 446–454.
- Cosgrove D. 2006. Ultrasound contrast agents: an overview. *Eur J Radiol*, 60, 324–330.
- Dirven HA, Rasmussen H, Johnsen H, Videm S, Walday P, Grant D. 2003. Intestinal and hepatic lesions in mice, rats, and other laboratory animals after intravenous administration of gas-carrier contrast agents used in ultrasound imaging. *Toxicol Appl Pharmacol*, 188, 165–175.
- EMA. 2004. Sonovue Scientific Discussion. European Medicines Agency, EU. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Scientific\\_Discussion/human/000303/WC500055376.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000303/WC500055376.pdf).
- EMA. 2008. Sonovue Summary & Label. European Medicines Agency, EU. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000303/WC500055380.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000303/WC500055380.pdf).
- FDA, 2008a. Optison. Food and Drug Administration, USA. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/020899s011lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020899s011lbl.pdf).
- FDA. 2008b. Definity. Food and Drug Administration, USA. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/021064s009lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021064s009lbl.pdf).
- Flynn HG. 1982. Generation of transient cavitation in liquids by microsecond pulses of ultrasound. *J Acoust Soc Am*, 72, 1926–1932.
- Forsberg F, Shi WT, Goldberg BB. 2000. Subharmonic imaging of contrast agents. *Ultrasonics*, 38, 93–98.
- Forsberg F, Shi WT, Merritt CR, Dai Q, Solcova M, Goldberg BB. 2005. On the usefulness of the mechanical index displayed on clinical ultrasound scanners for predicting contrast microbubble destruction. *J Ultrasound Med*, 24, 443–450.
- Goldberg BB, Raichlen JS, Forsberg F (editors). 2001. Ultrasound Contrast Agents Basic Principles and Clinical Applications. 2nd Edition. London, UK: Martin Dunitz, pp. 1–416.
- Gramiak R. 1997. The beginnings of ultrasound contrast. In Ultrasound Contrast Agents, Goldberg BB (editor). London, UK: Martin Dunitz, pp. 1–8.
- Grauer SE, Pantely GA, Xu J, Giraud GD, Shiota T, Sahn DJ. 1996. Myocardial imaging with a new transpulmonary lipid-fluorocarbon echo contrast agent: experimental studies in pigs. *Am Heart J*, 132, 938–945.
- ter Haar G. 2009. Safety and bio-effects of ultrasound contrast agents. *Med Biol Eng Comput*, 47, 893–900.
- Jiménez C, de Gracia R, Aguilera A, Alonso S, Cirugeda A, Benito J, *et al.* 2008. *In situ* kidney insonation with microbubble contrast agents does not cause renal tissue damage in a porcine model. *J Ultrasound Med*, 27, 1607–1615.
- Jungehulsing GJ, Brunecker P, Nolte CH, Fiebach JB, Kunze C, Doepp F, *et al.* 2008. Diagnostic transcranial ultrasound perfusion-imaging at 2.5 MHz does not affect the blood–brain barrier. *Ultrasound Med Biol*, 34, 147–150.
- Killam A, Dittrich HC. 1997. Cardiac applications of Albunex and FS069. In Ultrasound Contrast Agents, Goldberg BB (editor). London, UK: Martin Dunitz Ltd, pp. 43–55.

- Knebel F, Schimke I, Eddicks S, Walde T, Ziebig R, Schattke S, *et al.* 2005. Does contrast echocardiography induce increases in markers of myocardial necrosis, inflammation and oxidative stress suggesting myocardial injury? *Cardiovasc Ultrasound*, 3, 21.
- Kobayashi N, Yasu T, Yamada S, Kudo N, Kuroki M, Kawakami M, *et al.* 2002. Endothelial cell injury in venule and capillary induced by contrast ultrasonography. *Ultrasound Med Biol*, 28, 949–956.
- Kobayashi N, Yasu T, Yamada S, Kudo N, Kuroki M, Miyatake K, *et al.* 2003. Influence of contrast ultrasonography with perflutren lipid microspheres on microvessel injury. *Circ J*, 67, 630–636.
- Krishna PD, Newhouse VL. 1997. Second harmonic characteristics of the ultrasound contrast agents Albunex and FS069. *Ultrasound Med Biol*, 23, 453–459.
- Kusnetzky LL, Khalid A, Khumri TM, Moe TG, Jones PG, Main ML. 2008. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: results in 18,671 consecutive studies. *J Am Coll Cardiol*, 51, 1704–1706.
- Li P, Cao LQ, Dou CY, Armstrong WR, Miller DL. 2003. Impact of myocardial contrast echocardiography on vascular permeability: an *in vivo* dose response study of delivery mode, ultrasound power and contrast dose. *Ultrasound Med Biol*, 29, 1341–1349.
- Li P, Armstrong WR, Miller DL. 2004. Impact of myocardial contrast echocardiography on vascular permeability: comparison of three different contrast agents. *Ultrasound Med Biol*, 30, 83–91.
- Main ML, Ryan AC, Davis TE, Albano MP, Kusnetzky LL, Hibberd M. 2008. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent (multicenter registry results in 4,300,966 consecutive patients). *Am J Cardiol*, 102, 1742–1746.
- Marmottant P, van der Meer S, Emmer M, Versluis M, de Jong N, Hilgenfeldt S, *et al.* 2005. A model for large amplitude oscillations of coated bubbles accounting for buckling and rupture. *J Acoust Soc Am*, 118, 3499–3505.
- Mattrey RF, Pelura TJ. 1997. Perfluorocarbon-based ultrasound contrast agents. In *Ultrasound Contrast Agents*, Goldberg BB (editor). London, UK: Martin Dunitz Ltd, pp. 83–99.
- Miller DL. 2000. The safety of ultrasound contrast agents. In *The Safe Use of Ultrasound in Medical Diagnosis*, ter Haar G, Duck FA (editors). 2nd Edition. London, UK: British Medical Ultrasound Society & The British Institute of Radiology, pp. 72–85.
- Miller DL. 2007. WFUMB safety symposium on echo-contrast agents: *in vitro* bioeffects. *Ultrasound Med Biol*, 33, 197–204.
- Miller DL, Dou C. 2004a. Membrane damage thresholds for 1- to 10-MHz pulsed ultrasound exposure of phagocytic cells loaded with contrast agent gas bodies *in vitro*. *Ultrasound Med Biol*, 30, 973–977.
- Miller DL, Dou C. 2004b. Theoretical gas body pulsation in relation to empirical gas-body destabilization and to cell membrane damage thresholds. *J Acoust Soc Am*, 116, 3742–3749.
- Miller DL, Dou C. 2005. Contrast-aided diagnostic ultrasound does not enhance lung metastasis in a mouse melanoma tumor model. *J Ultrasound Med*, 24, 349–354.
- Miller DL, Gies RA. 1998. Gas-body-based contrast agent enhances vascular bio-effects of 1.09 MHz ultrasound on mouse intestine. *Ultrasound Med Biol*, 24, 1201–1208.

- Miller DL, Quddus J. 2000a. Sonoporation of monolayer cells by diagnostic ultrasound activation of contrast-agent gas bodies. *Ultrasound Med Biol*, 26, 661–667.
- Miller DL, Quddus J. 2000b. Diagnostic ultrasound activation of contrast agent gas bodies induces capillary rupture in mice. *Proc Natl Acad Sci USA*, 97, 10179–10184.
- Miller DL, Quddus J. 2001. Lysis and sonoporation of epidermoid and phagocytic monolayer cells by diagnostic ultrasound activation of contrast agent gas bodies. *Ultrasound Med Biol*, 27, 1107–1113.
- Miller DL, Li P, Gordon D, Armstrong WF. 2005a. Histological characterization of microlesions induced by myocardial contrast echocardiography. *Echocardiography*, 22, 25–34.
- Miller DL, Li P, Dou C, Gordon D, Edwards CA, Armstrong WF. 2005b. Influence of contrast agent dose and ultrasound exposure on cardiomyocyte injury induced by myocardial contrast echocardiography in rats. *Radiology*, 237, 137–143.
- Miller DL, Driscoll EM, Dou C, Armstrong WF, Lucchesi BR. 2006. Microvascular permeabilization and cardiomyocyte injury provoked by myocardial contrast echocardiography in a canine model. *J Am Coll Cardiol*, 47, 1464–1468.
- Miller DL, Dou C, Wiggins RC, Wharram BL, Goyal M, Williams AR. 2007a. An *in vivo* rat model simulating imaging of human kidney by diagnostic ultrasound with gas-body contrast agent. *Ultrasound Med Biol*, 33, 129–135.
- Miller DL, Dou C, Wiggins RC. 2007b. Doppler mode pulse sequences mitigate glomerular capillary hemorrhage in contrast-aided diagnostic ultrasound of rat kidney. *IEEE Trans Ultrason Ferroelectr Freq Control*, 54, 1802–1810.
- Miller DL, Averkiou MA, Brayman AA, Everbach EC, Holland CK, Wible Jr JH, *et al.* 2008a. Bioeffects considerations for diagnostic ultrasound contrast agents. *J Ultrasound Med*, 27, 611–632.
- Miller DL, Dou C, Wiggins RC. 2008b. Frequency dependence of kidney injury induced by contrast-aided diagnostic ultrasound in rats. *Ultrasound Med Biol*, 34, 1678–1687.
- Miller DL, Dou C, Wiggins RC. 2009. Glomerular capillary hemorrhage induced in rats by diagnostic ultrasound with gas-body contrast agent produces intratubular obstruction. *Ultrasound Med Biol*, 35, 869–877.
- Miller DL, Dou C, Wiggins RC. 2010a. Contrast-enhanced diagnostic ultrasound causes renal tissue damage in a porcine model. *J Ultrasound Med*, 29, 1391–1401.
- Miller DL, Dou C, Wiggins RC. 2010b. *In vivo* gas body efficacy for glomerular capillary hemorrhage induced by diagnostic ultrasound in rats. *IEEE Trans BioMed Eng*, 57, 167–174.
- Miller DL, Dou C, Lucchesi BR. 2011. Are ECG premature complexes induced by ultrasonic cavitation electrophysiological responses to irreversible cardiomyocyte injury? *Ultrasound Med Biol*, 37, 312–320.
- Molina CA, Ribo M, Rubiera M, Montaner J, Santamarina E, Delgado-Mederos R, *et al.* 2006. Microbubble administration accelerates clot lysis during continuous 2-MHz ultrasound monitoring in stroke patients treated with intravenous tissue plasminogen activator. *Stroke*, 37, 425–429.
- Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, Bierig SM, *et al.* 2008. American Society of Echocardiography Consensus Statement on the clinical applications of ultrasonic contrast agents in echocardiography. *J Am Soc Echocardiogr*, 21, 1179–1201.
- Mychaskiw 2nd G, Badr AE, Tibbs R, Clower BR, Zhang JH. 2000. Optison (FS069) disrupts the blood-brain barrier in rats. *Anesth Analg*, 91, 798–803.

- Nanda NC, Schlieff R, Goldberg BB (editors). 1997. *Advances in Echo Imaging Using Contrast Enhancement*. 2nd Edition. London, UK: Kluwer Academic Publishers, pp. 1–698.
- NCRP. 2002. *Exposure Criteria for Medical Diagnostic Ultrasound: II. Criteria Based on All Known Mechanisms*. Report no. 140. Bethesda, MD: National Council on Radiation Protection and Measurements, pp. 213–239.
- Okazaki J, Ishikura F, Asanuma T, Otani K, Beppu S. 2004. Premature ventricular contraction during myocardial contrast echocardiography: relationship with imaging method, acoustic power and dose of contrast agent. *J Cardiol*, 43, 69–74.
- Ostensen J, Hede R, Myreng Y, Ege T, Holtz E. 1992. Intravenous injection of Albunex microspheres causes thromboxane mediated pulmonary hypertension in pigs, but not in monkeys or rabbits. *Acta Physiol Scand*, 144, 307–315.
- Perren F, Loulidi J, Poglia D, Landis T, Sztajzel R. 2008. Microbubble potentiated transcranial duplex ultrasound enhances IV thrombolysis in acute stroke. *J Thromb Thrombolysis*, 25, 219–223.
- Piscaglia F, Bolondi L, Italian Society for Ultrasound in Medicine and Biology (SIUMB) Study Group on Ultrasound Contrast Agents. 2006. The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations. *Ultrasound Med Biol*, 32, 1369–1375.
- Porter TM, Smith DA, Holland CK. 2006. Acoustic techniques for assessing the Optison destruction threshold. *J Ultrasound Med*, 25, 1519–1529.
- Porter TR, Xie F. 2010. Myocardial perfusion imaging with contrast ultrasound. *JACC Cardiovasc Imaging*, 3, 176–187.
- Rasmussen H, Dirven HA, Grant D, Johnsen H, Midtvedt T. 2003. Etiology of cecal and hepatic lesions in mice after administration of gas-carrier contrast agents used in ultrasound imaging. *Toxicol Appl Pharmacol*, 188, 176–184.
- Rubiera M, Alexandrov AV. 2010. Sonothrombolysis in the management of acute ischemic stroke. *Am J Cardiovasc Drugs*, 10, 5–10.
- Schlachetzki F, Hölscher T, Koch HJ, Draganski B, May A, Schuierer G, *et al.* 2002. Observation on the integrity of the blood–brain barrier after microbubble destruction by diagnostic transcranial color-coded sonography. *J Ultrasound Med*, 21, 419–429.
- Schlieff R, Schurmann R, Balzer T, Zomack M, Niendorf H. 1993. Saccharide based contrast agents. In *Advances in Echo Imaging Using Contrast Enhancement*, Nanda NC, Schlieff R (editors). Dordrecht, the Netherlands: Kluwer Academic Publishers, pp. 71–96.
- Schneider M, Arditi M, Barrau M, Brochot J, Broillet A, Bentrone R, *et al.* 1995. BR1: a new ultrasonographic contrast agent based on sulfur hexafluoride-filled microbubbles. *Invest Radiol*, 30, 451–457.
- Shah RR. 2005. Drugs, QTc interval prolongation and final ICH E14 guideline: an important milestone with challenges ahead. *Drug Saf*, 28, 1009–1028.
- Shi WT, Forsberg F, Tornes A, Ostensen J, Goldberg BB. 2000. Destruction of contrast microbubbles and the association with inertial cavitation. *Ultrasound Med Biol*, 26, 1009–1019.
- Shigeta K, Itoh K, Ookawara S, Taniguchi N, Omoto K. 2004. Endothelial cell injury and platelet aggregation induced by contrast ultrasonography in the rat hepatic sinusoid. *J Ultrasound Med*, 23, 29–36.
- Shigeta K, Itoh K, Ookawara S, Taniguchi N, Omoto K. 2005. The effects of Levovist and DD-723 in activating platelets and damaging hepatic cells of rats. *J Ultrasound Med*, 24, 967–974.

- Skyba DM, Price RJ, Linka AZ, Skalak TC, Kaul S. 1998. Direct *in vivo* visualization of intravascular destruction of microbubbles by ultrasound and its local effects on tissue. *Circulation*, 98, 290–293.
- Stride E, Saffari N. 2003. On the destruction of microbubble ultrasound contrast agents. *Ultrasound Med Biol*, 29, 563–573.
- Szebeni J, Alving CR, Rosivall L, Bünger R, Baranyi L, Bedöcs P, *et al.* 2007. Animal models of complement-mediated hypersensitivity reactions to liposomes and other lipid-based nanoparticles. *J Liposome Res*, 17, 107–117.
- Thomsen HS, Muller RN, Mattrey RF (editors). 1999. Trends in Contrast Media. Berlin, Germany: Springer-Verlag, pp. 1–480.
- Unger E, Fritz T, McCreery T, Sahn D, Barrette T, Yellowhair D, *et al.* 1997. Liposomes as myocardial perfusion ultrasound contrast agents. In *Ultrasound Contrast Agents*, Goldberg BB (editor). London, UK: Martin Dunitz, pp. 57–74.
- Vancraeynest D, Havaux X, Pouleur AC, Pasquet A, Gerber B, Beauloye C, *et al.* 2006. Myocardial delivery of colloid nanoparticles using ultrasound-targeted microbubble destruction. *Eur Heart J*, 27, 237–245.
- Vancraeynest D, Kefer J, Hanet C, Fillee C, Beauloye C, Pasquet A, *et al.* 2007. Release of cardiac bio-markers during high mechanical index contrast-enhanced echocardiography in humans. *Eur Heart J*, 28, 1236–1241.
- Vancraeynest D, Havaux X, Pasquet A, Gerber B, Beauloye C, Rafter P, *et al.* 2009. Myocardial injury induced by ultrasound-targeted microbubble destruction: evidence for the contribution of myocardial ischemia. *Ultrasound Med Biol*, 35, 672–679.
- Van der Wouw P, Brauns AC, Bailey SE, Powers JE, Wilde AA. 2000. Premature ventricular contractions during triggered imaging with ultrasound contrast. *J Am Soc Echocardi*, 13, 288–294.
- Whellan DJ, Green CL, Piccini JP, Krucoff MW. 2009. QT as a safety biomarker in drug development. *Clin Pharmacol Ther*, 86, 101–104.
- Wible Jr JH, Galen KP, Wojdyla JK, Hughes MS, Klibanov AL, Brandenburger GH. 2002. Microbubbles induce renal hemorrhage when exposed to diagnostic ultrasound in anesthetized rats. *Ultrasound Med Biol*, 28, 1535–1546.
- Williams AR, Wiggins RC, Wharram BL, Goyal M, Dou C, Johnson KJ, *et al.* 2007. Nephron injury induced by diagnostic ultrasound imaging at high mechanical index with gas body contrast agent. *Ultrasound Med Biol*, 33, 1336–1344.
- Wilson SR, Burns PN. 2010. Microbubble-enhanced US in body imaging: what role? *Radiology*, 257, 24–39.

# Chapter 9

## Epidemiological prenatal ultrasound studies

**Kjell Å. Salvesen**

*Department of Obstetrics and Gynaecology, Clinical Sciences,  
Lund University, Lund, Sweden*

### Summary

- Systematic reviews of epidemiological studies have shown no association between prenatal ultrasound and adverse outcomes.
- There is a weak statistical significant association between prenatal ultrasound and being non-right handed.
- Most epidemiologic evidence derives from B-mode scanners in commercial use 20–25 years ago, and acoustic outputs from modern scanners are higher. One must acknowledge that the available epidemiological data are limited.

### 9.1 Introduction

Ultrasound has an extraordinary safety record. It has been used in obstetrics for almost four decades with no proven harmful effects. However, absence of evidence of harm is not evidence of absence of harm. Thus, it is necessary to study the effect of prenatal ultrasound exposure on human populations directly before any definitive statements regarding risk can be made.

Epidemiological studies may be divided into observational and experimental studies (see [Figure 9.1](#)). The observational studies are in turn subdivided into descriptive and analytical studies. Descriptive studies are suitable for generating new hypotheses about associations between exposure and disease, whereas analytical studies are designed to test such hypotheses. The simplest descriptive study is the cross-sectional study, in which patients are examined only once. In a longitudinal study, the patients are followed over time, but the study is still classified as hypothesis generating. Analytical studies, on the other hand, have a prior hypothesis of a possible association between exposure and disease. They, in turn, are subdivided into cohort and case–control studies depending on whether the scientist starts out with a hypothesis about the exposure or about the disease. In the simplest case–control design, patients are examined only once, whereas

The best studies involve randomized controlled trials

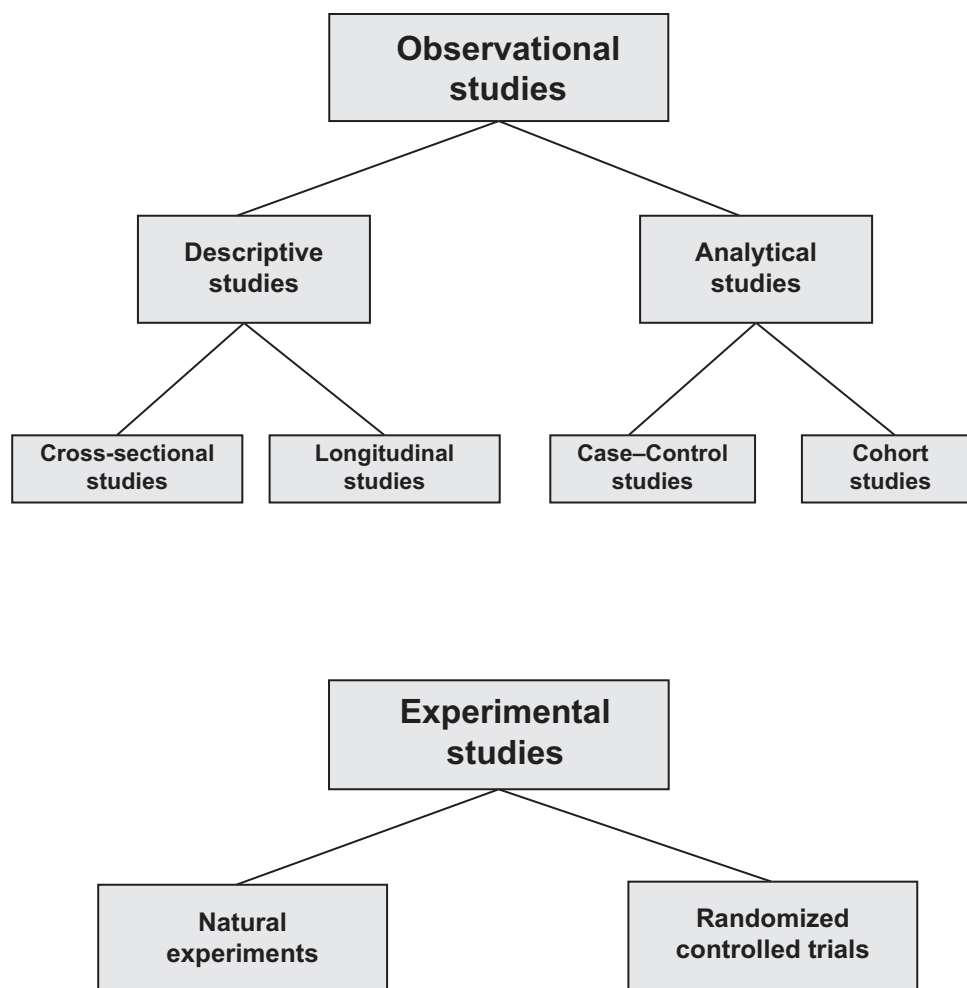


Figure 9.1. Classification of epidemiological studies.

in a cohort study it is necessary to follow patients over time. The randomized controlled trial is regarded as being the best way to examine possible cause–effect relationships in human populations. Evidence based medicine is usually derived from systematic review of data obtained from randomized controlled trials and/or observational studies. For interpretation of data derived from epidemiological studies, there is a hierarchy of studies based on study design and the quality of the research methods. Greatest value should be given to systematic reviews of randomized controlled trials, and less to cohort studies, case–control studies and other observational studies (in that order).

Two systematic reviews of epidemiological studies of the safety of ultrasound in pregnancy have been published (Torloni *et al.*, 2009; Whitworth *et al.*, 2010). The literature was searched extensively by the authors of the ISUOG-WHO review (up to October 2007) (Torloni *et al.*, 2009) and the Cochrane review (up to September 2009) (Whitworth *et al.*, 2010). The Cochrane review (Whitworth *et al.*, 2010) included all registered published and ongoing randomized controlled trials and quasi-randomized trials, but no analytical studies. The ISUOG-WHO review (Torloni *et al.*, 2009) included 16 randomized controlled trials, 13 cohort and 12 case–control studies published

between January 1950 and October 2007 that assessed any type of short- and long-term effects of at least one exposure to ultrasound during pregnancy. The authors screened 6716 titles/abstracts and included 61 papers in the systematic review. The outcomes assessed included maternal outcomes, perinatal outcomes, childhood growth, neurological development and school performance, non-right handedness, childhood malignancies, intellectual performance and mental diseases after childhood (Torloni *et al.*, 2009).

This chapter adopts the main results from the ISUOG-WHO systematic review and is expanded with the results from two epidemiological studies published after 2007 (Stålberg *et al.*, 2009; Heikkilä *et al.*, 2011). There is, however, one caveat about the data from epidemiological studies. The acoustic outputs from modern devices have increased 10–15-fold during the last decades (Henderson *et al.*, 1997), and most epidemiologic evidence derives from B-mode scanners in commercial use 20–25 years ago. If adverse effects of ultrasound during pregnancy are dose dependent, one must acknowledge that the available epidemiological data are limited.

Evidence based medicine is based on systematic reviews

## 9.2 Adverse perinatal outcomes

### 9.2.1 Birth weight

The question of whether ultrasound exposure *in utero* leads to reduced birth weight has probably been given more attention than any other perinatal outcome. This may be due to the existence of such an effect in some animal models, and/or because it is relatively quick and easy to measure. In 9 controlled trials involving over 35,000 women (Duff 1993; Ewigman *et al.*, 1993; Doppler French study group, 1997; Geerts *et al.*, 1996; Kieler *et al.*, 1998c; Mason *et al.*, 1993; Newnham *et al.*, 2004; Omtzigt *et al.*, 1994; Secher *et al.*, 1986) and 4 cohort studies with another 2000 women (Bellieni *et al.*, 2005; Geerts *et al.*, 2004; Smith, 1984; Stark *et al.*, 1984) exposure to ultrasound during pregnancy did not significantly influence the mean birth weight of the offspring. Similarly pooled odds ratios (ORs) from controlled trials and cohort studies do not seem to increase the proportions of low-birth weight children (Torloni *et al.*, 2009).

There is no convincing evidence that ultrasound exposure *in utero* affects birth weight

### 9.2.2 Perinatal mortality

Perinatal mortality has been regarded as the most important outcome to study in controlled trials related to introducing routine ultrasound screening into antenatal care. Sceptics about new technology argue that if one cannot demonstrate a reduction in perinatal mortality, pregnant women should not be offered routine ultrasound screening. From a safety perspective it is just as important to demonstrate that ultrasound exposure in pregnancy does not increase perinatal mortality.

Perinatal mortality has been studied in 13 controlled trials (Bakketeig *et al.*, 1984; Crowther *et al.*, 1999; Davies *et al.*, 1992; Duff, 1993; Eik-Nes *et al.*, 2000; Ewigman *et al.*, 1990; Ewigman *et al.*, 1993; Doppler French study group, 1997; Geerts *et al.*, 1996; Omtzigt *et al.*, 1994; Saari-Kemppainen *et al.*, 1990; Secher *et al.*, 1986; Waldenström, 1988). Among 46,553

There is no evidence that ultrasound exposure *in utero* affects perinatal morbidity or mortality

women included in the controlled trials there was a non-significant 14% reduction in perinatal mortality in the ultrasound group [OR 0.86, 95% confidence interval (CI) 0.70–1.07] (Torloni *et al.*, 2009). A similar non-significant reduction in perinatal mortality (OR 0.89, 95% CI 0.75–1.07) was found in a cohort study of approximately 210,000 Swedish women (Sylvan *et al.*, 2005).

### 9.2.3 Other perinatal outcomes

Obstetricians and neonatologists commonly assess neonatal morbidity and labour outcomes from the rates of preterm birth, low Apgar score at 5 min and admission to neonatal intensive care unit (NICU). Preterm birth has been studied in 8 controlled trials involving 34,000 women, and no association was found (Torloni *et al.*, 2009). Similarly, for low Apgar score at 5 min (12 controlled trials involving 22,000 women) and admission to NICU (13 controlled trials involving 33,000 women) there were no adverse effects of ultrasound during pregnancy (Torloni *et al.*, 2009).

## 9.3 Childhood malignancies

There is no evidence that ultrasound exposure *in utero* is associated with childhood malignancies

When the outcome under study is rare, such as with childhood malignancies, any approach other than the case–control design is unsuitable. For childhood malignancies there are data from 8 studies including more than 14,000 children (Bunin *et al.*, 1994; Cartwright *et al.*, 1984; Wilson and Waterhouse, 1984; Naumburg *et al.*, 2000; Shu *et al.*, 1994, 2002; Sorahan *et al.*, 1995; Ståhlberg *et al.*, 2008). No associations between prenatal ultrasound exposure and childhood malignancies have been found (Torloni *et al.*, 2009). Analyses have also been carried out for subgroups of malignancies. For leukaemia there are data from 5 case–control studies with 6334 children (Cartwright *et al.*, 1984; Wilson and Waterhouse, 1984; Naumburg *et al.*, 2000; Shu *et al.*, 1994, 2002), and for central nervous system (CNS) tumours there are data from 3 case–control studies with 1909 children (Bunin *et al.*, 1994; Cartwright *et al.*, 1984; Ståhlberg *et al.*, 2008). No associations have been found between prenatal ultrasound and leukaemia or CNS tumours.

## 9.4 Neurological development, dyslexia and speech development

These outcomes have been studied in two controlled trials with more than 5200 children (Kieler *et al.*, 1998a; Salvesen *et al.*, 1992; Salvesen *et al.*, 1994), one case–control study with 214 children (Campbell *et al.*, 1993) and one cohort study with 806 children (Stark *et al.*, 1984). The two observational studies (Campbell *et al.*, 1993; Stark *et al.*, 1984) published possible associations between prenatal ultrasound and dyslexia (Stark *et al.*, 1984) and delayed speech development (Campbell *et al.*, 1993). However, the controlled trials found no statistically significant associations between prenatal ultrasound and a long list of outcomes, such as dyslexia, delayed speech, stuttering, poor vocabulary, referral to speech therapist, various neurological tests, impaired vision or impaired hearing (Torloni *et al.*, 2009). Overall the results suggest that it is unlikely that prenatal ultrasound can “cause harm to the developing foetal brain”.

## 9.5 School performance

School performance has been studied in two controlled trials with almost 6500 children (Salvesen *et al.*, 1992; Stålberg *et al.*, 2009). Salvesen *et al.* followed up children at 8–9 years and found no association between prenatal ultrasound and poor school performance, including arithmetic scores, spelling, reading comprehension and oral reading (Salvesen *et al.*, 1992). Stålberg *et al.* followed up children at 15–16 years and found no statistically significant differences in school performance for boys or girls according to randomization or exposure to ultrasound in the second trimester (Stålberg *et al.*, 2009). Compared to those who were unexposed, boys exposed to ultrasound had a tendency towards lower mean school grades in general and in physical education, but the differences did not reach statistical significance (Stålberg *et al.*, 2009).

## 9.6 Intellectual performance and mental disease in adult life

In a Swedish cohort study of 7999 prenatally ultrasound exposed and 197,829 unexposed men aged 18 years, there was an increased risk of subnormal intellectual performance (OR 1.19, 95% CI 1.12–1.27) among exposed men (Kieler *et al.*, 2005). However, this association was probably confounded by sociogeographical factors, and within pairs of brothers there was no association between ultrasound exposure and intellectual performance. Thus, the authors concluded that “the study failed to demonstrate a clear association between ultrasound and intellectual performance” (Kieler *et al.*, 2005). In another Swedish cohort study of 370,945 individuals there was no association between prenatal ultrasound and schizophrenia (OR 1.47, 95% CI 0.99–2.16) or other psychoses (OR 1.03, 95% CI 0.80–1.33) (Stålberg *et al.*, 2007).

There is no evidence that ultrasound exposure *in utero* affects neurological development, dyslexia, speech development, school performance, intellectual performance or adult mental disease

## 9.7 Handedness

There is, however, one statistically significant association between prenatal ultrasound exposure and behaviour that holds up through all epidemiological studies and systematic reviews. The controversy is handedness.

The first meta-analysis demonstrating an association between ultrasound and non-right handedness was published in 1999 (Salvesen and Eik-Nes, 1999). There was no statistically significant difference in the prevalence of non-right handedness between ultrasound screened children and controls (OR 1.13, 95% CI 0.97–1.32), but there was a difference in a subgroup analysis of boys (OR 1.26, 95% CI 1.03–1.34) (Salvesen and Eik-Nes, 1999). In the most recent Cochrane review (Whitworth *et al.*, 2010) a conservative approach towards subgroup analyses is advocated. The Cochrane review reports no association between ultrasound and non-right handedness in an intention-to-treat analysis of all children (OR 1.12, 95% CI 0.92–1.36) and abstains from doing a gender specific subgroup analysis. The ISUOG-WHO review (Torloni *et al.*, 2009) has adopted a less conservative analytical approach and included two randomized trials (Salvesen *et al.*, 1993a,b; Kieler *et al.*, 1998b) and two cohort studies (Kieler *et al.*, 2001, 2002). The ISUOG-WHO review confirms the findings from the first meta-analysis (Salvesen and Eik-Nes, 1999), and adds: “When boys

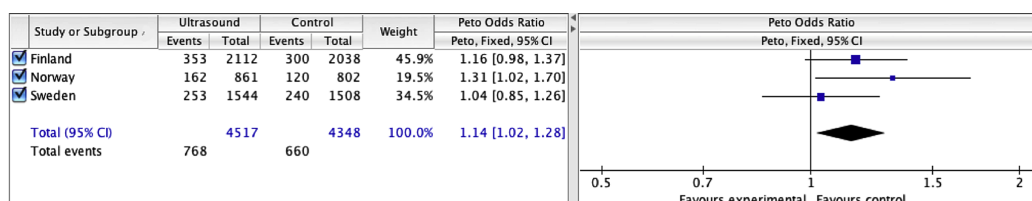


Figure 9.2. Non-right handedness among all children compared according to the randomized groups from three follow-up studies of randomized controlled trials (Heikkilä *et al.*, 2011; Salvesen *et al.*, 1993a; Kieler *et al.*, 1998c).

Table 9.1. Non-right handedness (NRH) according to randomized groups

Study	Ultrasound group (n)		Controls (n)		Weight (%)	OR (95% CI)
	NRH	Total	NRH	Total		
Heikkilä <i>et al.</i> , 2011	353	2112	300	2038	45.9	1.16 (0.98–1.37)
Salvesen <i>et al.</i> , 1993a	162	861	120	802	19.5	1.31 (1.02–1.70)
Kieler <i>et al.</i> , 1998b	253	1544	240	1508	34.5	1.04 (0.85–1.26)
Total	768	4517	660	4348	100	1.14 (1.02–1.28)

were considered separately, there is a weak association between ultrasound screening and being non-right handed, both in the randomized trials (OR 1.26, 95% CI 1.03–1.34) and in the cohort studies (OR 1.17, 95% CI 1.07–1.28)” (Torloni *et al.*, 2009).

A follow-up study of a Finnish randomized trial was published in 2011 (Heikkilä *et al.*, 2011). At first glance this study appeared reassuring since there is no difference in non-right handedness between ultrasound screened children and controls (OR 1.16, 95% CI 0.98–1.37), nor in a subgroup analysis of boys (OR 1.12, 95% CI 0.89–1.41) (Heikkilä *et al.*, 2011). However, when the results of the Finnish trial were included in a new meta-analysis of three randomized controlled trials, there was a statistically significant increased prevalence of non-right handedness in ultrasound screened children compared with controls (OR 1.14, 95% CI 1.02–1.28) (Salvesen, 2011) (Figure 9.2 and Table 9.1). The results in subgroups according to gender were consistent with overall results with no significant differences between boys and girls, but among boys the association became stronger when an exploratory analysis according to ultrasound exposure before 19–22 weeks was done (OR 1.30, 95% CI 1.10–1.53) (Salvesen, 2011).

A final conclusion of a possible association between prenatal ultrasound and handedness cannot yet be drawn. According to the data presented in the Cochrane review (Withworth, 2010), there is no statistically significant association between prenatal ultrasound and left-handedness. However, in the most recent meta-analysis including three randomized controlled trials there was a statistically significant association (Salvesen, 2011). If results from cohort studies are accepted (Kieler *et al.*, 2001, 2002), as was done in the

ISUOG-WHO review, the strength of the association was similar for randomized trials and cohort studies (Torloni *et al.*, 2009). Thus, the conclusion must be that five epidemiological studies report a 15% increase in the likelihood of sinistrality (in particular among males), and no other epidemiological evidence contradicts this association.

The discussion of prenatal ultrasound and left-handedness is complex and will not be extended here. An editorial explores this issue in detail (Salvesen, 2002). A statistical association between ultrasound and left-handedness should not lead to the conclusion that ultrasound causes harm to the developing brain. The current biological understanding of handedness is limited and partly contradictory to the epidemiological evidence (Salvesen, 2002).

## 9.8 Conclusion

Epidemiological studies have demonstrated no confirmed associations between prenatal ultrasound and adverse perinatal outcomes, childhood malignancies, neurological development, dyslexia, speech development, school performance, intellectual performance and adult mental disease. However, there is a weak statistical significant association between prenatal ultrasound and being non-right handed. This does not mean that there must be a causal relationship. We will have to live with uncertainty regarding ultrasound safety in the years to come.

## References

- Bakketeig L, Jacobsen G, Brodtkorb CJ, Eriksen BC, Eik-Nes SH, Ulstein MK, *et al.* 1984. Randomised controlled trial of ultrasonographic screening in pregnancy. *Lancet*, 2, 207–211.
- Bellieni CV, Buonocore G, Bagnoli F, Cordelli DM, Gasparre O, Calonaci F, *et al.* 2005. Is an excessive number of prenatal echographies a risk for fetal growth? *Early Hum Dev*, 81, 689–693.
- Bunin GR, Buckley JD, Boesel CP, Rorke LB, Meadows AT. 1994. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the Children's Cancer Group. *Cancer Epidemiol Biomark Prev*, 3, 197–204.
- Cartwright RA, McKinney PA, Hopton PA, Birch JM, Hartley AL, Mann JR, *et al.* 1984. Ultrasound examination in pregnancy and childhood cancer. *Lancet*, 2, 999–1000.
- Campbell JD, Elford RW, Brant RF. 1993. Case–Control study of prenatal ultrasonography exposure in children with delayed speech. *Can Med Assoc J*, 149, 1435–1440.
- Crowther CA, Kornman L, O'Callaghan S, George K, Furness M, Wilson K. 1999. Is an ultrasound assessment of gestational age at the first antenatal visit of value? A randomised clinical trial. *Br J Obstet Gynaecol*, 106, 1273–1279.
- Davies J, Gallivan S, Spencer J. 1992. Randomised controlled trial of Doppler ultrasound screening of placental perfusion during pregnancy. *Lancet*, 340, 1299–1303.
- Doppler French Study Group. 1997. A randomised controlled trial of Doppler ultrasound velocimetry of the umbilical artery in low risk pregnancies. *Br J Obstet Gynaecol*, 104, 419–424.
- Duff GB. 1993. A randomized controlled trial in a hospital population of ultrasound measurement screening for the small for dates baby. *Aust N Z J Obstet Gynaecol*, 33, 374–378.
- Eik-Nes SH, Salvesen KA, Okland O, Vatten LJ. 2000. Routine ultrasound fetal examination in pregnancy: the “Alesund” randomized controlled trial. *Ultrasound Obstet Gynecol*, 15, 473–478.

- Ewigman BG, Crane JP, Frigoletto FD, LeFevre M, Bain RP, McNellis D. 1993. Effect of prenatal ultrasound screening on perinatal outcome. RADIUS Study Group. *N Engl J Med*, 329, 821–827.
- Ewigman BG, LeFevre M, Hesser J. 1990. A randomized trial of routine prenatal ultrasound. *Obstet Gynecol*, 76, 189–194.
- Geerts L, Theron AM, Grove D, Theron GB, Odendaal HJ. 2004. A community-based obstetric ultrasound service. *Int J Gynaecol Obstet*, 84, 23–31.
- Geerts L, Brand E, Theron G. 1996. Routine ultrasound examinations in South Africa: cost and effect on perinatal outcome – a prospective randomised controlled trial. *Br J Obstet Gynaecol*, 103, 501–507.
- Henderson J, Whittingham TA, Dunn T. 1997. A review of the acoustic output of modern diagnostic ultrasound equipment. *BMUS Bull*, 10–14.
- Heikkilä K, Vuoksima E, Oksava K, Saari-Kemppainen A, Iivanainen M. 2011. Handedness in the Helsinki ultrasound trial. *Ultrasound Obstet Gynecol*, 37, 638–642. doi: 10.1002/uog.8962.
- Kieler H, Hellberg D, Nilsson S, Waldenström U, Axelsson O. 1998c. Pregnancy outcome among non-participants in a trial on ultrasound screening. *Ultrasound Obstet Gynecol*, 11, 104–109.
- Kieler H, Haglund B, Cnattingius S, Palmgren J, Axelsson O. 2005. Does prenatal sonography affect intellectual performance? *Epidemiology*, 16, 304–310.
- Kieler H, Ahlsten G, Haglund B, Salvesen K, Axelsson O. 1998a. Routine ultrasound screening in pregnancy and the children's subsequent neurologic development. *Obstet Gynecol*, 91, 750–756.
- Kieler H, Axelsson O, Haglund B, Nilsson S, Salvesen K. 1998b. Routine ultrasound screening in pregnancy and the children's subsequent handedness. *Early Hum Dev*, 50, 233–245.
- Kieler H, Cnattingius S, Haglund B, Palmgren J, Axelsson O. 2001. Sinistrality – a side-effect of prenatal sonography: a comparative study of young men. *Epidemiology*, 12, 618–623.
- Kieler H, Cnattingius S, Palmgren J, Haglund B, Axelsson O. 2002. First trimester ultrasound scans and left-handedness. *Epidemiology*, 13, 370.
- Mason GC, Lilford RJ, Porter J, Nelson E, Tyrell S. 1993. Randomised comparison of routine versus highly selective use of Doppler ultrasound in low risk pregnancies. *Br J Obstet Gynaecol*, 100, 130–133.
- Naumburg E, Bellocco R, Cnattingius S, Hall P, Ekblom A. 2000. Prenatal ultrasound examinations and risk of childhood leukaemia: case-control study. *Br Med J*, 320, 282–283.
- Newnham J, Doherty DA, Kendall GE, Zubrick SR, Landau LL, Stanley FJ. 2004. Effects of repeated prenatal ultrasound examinations on childhood outcome up to 8 years of age: follow-up of a randomised controlled trial. *Lancet*, 364, 2038–2044.
- Omtzigt AM, Reuwer PJ, Bruinse HW. 1994. A randomized controlled trial on the clinical value of umbilical Doppler velocimetry in antenatal care. *Am J Obstet Gynecol*, 170, 625–634.
- Saari-Kemppainen A, Karjalainen O, Ylostalo P, Heinonen OP. 1990. Ultrasound screening and perinatal mortality: controlled trial of systematic one-stage screening in pregnancy. *Lancet*, 336, 387–391.
- Salvesen KÅ, Vatten LJ, Bakketeig LS, Eik-Nes SH. 1994. Routine ultrasonography *in utero* and speech development. *Ultrasound Obstet Gynecol*, 4, 101–103.
- Salvesen KÅ, Bakketeig LS, Eik-Nes SH, Undheim JO, Økland O. 1992. Routine ultrasonography *in utero* and school performance at age 8–9 years. *Lancet*, 339, 85–89.

- Salvesen KÅ, Vatten LJ, Eik-Nes SH, Hugdahl K, Bakketeig LS. 1993a. Routine ultrasonography *in utero* and subsequent handedness and neurological development. *Br Med J*, 307, 159–164.
- Salvesen KÅ, Eik-Nes SH, Vatten LJ, Hugdahl K, Bakketeig LS. 1993b. Routine ultrasound scanning in pregnancy – Authors’ reply. *BMJ*, 307, 1562.
- Salvesen KÅ, Eik-Nes SH. 1999. Ultrasound during pregnancy and subsequent childhood non-right handedness: a meta-analysis. *Ultrasound Obstet Gynecol*, 13, 241–246.
- Salvesen KÅ. 2002. Ultrasound and left-handedness: a sinister association? *Ultrasound Obstet Gynecol*, 19, 217–221.
- Salvesen KÅ. 2011. Ultrasound in pregnancy and non-right handedness – meta-analysis of randomized trials. *Ultrasound Obstet Gynecol*, 38, 267–271.
- Secher NJ, Hansen PK, Lenstrup C, Eriksen PS. 1986. Controlled trial of ultrasound screening for light for gestational age (LGA) infants in late pregnancy. *Eur J Obstet Gynecol Reprod Biol*, 23, 307–313.
- Shu XO, Jin F, Linet MS, Zheng W, Clemens J, Mills J, *et al.* 1994. Diagnostic X-ray and ultrasound exposure and risk of childhood cancer. *Br J Cancer*, 70, 531–536.
- Shu XO, Potter JD, Linet MS, Severson RK, Han D, Kersey JH, *et al.* 2002. Diagnostic X-rays and ultrasound exposure and risk of childhood acute lymphoblastic leukemia by immunophenotype. *Cancer Epidemiol Biomarkers Prev*, 11, 177–185.
- Smith CB. 1984. Birth weights of fetuses exposed to diagnostic ultrasound. *J Ultrasound Med*, 3, 395–396.
- Sorahan T, Lancashire R, Stewart A, Peck I. 1995. Pregnancy ultrasound and childhood cancer: a second report from the Oxford Survey of Childhood Cancers. *Br J Obstet Gynaecol*, 102, 831–832.
- Stark C, Orleans M, Haverkamp A, Murphy J. 1984. Short and long term risks after exposure to diagnostic ultrasound *in utero*. *Obstet Gynecol*, 63, 194–200.
- Stålberg K, Haglund B, Axelsson O, Cnattingius S, Pfeifer S, Kieler H. 2008. Prenatal ultrasound and the risk of childhood brain tumour and its subtypes. *Br J Cancer*, 98, 1285–1287.
- Stålberg K, Haglund B, Axelsson O, Cnattingius S, Hultman CM, Kieler H. 2007. Prenatal ultrasound scanning and the risk of schizophrenia and other psychoses. *Epidemiology*, 18, 577–582.
- Stålberg K, Axelsson O, Haglund B, Hultman CM, Lambe M, Kieler H. 2009. Prenatal ultrasound exposure and children’s school performance at age 15–16: follow-up of a randomized controlled trial. *Ultrasound Obstet Gynecol*, 34, 297–303.
- Sylvan K, Ryding EL, Rydhstrom H. 2005. Routine ultrasound screening in the third trimester: a population based study. *Acta Obstet Gynecol Scand*, 84, 1154–1158.
- Torloni MR, Vedmedovska N, Merialdi M, Betran AP, Allen T, Gonzalez R, *et al.* 2009. Safety of ultrasonography in pregnancy: WHO systematic review of the literature and meta-analysis. *Ultrasound Obstet Gynecol*, 33, 599–608.
- Waldenström U, Axelsson O, Nilsson S, Eklund G, Fall O, Lindeberg S, *et al.* 1988. Effects of routine one-stage ultrasound screening in pregnancy: a randomised controlled trial. *Lancet*, 2, 585–588.
- Whitworth M, Bricker L, Neilson JP, Dowswell T. 2010. Ultrasound for fetal assessment in early pregnancy. *Cochrane Database Syst Rev*, (4), Art. No.: CD007058. doi: 10.1002/14651858.CD007058.pub2.
- Wilson LMK, Waterhouse JA. 1984. Obstetric ultrasound and childhood malignancies. *Lancet*, 2, 997–999.

# Chapter 10

## Safety standards and regulations: the manufacturers' responsibilities

**Francis A. Duck**

*University of Bath, Bath, UK*

### Summary

- All medical diagnostic ultrasound equipment must be manufactured to conform to safety standards and regulations.
- Separate regulations exist in Europe, in the USA and internationally.
- The International Electrotechnical Commission sets international safety standards, including maximum allowable transducer surface temperatures.
- The United States Food and Drug Administration (FDA) sets upper limits for ultrasound exposure.
- In order to use the highest output levels allowed by the FDA, manufacturers must display safety indices: the mechanical index and the thermal index.
- In Europe, the Medical Devices Directive requires manufacturers to demonstrate both safety and measurement accuracy.

### 10.1 Introduction

The design and manufacture of all medical equipment, including diagnostic ultrasound equipment, is subject to a number of regulatory controls and standards that are intended to ensure that it may be operated safely. The ultrasound equipment industry is now truly international, and as a result the most important regulations are those that have international status, or have an equivalent impact. The three sources of regulations and standards which have effect in the UK are:

1. Standards of the International Electrotechnical Committee (IEC). IEC standards are generally accepted in full as European Standards and also as British Standards.
2. Standards and regulations used in the USA, including those of the US Government Department of Health and Human Services, Food and Drug Administration (FDA).
3. European directives.

Ultrasound safety is subject to national and international standards and regulations

Table 10.1. The main purposes of some key regulations and standards for diagnostic ultrasound safety.

Body	Regulation or standard	Purpose
FDA	510(k) (FDA, 1997)	To limit the maximum allowed acoustic output
AIUM/NEMA	"Output Display Standard" (AIUM/NEMA, 1998)	To define methods for calculation and display of safety indices
IEC	IEC60601 Part 1 (IEC, 2005)	To regulate for the safe design and manufacture of all medical equipment, including thermal, electrical and mechanical aspects
IEC	IEC60601 Part 2-37 (IEC, 2001)	To define display of safety indices, and to limit transducer surface temperature
IEC	IEC62359 (IEC, 2006)	To define safety indices
EC	MDD (European Communities, 1993)	To set general requirements for safety and measurement precision for all medical devices

Each of the regulations has a particular primary purpose, which generally distinguishes it from the others. These purposes are set out in Table 10.1 for some of the more important of them. The regulations are referred to by their commonly-used abbreviations. Details are given later in the text. Inspection of Table 10.1 makes clear that there is only one regulation that serves to limit the ultrasound output that transducers may emit, and that is due to the FDA in the USA. Further regulations exist which serve as general standards for safety for all electro-medical equipment, of which ultrasound diagnostic equipment is one part, but which equally apply to such devices.

Each safety regulation or standard has a different purpose

## 10.2. International Standards from the International Electrotechnical Commission

### 10.2.1 IEC60601 Part 1: General safety requirements

The general requirements for the safe design of electro-medical equipment are set out in IEC60601 Part 1 (IEC, 2005). Contained within this standard are requirements for the safe design of mechanical parts, for electrical safety and for thermal safety. Of specific importance are the electrical earth leakage current associated with an ultrasound transducer (up to 1 kHz), which for normal condition use is 0.5 mA, and the patient leakage current, limited to 100 mA for general use and to 10 mA for intra-cardiac use. The

All ultrasound scanners also must conform to electrical and thermal safety standards

safe management of heated parts that may make contact with the body is also considered. Particular specifications for ultrasound transducers are discussed below.

### 10.2.2 IEC60601 Part 2-37: Ultrasound diagnostic and monitoring equipment

IEC60601-2-37 sets limits to transducer surface temperatures, and specifies use of safety indices

The IEC standard for diagnostic and monitoring equipment, IEC60601-2-37 (IEC, 2001), sets some further requirements over those set in IEC60601 Part 1. It specifies how a user shall be informed about potential hazard, through displayed indices related to exposure and safety. This approach to protection casts a responsibility on the user, requiring for its success an appropriate level of training and competence for all practitioners using ultrasound diagnostic equipment. The philosophy and definitions for index display are identical to those developed in the USA in the early 1990s, and first published in the so-called "Output Display Standard" (ODS; AIUM/NEMA, 1998) details of which are given in section 10.3. The methods for determination of the safety indices are also published in IEC62359 (IEC, 2006). IEC60601-2-37 also places limits on the allowed temperature of the surface of the transducer (Table 10.2). In air this is 50 °C, considerably higher than the temperature of 43 °C allowed in contact with tissue. Higher increases in temperature are allowed for transducers in contact with the skin than for those used internally, such as transvaginal or intra-rectal probes. These temperatures are not only of theoretical interest, since many scanners can now drive transducers at levels that approach them.

## 10.3. Regulations and standards from the USA

### 10.3.1 FDA regulations (510k)

FDA regulations are very influential in setting ultrasound output levels

The USA operates its own regulatory structure, through its FDA. These regulations have until now had world-wide impact, because they control the sale of ultrasound equipment in the USA, and the actions of US manufacturers elsewhere in the world. In spite of the emergence of stronger international and, now, European regulations, it seems likely that the FDA regulations will continue to influence manufacturers for a considerable time. The current situation in the USA is set out below.

Table 10.2. Limits on surface temperature and surface temperature rise specified by IEC60601-2-37 Amendment 1 (IEC, 2001).

	In air	On tissue (external use)	On tissue (internal use)
Maximum temperature (°C)	50	43	43
Maximum temperature rise (°C)	27	10	6

Within the US Department of Health and Human Services, the FDA receives applications for “market approval” to sell equipment, through a process known as “510(k)” from the code used on earlier guidance documents issued by the FDA. The most recent guidance document was issued in 1997 (FDA, 1997). Two “tracks” are defined. These are known as Track 1 and Track 3. A very large proportion of modern equipment is designed according to requirements of Track 3, and so this is given emphasis here. Track 3 gives the provision for exploiting higher time-averaged intensities than those that were available under Track 1. These are allowed provided that the equipment has “real-time labelling” of exposure in accordance with the ODS published by AIUM/NEMA (American Institute of Ultrasound in Medicine/National Electrical Manufacturers' Association) (AIUM/NEMA, 1998). In order to comply, values of mechanical index (MI) and thermal index (TI) must be displayed to the user. Details of the requirements of the ODS are given below.

The FDA sets maximum allowed levels for output exposure. The highest intensities are allowed only if safety indices can be displayed

The upper limits set by the FDA for Track 3 clearance are set out in Table 10.3. Two categories of use are defined: one small category is for equipment that is designed for use exclusively for ophthalmology, and the second is for equipment for all other applications, including obstetrics. Limiting values are given for four exposure quantities: derated (*i.e.* estimated *in situ*) spatialpeak, temporal-average intensity ( $I_{\text{spta,d}}$ ), derated spatialpeak, pulse-average intensity ( $I_{\text{sppa,d}}$ ), MI and TI. (The suffix d is used here to indicate de-rating.) Definitions of the two safety indices, MI and TI, are given below.

FDA limits are the same for all clinical uses except for ophthalmology

The limiting values for pulse-average intensity and MI are not independent: provided that either one of them lies below the specified limit then the other is allowed to exceed it. However, the limits  $\text{TI}=1.9$  and  $I_{\text{sppa,d}}=190 \text{ W cm}^{-2}$  are deemed to be approximately equivalent. TI is used to control output only for ophthalmic applications. For any other application, manufacturers are required to provide the FDA with a justification for any use when the TI exceeds 6.0, but no absolute limiting value is specified.

For all quantities the value is not that measured in water but the “estimated *in situ*” value. This is derived by de-rating the free-field value by  $0.3 \text{ dB cm}^{-1} \text{ MHz}^{-1}$ . The position of which each quantity is to be calculated is where a derated value is maximum; for time-averaged intensity it is where  $I_{\text{ta,d}}$  is greatest; for MI it is where the derated pulse-intensity integral is greatest.

FDA sets limits using estimated *in situ* values. These are lower than the equivalent values in water

Table 10.3. The limits set by the US FDA on acoustic exposure allowed under “Track 3”. At least one of MI and  $I_{\text{sppa,d}}$  must be lower than the specified limit, but not necessarily both (FDA, 1997).

	Derated $I_{\text{spta,d}}$ ( $\text{mW cm}^{-2}$ )	Derated $I_{\text{sppa,d}}$ ( $\text{W cm}^{-2}$ )	MI	TI
All applications except ophthalmology	720	190	1.9	(6.0)*
Ophthalmology	50	Not specified	0.23	1.0

\*NB: The value of  $\text{TI} = 6$  is not an upper limit for non-ophthalmic applications. Manufacturers are required to give a justification if conditions exist for which the TI exceeds 6.0.

The potential for higher output levels is particularly important in obstetric scanning

The changes that were made to the FDA regulations in the early 1990s have meant that higher exposures, commonly associated with Doppler applications, may now exist on equipment intended for obstetric applications, for which the allowed upper limit for time-average intensity has increased about eight times.

Values of other quantities also have to be submitted to the FDA. These include total acoustic power, centre frequency, beam dimensions at the focus, position of the measurement, pulse repetition frequency and focal length. Tables giving values for these quantities are often included with the technical documentation supplied with the scanner.

### 10.3.2. AIUM/NEMA ODS

Definition of MI

As noted above, FDA Track 3 requires conformance with the AIUM/NEMA ODS (AIUM/NEMA, 1998). The quantities in this standard are derived by calculation from measured acoustic pressure, power, intensity and frequency, and are intended to give guidance as to the possibility that the operating conditions might cause heating or mechanical effects. The following definitions also form part of IEC standards 60601-2-37 and 62359 (IEC, 2001, 2006).

The MI is calculated from the peak derated rarefaction pressure,  $p_{r,d}$  in MPa:

$$MI = \frac{p_{r,d}}{\sqrt{f}} \quad (10.1)$$

where  $f$  is the centre frequency in MHz; MI is given without units.

Definition of TI

TI is defined as  $W/W_{deg}$ , where  $W$  is the acoustic power and  $W_{deg}$  is the power required to cause a maximum temperature rise of 1 °C under identical conditions of transducer, beam and tissue. TI is therefore taken to indicate broadly a reasonable estimate of the greatest steady-state temperature rise in degrees Celsius.

There are three TI categories, for soft tissue, for bone-at-focus and for cranial bone

There are a number of different formulae for TI. These depend on the expected target, on transducer size, and on whether the beam is scanned or unscanned (see Figure 10.1). There are three TI categories related to three targets: soft tissue (TIS), bone-at-focus (TIB) and adult cranial (TIC).

Formulae for soft-tissue TI depend on frequency: those for bone do not. Both depend on acoustic power

The formulae for TI can be simplified and summarized by dividing them into two types, those intended to predict temperature rise in soft tissue, and those for bone. In the first case, for soft-tissue heating, the formulae have the form  $TI = A f W$ , where  $f$  is the acoustic frequency, and  $W$  is the acoustic power. The constant  $A$  takes defined values for the specific scan modes and geometry (for example it is 1/210 for B-mode scanning). For exposure of bone, the formulae are of the form  $TI = B W$ , where the constant  $B$  again takes defined values. TI for bone does not depend on the acoustic frequency.

TI formulae also differ as to where the temperature rise is estimated. For stationary beams, for example for M-mode or spectral pulsed Doppler, greatest temperatures are

reached deeper within the tissue (for example see [Figure 10.1b](#)). On the other hand it is assumed that when beams are scanned the greatest heating is at the surface ([Figure 10.1a](#)). A thorough discussion of the rationale behind the formulae is given by [Abbott \(1999\)](#).

The ODS also prescribes the conditions for which the safety indices are to be displayed. In general, only one index value needs to be displayed, an index need not be displayed if its value is less than 0.4, and need not be displayed at all if it can never exceed 1.0 under any condition. In fact many manufacturers display values more fully than is strictly required by the ODS, both by showing values below 0.4 and by not restricting the display to a single index value.

TI is based upon calculations of temperature rise in tissue, but must not be considered as an accurate estimate of temperature rise. For example, the assumption that temperature rise can be predicted simply from an analysis of the absorption of ultrasound in tissue has been shown to be false for positions close to the transducer. This is because the transducer itself heats slightly, so warming the adjacent tissue by thermal conduction. Another error relates to the way in which the heating contributions are added together when several

Maximum heating is assumed to be at the surface when imaging, and at depth for Doppler and M-mode

It is not always required to display either MI or TI

Some problems remain with the safety index formulations

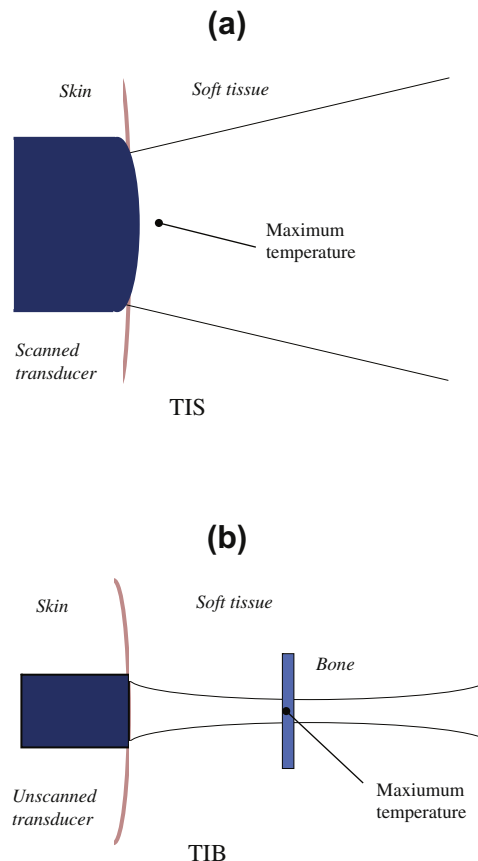


Figure 10.1. Simple models used for the calculation of (a) soft-tissue thermal index (TIS) and the (b) bone-at-focus thermal index, TIB. Soft tissue is modelled as a homogeneous material with an attenuation coefficient of  $0.3 \text{ dB cm}^{-1} \text{ MHz}^{-1}$ . The temperature variation along the axis reaches a maximum close to the transducer for soft-tissue exposure (TIS) and reaches a maximum at the focus for the bone-at-focus exposure (TIB).

diagnostic modes are used together. An additional difficulty arises from the incorrect assumption that *in situ* exposure can be calculated from measurements in water using simple linear assumptions, a problem that can cause underestimation of the MI.

### 10.4. European Medical Devices Directive

CE marking  
for medical  
equipment  
requires  
conformance  
with the EU  
MDD

The European Communities Medical Devices Directive or MDD ([European Communities, 1993](#)) is adopted into the national legal framework of many European member states, including the UK. Each state appoints a Competent Authority. For the UK this is the Medicines and Healthcare Products Regulatory Agency (MHRA). The Agency designates Notified Bodies whose function is to make assessments of new products under the MDD procedures. Manufacturers can use any appropriate Notified Body within the European Union. A CE mark on a device means that the device satisfies the requirements essential for it to be fit for its intended purpose. All medical devices (except custom-made and devices intended for clinical investigations), whether used in private or public hospitals and nursing homes, or sold in retail outlets, must carry the CE marking.

Classification  
of equipment  
depends on  
the level of  
risk

Annex IX of the MDD describes three general classes of equipment and a set of rules for establishing the class of any particular type of equipment. Almost all diagnostic ultrasonic devices lie in Class IIa, because they are “active devices intended for diagnosis”. Class IIb is specifically intended for monitoring vital physiological parameters, where the nature of the variations is such that they could result in immediate danger to the patient. Some Doppler devices used during surgery may be deemed to fall into this category. Intravascular ultrasound transducers are usually designated as Class III since they are invasive devices. Initially the manufacturer determines the class of his products, and selects an appropriate Notified Body to carry out the conformity assessment procedure. The assessment in all categories requires appropriate audits of manufacturer's production quality assurance systems. In addition, there is a provision for examination and testing of products or batches, although this is not mandatory, even for Class III products, provided that the design dossier is submitted. It is probable that most medical ultrasound devices gain a CE mark without practical independent assessment, being based substantially on inspection of required documentation. Manufacturers are also required to maintain a post-market surveillance system and report certain types of incidents to a Competent Authority.

Manufacturers  
must  
demonstrate  
both output  
safety and  
measurement  
accuracy

The MDD does not give any guidance specific to ultrasound emissions. The general statements of Clause 11 (on protection against radiation) and of Clause 12 (on equipment with an energy source) may be taken to apply, however. These require that “Devices shall be designed and manufactured in such a way that exposure to patients... shall be reduced as far as possible compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for therapeutic or diagnostic purposes”. Devices may emit hazardous levels of radiation if necessary for a specific medical purpose, but it must be possible to control them. Where radiation is “potentially hazardous”, devices must be “fitted, where practicable, with visual displays and/or warnings of such emissions”. Furthermore, “accessible parts of devices... must not attain potentially dangerous temperatures under normal use”. The normal method for a manufacturer to

demonstrate that they have complied with these requirements is to follow procedures laid down in international standards.

## References

- Abbott JG. 1999. Rationale and derivation of MI and TI—a review. *Ultrasound Med Biol*, 25, 431–441.
- American Institute of Ultrasound in Medicine/National Electrical Manufacturers Association. 1998. Standard for Real-time Display of Thermal and Mechanical Acoustic Output Indices on Diagnostic Ultrasound Equipment. 2nd Edn. Rockville, MD: AIUM.
- European Communities. 1993. Council directive 93/42/EEC, of 14 June 1993, concerning medical devices. *Off J Eur Communities*, 36, L169.
- Food and Drug Administration: US Department of Health and Human Services. 1997. Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers. [www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM070911.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM070911.pdf). Rockville, MD: Center for Devices and Radiological Health.
- IEC. 2001. IEC60601 Part 2-37: Medical Electrical Equipment: Particular Requirements for the Safety of Ultrasound Diagnostic and Monitoring Equipment 2001 & Amendment 1 2005. Geneva, Switzerland: International Electrotechnical Commission.
- IEC. 2005. IEC60601 Part 1: Medical Electrical Equipment: General Requirements for Safety and Essential Performance. Geneva, Switzerland: International Electrotechnical Commission.
- IEC. 2006. IEC62359: Ultrasonics – Field Characterization – Test Methods for the Determination of Thermal and Mechanical Indices Related to Medical Diagnostic Ultrasound Fields. Geneva, Switzerland: International Electrotechnical Commission.

# Chapter 11

## Guidelines and recommendations for the safe use of diagnostic ultrasound: the user's responsibilities

**Gail ter Haar**

*Institute of Cancer Research, Sutton, UK*

### Summary

- The responsibility for risk assessment has migrated from regulatory authorities to the user.
- There is a strong need for continuing education to ensure that appropriate risk/benefit assessments are made.
- Major national ultrasound societies have formulated guidelines for the safe use of ultrasound in medicine.

### 11.1 Introduction

The evolution of ultrasonographic equipment has led to the development of powerful diagnostic devices that are capable of substantial acoustic output. Coincidentally, the method of ensuring safe use of diagnostic ultrasound in medicine has undergone significant change towards a system of self-regulation. This change originated in the USA. This shift in responsibility for risk assessment from a regulatory authority to the user has created an urgent need for responsible attitudes to safety issues. To encourage this approach it is incumbent on authorities, ultrasound societies and expert groups to provide relevant information about the risk of producing biological effects during ultrasonographic procedures. There is a strong need for continuing education to ensure that appropriate risk/benefit assessments are made, based on an understanding of the probability of biological effects occurring with each type of ultrasound procedure. Some types of examinations involve a greater risk of adverse effect than do others. The probability of causing some of these bio-effects can be increased by the presence of gas bubbles such as are used for echo-contrast agents. Also, the sensitivity of the

tissue target has a significant impact on the type of bio-effect and on its consequences for human health.

The relaxation of intensity limits for pre-market approval by the United States Food and Drug Administration (FDA, 1985, 1993) allows a substantially increased intensity of ultrasound to be delivered to the foetus than was previously allowed. Studies with laboratory animals have shown that significant biological effects can be produced from exposures from modern diagnostic equipment operating at maximum output conditions. These issues have been addressed by the World Federation for Ultrasound in Medicine and Biology (WFUMB) in published conclusions and recommendations that represent international consensus on safe use of ultrasound in medicine. Major national ultrasound societies have formulated guidelines for the safe use of ultrasound in medicine. This chapter describes relevant published safety guidelines issued by national and international organizations concerned with the safe and effective application of ultrasound in medicine.

An important question that relates to the safe use of ultrasound in medicine is whether it is better to limit the acoustic output by law or to rely on optimum patient exposure and appropriate risk/benefit assessment based on informed use. The latter option is encouraged by the FDA through its acceptance of equipment output display using the so-called “Track 3” option for pre-market equipment approval (see [Chapter 10](#)). However, this option requires effort on the part of the user, authorities and ultrasound organizations to disseminate relevant information about potential risk.

The change from a regulated maximum intensity limit to control by personal judgement of the risk/benefit ratio for each type of examination allows the clinician or ultrasound technologist access to, and control of, potentially substantially higher acoustic outputs than before. It is appropriate that clinicians take the responsibility of risk assessment armed with information on bio-effects provided by the scientific community, and on equipment output conditions provided by the manufacturer. This increasingly places the responsibility on the end-user to maximize the benefit of ultrasound examinations, whilst minimizing the risk. Clearly, in order to make valid judgements radiologists and sonographers must be educated about safety issues. Attitudes that assume inherent safety under all conditions, simply because the equipment is commercially available, are inappropriate. Misplaced assumptions that the highest acoustic power always gives the best diagnostic information need to be replaced by an awareness of the relative risks for each application. Ultrasound technologists who have been trained in safety issues are best able to interpret information in the form of an output display, and it is the purpose of this chapter to draw attention to some important and relevant issues. It is essential that users of ultrasound equipment have an understanding of bio-effect mechanisms and are cognizant of the potential risks associated with different modes of operation. The risk/benefit changes significantly according to the medical reason for undertaking each type of ultrasonographic examination. For example, a current topic of debate is whether or not there is risk, or benefit, associated with routine use of pulsed Doppler (PD) ultrasound during the first trimester in uncomplicated pregnancy. While there is some uncertainty about the risk/benefit issues, it is well known that the developing embryo is particularly sensitive to damage by physical insult. It should also be remembered that both the

Appropriate use of safety related “output display” requires user education and dissemination of relevant information about potential risk

The introduction of displayed safety “indices” has resulted in higher available acoustic outputs

benefit and risk depend largely on the skill and competence of the person performing the examination.

There is a large data base of scientific papers and review articles on biological effects and safety of ultrasound. The WFUMB has published proceedings of symposia offering conclusions and recommendations on the safe use of ultrasound in medicine. The WFUMB Safety Committee has also published relevant scientific review papers ([Barnett et al., 1994, 1997, 2010](#)). Most national ultrasound societies have a safety committee or advisory group whose role is to provide information on the risk of bio-effects. Some of these expert groups also issue safety guidelines to promote responsible use of diagnostic ultrasound. Information on bio-effects and safety is disseminated through regular scientific presentations at medical ultrasound conferences. However, the low audience attendance at bio-effects sessions at clinical conferences suggests that the concept of voluntary attention to safety issues may not be appropriate or effective. The situation is made more difficult by the unknown number of clinicians and sonographers who practice outside tertiary centres and who do not have any affiliation with ultrasound societies. The purpose of this chapter is to draw attention to existing safety guidelines and to provide some background information on the current status of knowledge on biophysical aspects of ultrasound interaction.

Complacency about safety should be avoided. Each new technique needs separate evaluation

It is easy to become complacent in the knowledge that medical ultrasonography has enjoyed widespread use as a safe and effective diagnostic clinical tool, but it must be remembered that the fact that there is no evidence for harm does not provide evidence of absence of potential to do harm. However, it should be realized that each new technological development introduces new biophysical conditions that require evaluation with regard to safety; for example, echo-contrast agents enhance cavitation and harmonic generation in tissue. Improvements in resolution, grey-scale definition and image quality are particularly important in obstetrics. Image quality has been further enhanced with the advent of endovaginal examinations that allow closer access to anatomical structures and visualization of the embryo or foetus without suffering the beam-interference effects, or ultrasound attenuation, caused by overlying abdominal skin, fat and musculature. PD spectral flow analysis and Doppler colour flow imaging (CFI) techniques offer the potential to increase diagnostic effectiveness and may be attractive for applications in early pregnancy. Meanwhile, there is a developing trend towards prolonged daily use of transcranial PD spectral flow measurement in premature infants.

Non-linear harmonic imaging introduces another interesting variable into the potential bio-effects equation. Higher-frequency harmonics are generated in tissue by the use of high acoustic pressure amplitudes. In addition the introduction into the ultrasound field of echo-contrast gas bodies can generate harmonics locally. By these processes the non-linear effect is enhanced and the potential for biological effects may be also increased (see [Chapters 2 and 6](#)).

Major ultrasound societies and organizations have paid attention to the safety of diagnostic ultrasound and progress has been achieved towards identifying international consensus on important issues. In recent years, knowledge of the biophysical effects of

ultrasound has become a fundamental consideration in the process of setting international standards for safety of ultrasound in medicine, an important function of the International Electrotechnical Committee (IEC, 1992; see Chapter 10).

It is entirely appropriate to recognize that the scientific community does not have all the answers to basic questions, and that fresh questions are generated as new applications develop. This uncertainty may require the introduction of wide safety margins in international standards in order to ensure that risk is minimized.

The regulatory arrangements set up by the FDA in the USA, and its use of the AIUM/NEMA (1992) “Output Display Standard” (ODS) are discussed in Chapter 10. However, there are some important issues that need to be understood when considering the AIUM/NEMA output labelling scheme. The duration of exposure is not included in the index of risk, and this remains an important consideration, particularly for thermally mediated biological effects where the damage threshold is defined by a combination of temperature increase and time for which it is maintained (see Chapter 3). The higher the temperature increase, the shorter the duration required to produce adverse effects. This issue has been examined in detail by international panels of experts during symposia sponsored by the WFUMB. Following its safety symposium in 1996, the WFUMB published a recommendation (WFUMB, 1998) that “... safety guidelines should include an appropriate duration factor”. This aspect of safety issues has been recognized by the IEC in its deliberations towards developing international safety standards.

Another potential limitation of the thermal index (TI) is that it does not take account of patient temperature. This may be an important consideration for obstetrics. A relevant recommendation of the WFUMB (1998) states that “Care should be taken to avoid unnecessary additional embryonic and foetal risk from ultrasound examinations of febrile patients”.

In comparison with thermal mechanisms, gas-body effects from diagnostic ultrasound can occur almost instantaneously when the acoustic pressure exceeds a certain threshold value. The ODS does not give any indication of exposure duration or the effects on bio-effects thresholds of such factors as the presence of gas bodies/contrast agents, patient temperature or non-linear propagation.

The European Committee for Ultrasound Radiation Safety (ECURS) has published an informative tutorial paper on the thermal and mechanical indices (EFSUMB, 1996a,b) which draws attention to some of these problems. As an example, it suggests that the models used for deriving “reasonable worst-case” exposures for the indices may not be adequate to describe first-trimester scanning through a full bladder where the attenuating effect of overlying tissue is small. The purpose of the mechanical index (MI) is to predict the likelihood of cavitation type of bio-effects where the peak pressure amplitude is a critical parameter. The intended use is for the display of MI to be included in B-mode imaging. However, recent surveys (Duck and Henderson, 1998; Henderson *et al.*, 1997; Martin, 2010) show minimal differences in peak pressure values for different modes of operation (see Chapter 3).

Safety indices take no account of the duration of the exposure

TI takes no account of patient temperature

The importance of an MI, or similar indicator of risk of mechanical damage, is emphasized by recent research findings. Although there is no direct evidence of adverse effects in humans (no scientifically controlled studies with humans exist) from mechanical bio-effects, the scientific literature contains a considerable amount of information on both *in vitro* and *in vivo* effects in lower animals and mammals. The critical acoustic parameter is the *in situ* rarefaction pressure.

Surveys of acoustic output measurements reported for equipment in clinical use in the UK (Henderson *et al.*, 1997; Whittingham, 2000) have indicated that the peak rarefactional ( $p_r$ ) pressure amplitudes for Doppler systems range between 0.6 MPa and 5.5 MPa. A more recent survey of values declared by manufacturers puts this range as 2.1–6.7 MPa (Martin, 2010). For imaging systems, the measured range was 0.5–4.6 MPa, and the declared range was 2.3–6.4 MPa. The observation of haemorrhage in the mouse lung following exposure to pulsed ultrasound (Child *et al.*, 1990) at 1 MPa has demonstrated that these rarefactional pressure amplitudes are sufficient to lead to adverse biological effects in mammalian tissues. It is not certain to what extent these effects may occur in humans or their clinical significance (WFUMB, 1998; see Chapter 5).

## 11.2 International guidelines

### 11.2.1 World Federation for Ultrasound in Medicine and Biology

Since 1985, the WFUMB has sponsored a number of symposia on safety and standardization of ultrasound in medicine that have addressed topics related to known mechanisms for producing biological effects. These recommendations remain valid today, and are the basis for current recommendations. During these symposia the available scientific data base has been critically examined, conclusions drawn and the proceedings subject to widespread international review. As a result the WFUMB has published policy statements and a number of conclusions and recommendations, endorsed as internationally acceptable guidelines for the safe use of diagnostic ultrasound (WFUMB, 1992, 1998). These guidelines are also still valid today.

#### 11.2.1.1 WFUMB policy statement on safety of diagnostic ultrasound

##### *B-mode imaging*

*Known diagnostic ultrasound equipment as used today for simple B-mode imaging operates at acoustic outputs that are not capable of producing harmful temperature rises. Its use in medicine is therefore not contraindicated on thermal grounds. This includes endoscopic, transvaginal and transcutaneous applications.*

##### *Doppler*

*It has been demonstrated in experiments with unperfused tissue that some Doppler diagnostic equipment has the potential to produce biologically significant temperature rises, specifically at bone/soft tissue interfaces. The effects of elevated temperatures may be minimized by keeping the time for which the beam passes through any one point in tissue as short as possible. Where output*

power can be controlled, the lowest available power level consistent with obtaining the desired diagnostic information should be used. Although the data on humans are sparse, it is clear from animal studies that exposures resulting in temperatures less than 38.5 °C can be used without reservation on thermal grounds. This includes obstetric applications.

#### *Transducer heating*

A substantial source of heating may be the transducer itself. Tissue heating from this source is localized to the volume in contact with the transducer.

WFUMB  
policy  
statement

The findings of the WFUMB symposia on the safety of ultrasound in medicine are published in the scientific literature. These reports (WFUMB, 1992, 1998) contain comprehensive lists of conclusions and recommendations on a wide range of biological effects. Some of the clinically relevant conclusions and recommendations on the safe use of ultrasound in medicine are given below.

### **11.2.1.2 WFUMB conclusions**

#### *Thermal effects*

Developmental abnormalities have been observed in animals when the embryonic or foetal temperature is increased by 2 °C or more above their normal body temperature for extended duration.

Biologically significant temperature increases have been measured, at or near bone/soft tissue interfaces, during exposure to conditions similar to those used in Doppler diagnostic equipment. The effects of elevated temperatures may be minimized by keeping the time for which the beam passes through any one point in tissue as short as possible.

#### *Non-thermal effects*

Capillary bleeding has been observed in the lung after exposure of neonatal, young and adult mice, swine and adult rats, rabbits and monkeys to diagnostically relevant, pulsed ultrasound. Thresholds for capillary bleeding in adult mice and neonatal and young swine are of the order of 1 MPa at 2 MHz, which is within the range of output values of commercially available diagnostic ultrasound systems.

In the air-filled mammalian lung, bleeding from alveolar capillaries has been induced experimentally by ultrasound at diagnostic exposure levels. This effect has not been observed in the fluid-filled mammalian foetal lung. There is no direct evidence to date as to whether or not this effect can occur in humans.

WFUMB  
conclusions

### **11.2.1.3 WFUMB recommendations**

#### *Thermal effects*

A diagnostic exposure that produces a maximum temperature rise of no more than 1.5 °C above normal physiological levels (37 °C) may be used clinically without reservation on thermal grounds. A diagnostic exposure that elevates embryonic and foetal in situ temperature 41 °C (4 °C above normal temperature) for 5 min or more should be considered potentially hazardous.

The risk of adverse effects of heating is increased with the duration of exposure. Thus, safety guidelines should include an appropriate duration factor.

Care should be taken to avoid unnecessary additional embryonic and foetal risk from ultrasound examinations of febrile patients.

### *Non-thermal effects*

*Cavitation:* It has been shown experimentally that acoustic cavitation can alter mammalian tissue. The possible occurrence of cavitation, either inertial or non-inertial, should be considered in assessing the safety of diagnostic ultrasound and of other forms of medical ultrasound.

*Lung capillary bleeding:* Currently available animal data indicate that it is prudent to reduce ultrasound exposure of human postnatal lung to the minimum necessary to obtain the required diagnostic information.

A risk benefit analysis should be performed if the anticipated acoustic pressure amplitude at the surface of the postnatal lung exceeds 1 MPa.

*Contrast agents:* Gas bodies introduced by a contrast agent increase the probability of cavitation. A physician should take this into account when considering the benefit/risk ratio of an examination.

WFUMB  
recommendations

*B-mode imaging:* When tissue/gas interfaces or contrast agents are not present, the use of B-mode imaging need not be withheld because of concern for ultrasound safety. This statement also applies to endoscopic, transvaginal and transcutaneous applications. When tissue/gas interfaces or contrast agents are present, ultrasound exposure levels and duration should be reduced to the minimum necessary to obtain the required diagnostic information.

As mentioned above, the main area of concern in obstetric ultrasound scanning lies with the use of Doppler in the first trimester. Here several organizations (WFUMB, ISUOG, EFSUMB/AIUM) have agreed a single statement (WFUMB, 2011). This is:

### *Statement on the Safe Use of Doppler Ultrasound During 11–14 week scans (or earlier in pregnancy)*

1. PD (spectral, power and CFI) ultrasound should not be used routinely.
2. PD ultrasound may be used for clinical indications such as to refine risks for trisomies.
3. When performing Doppler ultrasound, the displayed TI should be less than or equal to 1.0 and exposure time should be kept as short as possible (usually no longer than 5–10 min) and not exceed 60 min.
4. When using Doppler ultrasound for research, teaching and training purposes, the displayed TI should be less than or equal to 1.0 and exposure time should be kept as short as possible (usually no longer than 5–10 min) and not exceed 60 min. Informed consent should be obtained.
5. In educational settings, discussion of first trimester pulsed or colour Doppler should be accompanied by information on safety and bio-effects (e.g. TI, exposure times and how to reduce the output power).
6. When scanning maternal uterine arteries in the first trimester, there are unlikely to be any foetal safety implications as long as the embryo/foetus lies outside the Doppler ultrasound beam.

WFUMB/EFUMB/  
AIUM/SUOG  
Doppler in the  
first trimester

## 11.2.2 Other international safety guidelines

The other professional Ultrasound societies also issue statements and guidelines relevant to ultrasound safety. Each has its own form of clinical safety statement, but the message is consistent. It is important to understand that these statements on clinical ultrasound safety are not regulatory. They provide essential information and serve a useful role in advising users of the potential risk from certain diagnostic ultrasound procedures. The most recent such statement is from EFSUMB, and is reproduced here. The interested reader is referred to the websites of AIUM, ISUOG and ASUM (Australian Society for Ultrasound in Medicine) for further information.

### 11.2.2.1 EFSUMB Clinical Safety Statement for Diagnostic Ultrasound (2011)

*Diagnostic ultrasound has been widely used in clinical medicine for many years with no proven deleterious effects. However, if used imprudently, diagnostic ultrasound is capable of producing harmful effects. The range of clinical applications is becoming wider, the number of patients undergoing ultrasound examinations is increasing and new techniques with higher acoustic output levels are being introduced. It is therefore essential to maintain vigilance to ensure the continued safe use of ultrasound.*

*Ultrasound examinations should only be performed by competent personnel who are trained and updated in safety matters. It is also important that ultrasound devices are appropriately maintained.*

*Ultrasound produces heating, pressure changes and mechanical disturbances in tissue. Diagnostic levels of ultrasound can produce temperature rises that are hazardous to sensitive organs and the embryo/foetus. Biological effects of non-thermal origin have been reported in animals but, to date, no such effects have been demonstrated in humans, except when a microbubble contrast agent is present.*

*The TI is an on-screen guide to the user of the potential for tissue heating. The MI is an on-screen guide of the likelihood and magnitude of non-thermal effects. Users should regularly check both indices while scanning and should adjust the machine controls to keep them as low as reasonably achievable (ALARA principle) without compromising the diagnostic value of the examination. Where low values cannot be achieved, examination times should be kept as short as possible. Guidelines issued by several ultrasound societies are available.*

*Some modes are more likely than others to produce significant acoustic outputs and, when using these modes, particular care should be taken to regularly check the TI and MI indices. Spectral pulse wave Doppler and Doppler imaging modes (CFI and power Doppler imaging) in particular can produce more tissue heating and hence higher TI values, as can B-mode techniques involving coded transmissions. Tissue harmonic imaging mode can sometimes involve higher MI values. 3D (three dimensional) imaging does not introduce any additional safety considerations, particularly if there are significant pauses during scanning to study or manipulate the reconstructed images. However, 4D scanning (real-time 3D) involves continuous exposure and users should guard against the temptation to prolong examination times unduly in an effort to improve the recorded image sequence beyond that which is necessary for diagnostic purposes.*

### *Ultrasound exposure during pregnancy*

*The embryo/foetus in early pregnancy is known to be particularly sensitive. In view of this and the fact that there is very little information currently available regarding possible subtle biological effects of diagnostic levels of ultrasound on the developing human embryo or foetus, care should be taken to limit the exposure time and the thermal and mechanical indices to the minimum commensurate with an acceptable clinical assessment.*

*Temperature rises are likely to be greatest at bone surfaces and adjacent soft tissues. With increasing mineralization of foetal bones, the possibility of heating sensitive tissues such as brain and spinal cord increases. Extra vigilance is advised when scanning such critical foetal structures, at any stage in pregnancy. Based on scientific evidence of ultrasound-induced biological effects to date, there is no reason to withhold diagnostic scanning during pregnancy, provided it is medically indicated and is used prudently by fully trained operators. This includes routine scanning of pregnant women. However, Doppler ultrasound examinations should not be used routinely in the first trimester of pregnancy.*

*The power levels used for foetal heart rate monitoring (cardiotocography) are sufficiently low that the use of this modality is not contraindicated on safety grounds, even when it is to be used for extended periods.*

### *Safety considerations for other sensitive organs*

*Particular care should be taken to reduce the risk of thermal and non-thermal effects during investigations of the eye and when carrying out neonatal cardiac and cranial investigations.*

### *Ultrasound contrast agents*

*These usually take the form of stable gas-filled microbubbles, which can potentially produce cavitation or microstreaming, the risk of which increases with MI value. Data from small animal models suggest that microvascular damage or rupture is possible. Caution should be considered for the use of ultrasound contrast agents (UCA) in tissues where damage to microvasculature could have serious clinical implications, such as in the brain, the eye and the neonate. As in all diagnostic ultrasound procedures, the MI and TI values should be continually checked and kept as low as possible. It is possible to induce premature ventricular contractions in contrast-enhanced echocardiography when using high MI and end-systolic triggering. Users should take appropriate precautions in these circumstances and avoid cardiac examinations in patients with recent acute coronary syndrome or clinically unstable ischaemic heart disease. The use of contrast agents should be avoided 24 h prior to extra-corporeal shock wave therapy.*

**In conclusions and recommendations on transvaginal sonography EFSUMB advises that (EFSUMB 1995):**

*“The absence of long-term, large scale, follow-up studies following first-trimester ultrasound exposures means that care is required in the application of transvaginal*

ultrasonography in early pregnancy. It should only be performed for pure medical reasons that are to the benefit of the mother and/or the embryo”.

### 11.2.2.2 British Medical Ultrasound Society

The British Medical Ultrasound Society (BMUS) is the only organization to have published guidelines on the safe use of ultrasound, with explicit recommendations related to the displayed safety indices (BMUS, 2010). This information is shown in [Tables 11.1](#) and [11.2](#). [Figure 11.1](#) shows a graphical representation providing easy reference for the recommended scanning time at any given TI for obstetric scans. Similar figures are available for neonatal transcranial and spinal scans, general neonatal and cardiac scans, and adult transcranial, peripheral vascular and general abdominal scanning. For obstetrics, TIs of 0.7 can be used without restriction, and the recommendation is that those greater than 3 should be avoided. The time limits were reached using the thermal guidelines produced by WFUMB (1998), rounding the times down where appropriate to ensure continued safety. This is discussed in more detail in [Chapter 3](#). In discussing the recommended time restrictions, the Guidelines state that:

“The operator should aim to stay within BMUS recommended scan times. If there is a clinical need to exceed these recommended times, the ALARA principle should still be followed. When overall times longer than those recommended here are essential, the probe should be removed from the patient whenever possible, to minimize exposure.”

## 11.3 Souvenir scanning

All the societies mentioned above have issued statements about the use or the production of souvenir scans (also known as keepsake, or bonding scans). The message of these statements is that this practice cannot be recommended, giving safety grounds as the basis for this (WFUMB, AIUM, ISUOG, EFSUMB, BMUS). At first sight this may seem to contradict the “clinical” safety statements from these same organizations in which routine scans during pregnancy are said to be safe. An ultrasound scan conducted in a souvenir scanning centre is not inherently more harmful than the same scan conducted for clinical reasons if carried out by a qualified practitioner. The difference lies in the perceived benefit obtained compared to any potential risk. A “routine” obstetric ultrasound scan is conducted with the expectation that it will inform the management of the pregnancy beneficially, whereas a souvenir scan is carried out solely for “recreational” purposes. A compromise is reached by conceding that providing a “souvenir” image at the end of a clinically indicated scan does not add significantly to any potential risk, and may dissuade the pregnant mother from resorting to a high street “boutique” with unknown skills and qualifications to obtain such a scan (Brezinka, 2010; Phillips *et al.*, 2010).

The EFSUMB, ISUOG and WFUMB statements are given below. The EFSUMB statement has been endorsed as BMUS policy.

Table 11.1. Recommended exposure time and index values for obstetric and neonatal ultrasound.

Application	Values to monitor (A)	TI value			MI value		
		0–0.7	0.7–3.0	>3.0	0–0.3	>0.3	>0.7
Obstetrics up to 10 weeks after LMP (and gynaecology when pregnancy is possible)	TIS and MI	✓	(B) restrict time to 0.7 < TIS ≤ 1.0: 60 min 1.0 < TIS ≤ 1.5: 30 min 1.5 < TIS ≤ 2.0: 15 min 2.0 < TIS ≤ 2.5: 4 min 2.5 < TIS ≤ 3.0: 1 min	Scanning of an embryo or foetus is not recommended, however briefly	✓	✓	(E) risk of cavitation with contrast agents
Obstetrics more than 10 weeks after LMP	TIB and MI	✓	(B) restrict time to 0.7 < TIB ≤ 1.0: 60 min 1.0 < TIB ≤ 1.5: 30 min 1.5 < TIB ≤ 2.0: 15 min 2.0 < TIB ≤ 2.5: 4 min 2.5 < TIB ≤ 3.0: 1 min	Scanning of an embryo or foetus is not recommended, however briefly	✓	✓	(E) risk of cavitation with contrast agents
Neonatal—transcranial and spinal	TIC and MI	✓	(B) restrict time to 0.7 < TIC ≤ 1.0: 60 min 1.0 < TIC ≤ 1.5: 30 min 1.5 < TIC ≤ 2.0: 15 min 2.0 < TIC ≤ 2.5: 4 min 2.5 < TIC ≤ 3.0: 1 min	Scanning of an embryo or foetus is not recommended, however briefly	✓	✓	(E) risk of cavitation with contrast agents
Neonatal—general and cardiac imaging	TIB and MI recommended	✓	(C) restrict time to 1.0 < TIB ≤ 1.5: 120 min 1.5 < TIB ≤ 2.0: 60 min 2.0 < TIB ≤ 2.5: 15 min 2.5 < TIB ≤ 3.0: 4 min TIB > 3.0: not recommended.		✓	(D) possibility of minor damage to lung or intestine. Minimize exposure time.	(E) risk of cavitation with contrast agents
Foetal Doppler heart monitoring	TI or MI are not usually available for dedicated foetal heart monitors	The power levels used by dedicated foetal heart monitors are sufficiently low that the use of this modality is not contraindicated, on safety grounds, even when it is to be used for extended periods					

✓: There is no known reason to restrict scanning times in this region.

A: Many scanners allow MI and one of the TI values to be displayed simultaneously: the most appropriate TI value depends on the clinical application.

B: TI > 0.7—the overall exposure time (including pauses) of an embryo or foetus or of the neonatal central nervous system should be restricted.

C: TI > 1.0—the overall exposure time (including pauses) of other parts of the neonate should be restricted.

D: MI > 0.3—there is a possibility of minor damage to neonatal lung or intestine. If such exposure is necessary, try to reduce the exposure time as much as possible.

E: MI > 0.7—there is a risk of cavitation if an ultrasound contrast agent containing gas microspheres is being used. There is a theoretical risk of cavitation without the presence of ultrasound contrast agents. The risk increases with MI values above this threshold.

Table 11.2. Recommended exposure time and index values for non-obstetric and non- neonatal ultrasound.

Application	Values to monitor (A)	TI value		MI value	
		0–1.0	>1.0	0–0.3	>0.7
General abdominal Peripheral vascular Unlisted applications	Usually TIB and MI  [use TIC and MI if bone closer than 1 cm; TIS and MI only if bone does not come into the image]	✓	(B) restrict time to 1.0 < TIB ≤ 1.5: 120 min 1.5 < TIB ≤ 2.0: 60 min 2.0 < TIB ≤ 2.5: 15 min 2.5 < TIB ≤ 3.0: 4 min 3.0 < TIB ≤ 4.0: 1 min 4.0 < TIB ≤ 5.0: 15 s 5.0 < TIB ≤ 6.0: 5 s TIB > 6: not recommended	✓	(C) risk of cavitation with contrast agents
Eye	TIS and MI recommended	✓	Scanning of the eye is not recommended	✓	(C) risk of cavitation with contrast agents
Adult transcranial (imaging and stand-alone) (D)	TIC and MI	✓	(B) restrict time to 0.7 < TIC ≤ 1.0: 60 min 1.0 < TIC ≤ 1.5: 30 min 1.5 < TIC ≤ 2.0: 15 min 2.0 < TIC ≤ 2.5: 4 min 2.5 < TIC ≤ 3.0: 1 min TIC > 3: not recommended	✓	(C) risk of cavitation with contrast agents
Peripheral pulse monitoring	TI or MI are not usually available for dedicated peripheral pulse monitoring	The output from CW Doppler devices intended for monitoring peripheral pulses is sufficiently low that their use is not contraindicated, on safety grounds			

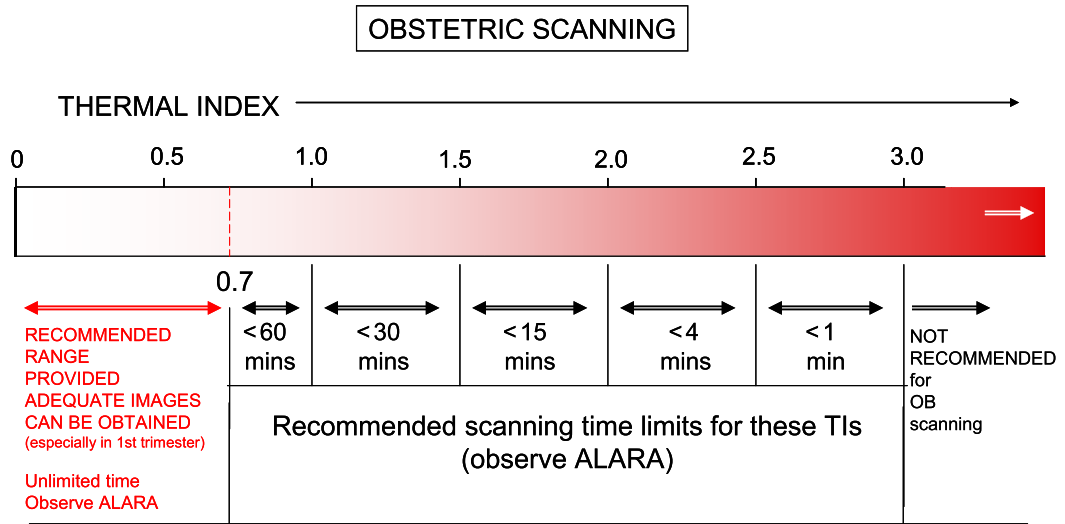
✓: There is no known reason to restrict scanning times in this region.

A: Many scanners allow MI and one of the TI values to be displayed simultaneously: the most appropriate TI value depends on the clinical application.

B: TI > 1.0—the overall exposure time (including pauses) should be restricted.

C: MI > 0.7—there is a risk of cavitation if an ultrasound contrast agent containing gas microspheres is being used. There is a theoretical risk of cavitation without the presence of ultrasound contrast agents. The risk increases with MI values above this threshold.

D: Transcranial ultrasound investigations may require higher acoustic output or longer monitoring times than other applications. When times longer than those recommended here are required, it is recommended that monitoring is paused regularly to minimize exposure.



Monitor TIS up to 10 weeks post-LMP, TIB thereafter.

Figure 11.1. Graphical representation of the recommended exposure times at different index values for obstetric ultrasound, as listed in Table 11.1.

### 11.3.1 EFSUMB (2009)

Developments in real-time three-dimensional ultrasonic imaging have led to parents asking for souvenir (keepsake) video recordings of the foetus, sometimes at several stages during the pregnancy. An area of concern is the growth of services designed to provide such images and recordings without any diagnostic element to the scan. Often, such services are unable to provide counselling or offer guidance if signs of a foetal abnormality are unexpectedly revealed. Apart from such services, there many instances of diagnostic scans being prolonged in order to provide such recordings.

Very little information is currently available regarding possible subtle biological effects of diagnostic levels of ultrasound on the developing human embryo or foetus, and the possibility of developmental effects in the brain cannot be ruled out. There is evidence that diagnostic levels of ultrasound can influence development of the brain in small animals, although it is not possible to extrapolate this finding to the human situation. A balance must always be maintained between diagnostic benefit and risk to the patient. Therefore, it is difficult to justify souvenir or keepsake scanning that has no diagnostic benefit.

Recommendations:

1. Ultrasound scans should not be performed solely for producing souvenir images or recordings of a foetus or embryo.
2. The production of souvenir images or recordings for the parents to keep is reasonable if they are produced during a diagnostic scan, provided that this does not require the ultrasound exposure to be greater in time or magnitude (as indicated by the displayed MI and TI) than that necessary to produce the required diagnostic information.
3. Attention is drawn to the recommendation of the EFSUMB Clinical Safety Statement for Diagnostic Ultrasound that ultrasound examinations should be performed only by competent personnel who are trained and updated in ultrasound safety matters.

### 11.3.2 WFUMB Policy Statement on Non-medical Use of Ultrasound (2008)

*The WFUMB disapproves of the use of ultrasound for the sole purpose of providing souvenir images of the foetus. Because the safety of an ultrasound examination cannot be assured, the use of ultrasound without medical benefit should be avoided. Furthermore, ultrasound should be employed only by health professionals who are well trained and updated in ultrasound clinical usage and bio-effects.*

#### 11.3.2.1 WFUMB Recommendations on Non-medical Use of Ultrasound

- *The WFUMB disapproves of the use of ultrasound for the sole purpose of providing keepsake or souvenir images of the foetus.*
- *Ultrasonography is a medical procedure that should only be carried out in the clinical setting where there is a medical indication and when carried out under the supervision of a physician or an expert.*
- *The use of ultrasound to provide keepsake images or videos of the foetus may be acceptable if it is undertaken as part of the normal clinical diagnostic ultrasound examination, provided that it does not increase exposure to the foetus.*
- *In the absence of supporting evidence of safety, caution should be used to minimize ultrasound exposure to the foetus.*
- *When using ultrasound for non-medical reasons the ultrasound equipment display should be used to ensure that  $TI < 0.5$  and  $MI < 0.3$ .*
- *Ultrasound imaging for non-medical reasons is not recommended unless carried out for education, training or demonstration purposes.*
- *Live scanning of pregnant models for equipment exhibitions at ultrasound congresses is considered a non-medical practice that should be prohibited since it provides no medical benefit and affords potential risk to the foetus.*

#### 11.3.3 ISUOG (2009)

*ISUOG disapproves of the use of ultrasound for the sole purpose of providing souvenir images of the foetus. There have been no reported incidents of human foetal harm in over 40 years of extensive use of medically indicated and supervised diagnostic ultrasound. Nevertheless, ultrasound involves exposure to a form of energy, so there is the potential to initiate biological effects. Some of these effects might, under certain circumstances, be detrimental to the developing foetus. Therefore, the uncontrolled use of ultrasound without medical benefit should be avoided.*

## 11.4 Conclusion

Professional medical ultrasound society websites provide statements and guidelines addressing the continued safe practice of diagnostic ultrasound. These are regularly updated and should be consulted for the most up to date information. Many of these organizations also have rapid response groups whose job it is to provide informed comment when new safety issues arise.

## Acknowledgement

This chapter is a revised version of [Chapter 11](#) in the second edition. The contribution of Stan Barnett to that chapter is acknowledged.

## References

- AIUM/NEMA. 1992. Standard for Real-time Display of Thermal and Mechanical Acoustic Output Indices on Diagnostic Ultrasound Equipment. Rockville, MD: American Institute of Ultrasound in Medicine.
- Barnett SB, ter Haar GR, Ziskin MC, Nyborg WL, Maeda K, Bang J. 1994. Current status of research on biophysical effects of ultrasound. *Ultrasound Med Biol*, 20, 205–218.
- Barnett SB, Rott HD, ter Haar GR, Ziskin MC, Maeda K. 1997. The sensitivity of biological tissue to ultrasound. *Ultrasound Med Biol*, 23, 805–812.
- Barnett SB, Abramowicz JS, Ziskin MC, Marsal K, Claudon C. 2010. Safety of nonmedical use of ultrasound. *Ultrasound Med Biol*, 36, 1209–1212.
- BMUS. 2010. Guidelines for the safe use of diagnostic ultrasound equipment. *Ultrasound*, 18, 52–59.
- Brezinka C. 2010. Non-medical use of ultrasound in pregnancy; ethical issues, patient's rights and potential mis-use. *Ultrasound Med Biol*, 36, 1233–1236.
- Child SZ, Hartman CL, Schery LA, Carstensen EL. 1990. Lung damage from exposure to pulsed ultrasound. *Ultrasound Med Biol*, 16, 817–825.
- Duck FA, Henderson J. 1998. Acoustic output of modern ultrasound equipment: is it increasing? In *Safety of Diagnostic Ultrasound*, Barnett SB, Kossoff G (editors). New York, NY: Parthenon Publishing Group, pp. 15–26.
- EFSUMB. 1995. European Committee for Ultrasound Radiation Safety, Tutorial paper on transvaginal ultrasonography—safety aspects. *Eur J Ultrasound*, 1, 355–357.
- EFSUMB. 1996a. European Federation of Societies for Ultrasound in Medicine and Biology, Clinical safety statement for diagnostic ultrasound. Report from the European Committee for Ultrasound Radiation Safety. *Eur J Ultrasound*, 3, 283.
- EFSUMB. 1996b. Tutorial paper: thermal and mechanical indices. European Committee for Ultrasound Radiation Safety. *Eur J Ultrasound*, 4, 145–150.
- FDA. 1985. 510(k) Guide for Measuring and Reporting Acoustic Output of Diagnostic Ultrasound. Rockville, MD: Food and Drug Administration, Centre for Devices and Radiological Health.
- FDA. 1993. Revised 510(k) Diagnostic Ultrasound Guidance for 1993. Rockville, MD: Centre for Devices and Radiological Health, US Food and Drug Administration.
- Henderson J, Whittingham TA, Dunn T. 1997. A review of the acoustic output of modern diagnostic ultrasound equipment. *BMUS Bull*, 5, 10–14.
- IEC. 1992. Standard 1157: Requirement for the Declaration of Acoustic Output of Medical Diagnostic Equipment. Geneva, Switzerland: International Electrotechnical Commission.
- Martin K. 2010. The acoustic safety of new ultrasound technologies. *Ultrasound*, 18, 110–118.
- Phillips RA, Stratmeyer M, Harris G. 2010. Safety and U.S. regulatory considerations in the non-medical use of medical ultrasound devices. *Ultrasound Med Biol*, 36, 1224–1228.

WFUMB. 1992. World Federation for Ultrasound in Medicine and Biology Symposium on Safety and Standardisation in Medical Ultrasound. Issues and recommendations regarding thermal mechanisms for biological effects of ultrasound, Barnett SB, Kossoff G (editors). *Ultrasound Med Biol*, 18, 731–814.

WFUMB. 1998. World Federation for Ultrasound in Medicine and Biology Symposium on Safety of Ultrasound in Medicine: conclusions and recommendations on thermal and non-thermal mechanisms for biological effects of ultrasound, Barnett SB (editor). *Ultrasound Med Biol*, 24, 1–55.

WFUMB. 2011. Statement on the Safe Use of Doppler Ultrasound During 11–14 week scans. *Ultrasound Med Biol*, 36, 1210.

Whittingham TA. 2000. The acoustic output of diagnostic machines. In *The Safe Use of Ultrasound in Medical Diagnosis*, ter Haar G, Duck FA (editors). 2nd Edition. London, UK: The British Medical Ultrasound Society & The British Institute of Radiology, pp.16–31.



# Glossary

**Absorption coefficient:** measure of the rate of decrease in the energy of an acoustic wave due to viscosity, thermal effects, chemical relaxation, etc., but excluding scattering. See also *Attenuation coefficient*

**Acoustic cavitation:** formation and/or activity of gas-filled bodies in a medium exposed to an acoustic field. Commonly used with regard to cavitation associated with ultrasonic field as well

**Acoustic impedance:** ratio of acoustic pressure to particle velocity in a medium exposed to an ultrasound wave, equal to the product of density and speed of sound

**Acoustic intensity:** rate of acoustic energy flow through a unit area normal to the direction of wave propagation

**Acoustic streaming:** the flow of fluid within an ultrasonic beam, in the direction of wave propagation: originally termed “quartz wind”

**AIUM:** American Institute for Ultrasound in Medicine

**Attenuation coefficient:** coefficient that describes the energy lost, by absorption and scattering, when an ultrasonic beam passes through a medium. The intensity absorption coefficient  $\mu$  of a homogeneous medium is defined for a single frequency by the equation  $I = I_0 e^{-\mu x}$ , where  $I_0$  is the initial intensity and  $I$  is the intensity after the beam has travelled distance  $x$ . An amplitude attenuation coefficient  $\alpha$  can also be defined, where  $\mu = 2\alpha$ . Units: dB cm<sup>-1</sup>, or Np cm<sup>-1</sup>

**ASUM:** Australasian Society for Ultrasound in Medicine

**BECA:** beam calibrator; a device for quantifying acoustic fields. Also referred to as the NPL Ultrasound Beam Calibrator (UBC)

**BIR:** The British Institute of Radiology

**BMUS:** The British Medical Ultrasound Society

**Cavitation:** see *Acoustic cavitation*

**Cavitation nucleus:** point (e.g. impurity or structural irregularity in a liquid or soft tissue) from which a gas bubble may grow and oscillate under the action of an ultrasonic field

**CEN:** Comité Européen de Normalisation

**CENELEC:** Comité Européen de Normalisation Electrotechnique

**CFM:** colour flow mapping using Doppler shift methods. Sometimes referred to as colour Doppler

**Collapse cavitation:** see *Inertial cavitation*

**Contrast agents:** agents that can be administered to patients to improve or enhance the diagnostic information in a scan specifically for ultrasound by differentially altering echogenicity; ultrasound contrast agents usually consist of a suspension of small gas bubbles stabilized against dissolution by the presence of an encapsulating shell of lipid, protein or polymer

**Derating:** process by which the attenuating effects of overlying structures in an ultrasonic beam are accounted for. See also *in situ intensity*

**ECURS:** European Committee for Ultrasound Radiation Safety

**EFSUMB:** European Federation of Societies for Ultrasound in Medicine and Biology

**Embryo:** unborn offspring in first trimester of pregnancy

**ESWL:** extracorporeal shockwave lithotripsy

**Extravasation:** leakage of blood cells through vessel walls

**FDA:** Food and Drug Administration (USA)

**Fetus:** unborn offspring in second or third trimester of pregnancy

**Fluid inertia:** the tendency of a moving fluid to continue with a constant velocity

**Free radical:** an atom or molecule having at least one unpaired electron and typically unstable and highly reactive. In animal tissue, free radicals can damage cells and promote the progression of disease

**Gas bodies:** accumulations of gas; examples include bubbles, intestinal gas and lung alveoli

**Hydrophone:** device used for measuring acoustic pressure

**Hyperthermia:** a temperatures above normal

**IEC:** International Electrotechnical Commission

***in situ intensity:*** intensity at a target. This is usually calculated to take into account the attenuation of overlying tissues

***in vitro:*** literally “in glass”. Used to refer to experiments carried out in the laboratory, in which samples can be studied in isolation from their host

***in vivo:*** used to refer to studies carried out in the intact living organism

**Inertial cavitation:** activity of a gas body in an acoustic field characterized by rapid growth and subsequent collapse to a very small size, converting sound energy into heat, light, and shock waves. The motion during the collapse phase is governed by the inertia of the surrounding material rather than the acoustic and hydrodynamic pressure, hence “inertial”. Previously referred to as collapse cavitation or transient cavitation

**Intensity:** see *Acoustic intensity*

$I_{ob}$ : output beam intensity; the spatial-average intensity at the transducer face

$I_{sata}$ : spatial-average temporal-average intensity

$I_{sppa}$ : spatial-peak pulse-average intensity

$I_{spta}$ : spatial-peak temporal-average intensity

$I_{ta}$ : temporal-average intensity

**Lysis:** cell disruption resulting from extracellular membrane damage

**Mechanical index:** an output parameter related to the probability of an acoustic field giving rise to cavitation, used as an “on screen” label for the Output Display Standard

**MI:** see *Mechanical index*

**Microstreaming:** highly localized fluid movement in the vicinity of an oscillating gas body

**NCRP:** National Council on Radiation Protection and Measurements (USA)

**NEMA:** National Electrical Manufacturers Association (USA)

**Non-inertial cavitation:** activity of a gas body in an acoustic field below the threshold acoustic pressure for inertial cavitation. Previously also known as stable cavitation.

**NPL:** National Physical Laboratory (UK)

**ODS:** see *Output Display Standard*

**Output Display Standard:** AIUM/NEMA requirement for the display of safety-related indices on the screen of an ultrasonic scanner; the equivalent international standard promulgated by the IEC is “Medical electrical equipment. Part 2-37: Particular requirements for the safety of ultrasonic medical diagnosis and monitoring equipment”, edition 2.0

**Peak negative pressure:** see *Peak rarefaction pressure*

**Peak rarefaction pressure:** maximum negative pressure amplitude in an ultrasonic wave

**Petechia:** a very small spot of haemorrhage, typically on a surface such as skin or mucous membrane: also called petechial hemorrhage

**PPSI:** pulse-pressure-squared integral; the integral of the square of the acoustic pressure over one pulse.

**prf:** pulse repetition frequency

**PVDF:** polyvinylidene fluoride; material used as the sensor in some hydrophones

**Radiation force:** the force experienced by a solid object when it is placed in a progressive ultrasound wave. The force is directed along the beam in the direction of propagation

**Resonant bubble:** a bubble in an ultrasonic field pulsating at one of its resonant frequencies; the term generally refers to the case for which the response consists of one radial maximum and one radial minimum per acoustic period. The amplitude of oscillation of a bubble is largest at its resonant frequency

**Resonant frequency:** a frequency of vibration of an object determined by the physical characteristics of the object and characterized at low acoustic intensities by the response of the object being maximal

**Scattering coefficient:** coefficient defining the portion of ultrasonic energy loss that is due to scattering. See *Attenuation coefficient*

**Sonoporation:** ultrasonic induction of pores in the cellular membrane

**Spectral Doppler:** a pulsed Doppler technique for blood flow waveform analysis

**Teratogenic effects:** effects resulting in abnormal development of the embryo and foetus

**Thermal index:** an output parameter calculated as the ratio of attenuated acoustic power at a specified point to the attenuated acoustic power required to raise the temperature at that point in a specific tissue model by 1°C; used as an “on screen” label for the Output Display Standard

**TI:** see *Thermal index*

**Transducer:** source of ultrasound (also referred to as the “probe”)

**Transducer self-heating:** heating of an ultrasonic source (probe) due to dissipation of electrical energy within the probe itself

**Ultrasound bioeffects:** the biological and physiological consequences of the passage of an ultrasonic wave through tissue

**WFUMB:** World Federation for Ultrasound in Medicine and Biology

# Index

## A

Absorption, 8, 19, 23, 28, 82  
 Absorption coefficient, 9, 13, 15, 63  
 Absorption coefficient of bone, 48  
 Acoustic absorption coefficient, 48  
 Acoustic cavitation, 91  
 Acoustic frequencies, 82  
 Acoustic impedance, 7, 16  
 Acoustic intensity, 4, 82  
 Acoustic output (or output)  
     manufacturer declared values, 36–39  
     regulation, 36, 42  
     surveys, 33–40, 42  
     trends, 39–40  
     values, 33–40, 42  
 Acoustic power (or power), 10  
     measurement of, 19–20, 28, 33  
 Acoustic pressure, 5  
     measurement of, 19–21, 25–26, 33  
     peak compression pressure, 19, 34  
     peak rarefaction pressure, 18, 19, 21, 23,  
         34–37, 39, 40, 42  
 Acoustic radiation force impulse (ARFI),  
     20, 82  
 Acoustic shock, 11  
 Acoustic streaming, 20, 81, 83, 87  
 AIUM/NEMA, 135, 138  
 ALARA principle, 2  
 Alveoli of the lung, 16  
 Amniotic fluid, 83  
 Attenuation, 8, 21, 32  
 Attenuation coefficient, 7–9, 15, 82, 85

## B

Backscattered energy, 9  
 Bio-effects, 50, 81, 87, 88, 91  
 Birth weight, 91  
 Blanching of the choroid, 86  
 Blood, 96

Bone, 4, 10, 16, 94, 138  
 Bone healing, 95  
 Bone heating, 95  
 Bone marrow, 51  
 British Medical Ultrasound Society  
     (BMUS), 151

## C

Calibration  
     hydrophone, 25, 26  
     radiation force balance, 28  
 Cardiac adverse effects, 109, 110, 118  
 Cardiac response, 87  
 Cavitation, 2, 14, 16, 18, 19, 22, 23, 37, 69–72,  
     75, 81, 92, 93  
 Cell density, 92  
 Cell lysis, 91, 92  
 Cell membrane, 88  
 Cellular function, 94  
 Cellular mechano-transduction, 88  
 CE marking, 24  
 Central nervous system, 63  
 Choroid blanching, 87  
 Chromosomal effects, 93  
 Colour flow imaging, 47, 50  
 Congenital heart defects, 54  
 Contrast agent, 105–114, 116–118  
 Contrast medium, 16  
 Control settings  
     effects on acoustic output, 31  
     preset, 41  
     worst case, 31, 32

## D

Derated values, 21–22  
 De-rating, 137  
 Developmental effects, 86  
 Diagnostic ultrasound, 105–118  
 Divergent beam, 29

DNA, 93  
 Doppler, 82, 148  
 Doppler Ultrasound, 148  
 Dose, 2  
 Dose-response relationship, 59

## E

EC, 135  
 Echocardiography, 106, 109, 110,  
     112–113, 117  
 Efficiency, 15  
 EFSUMB, 149, 154  
 Elastography, 82  
 Electrical earth leakage current, 135  
 Electrical safety, 135  
 Embryos, 97  
 Epidemiology, 125–131  
 Energy deposition, 10  
 European Committee for Ultrasound  
     Radiation Safety (ECURS), 145  
 Exposure, 4  
 Exposure duration, 54  
 Exposure time, 152, 153  
 Extracellular membrane, 93

## F

FDA. *See* Food and Drug Administration  
 Febrile obstetric patients, 51  
 First trimester, 148  
 Fluid-filled cysts, 84  
 Fluid movement, 87  
 Focused beam, 29  
 Focusing, 10  
 Foetal gestational age, 49  
 Foetal neural tissue, 52  
 Foetal weight reduction, 98  
 Food and Drug Administration, 13, 18, 22,  
     36–38, 42, 43, 134–136, 143  
     510k, 136  
 Free-field values, 21–22  
 Free radical, 93  
 Frequencies, 4, 5, 49  
 Functional changes, 94

## G

Gas, 8, 14  
 Gene expression, 86  
 Gestation, 52, 54  
     in humans, 54

Guidelines, 62, 151  
 Guidelines and recommendations, 142

## H

Haemodynamic shear, 88  
 Haemorrhage, 86, 87  
 Handedness, 127, 129–131  
 Harmonics, 13  
 Hazard, 31  
 Healing of bone fractures, 86  
 Heat conduction, 15  
 Heating, 2, 4, 13, 46, 50  
     tissue, 18, 19, 21–23  
     transducer self heating, 22, 31  
     transducer surface temperature, 23, 30, 32  
 Heat shock proteins, 52  
 Homeostatic processes, 51  
 Hydrophone  
     calibration, 25, 26  
     measurement systems, 27–28  
     membrane, 25, 26, 28, 33  
     preamplifier, 25  
     probe (needle), 26  
 Hyperthermia, 51

## I

IEC. *See* International Electrotechnical  
     Commission  
 IEC60601 Part 2-37, 136  
 Imaging modes  
     B-mode, 18, 30, 32, 34–42  
     colour flow, 30, 32  
     harmonic imaging, 33, 38, 42  
     M-mode, 32  
     pulsed Doppler, 21, 34–40, 42  
     spectral Doppler, 18, 32, 33  
 Index values, 152, 153  
*In situ* exposure, 11, 137  
 Intensity, 10, 82  
     measurements, 20–21, 26–27, 33  
     spatial-average temporal-average  
         intensity, 21  
     spatial-peak pulse average intensity, 21  
     spatial-peak temporal-average intensity, 18,  
         21, 35, 40  
     temporal-average intensity, 21, 26, 27, 32  
     temporal-peak intensity, 19, 20, 32  
 International Electrotechnical Commission,  
     22, 23, 25, 26, 28, 30, 36, 134, 135

International guidelines, 146

Intestine, 14, 16

Intra-rectal probes, 136

ISUOG, 155

## L

Longitudinal compressional wave, 5

Longitudinal waves, 5, 16

Lung, 14

Lysosomes, 93

## M

Maternal fever, 54

Maternal hyperthermia, 54

MDD. *See* Medical Devices Directive

Mechanical effects, 13, 14, 69–72

Mechanical index, 2, 11, 61, 71–73, 76, 134, 137, 138, 145, 149

definition, 22

Mechanical process, 4

Medical Devices Directive, 36, 134, 140

MHRA, 140

MI. *See* Mechanical index

Mitochondria, 93

Mitosis, 92

M-mode, 10, 49, 82, 138

## N

National standards, 26, 29

Neonatal ultrasound, 152

Neper, 8

Neuronal migration, 98

Neurosensory responses, 86

Non-linear acoustic effects, 4

Non-linear enhancement, 82

Non-linearity coefficient, 7

Non-linear propagation, 25, 28, 42, 85

Non-linear propagation effects, 11

Non-medical use, 155

Non-thermal effects, 147, 148

## O

Obstetrics, 152

ODS. *See* Output Display Standard

Ophthalmology, 137

Organogenesis, 88

Output Display Standard, 48, 136, 138, 145

## P

Peak rarefaction pressure, 4

Permeability, 93

Phantom

thermal, 31, 41

Physical effects, 86

Piezoelectric transducer, 15

Plane-wave assumption, 26

Power, 82

Preset

scanner controls, 41

Pressure pulses, 12

Propagation, 4

Propagation speed, 7

Protein synthesis, 94

Pulsed Doppler, 10, 47, 49, 50, 63, 95

Pulsed radiation force, 87

## Q

Quality assurance (QA), 24

## R

Radiation force, 70–71, 75, 81, 82

Radiation force balance (RFB), 81

calibration, 28

target, 28–30

Radiation force in fluids and tissues, 85

Radiation force on soft tissue, 86

Radiation pressure, 14

Randomized controlled trials, 125, 126, 129–131

Rarefaction pressure, 11

Reflection, 7, 16

Regulations, 22, 134

Renal adverse effects, 109

Reproductive integrity, 91, 92

Risk, 143

Risk assessment, 143

Risk/benefit, 143

## S

Safety guidelines, 42

Safety indices, 134

Safety standards, 134

Scanned transducer, 139

Scanning time, 151

Scatter, 8

Scattering, 8, 9

Scattering coefficient, 9

Sensory effects, 86

Shear forces, 85  
 Shear stress, 88  
 Shear wave elasticity imaging (SWEI), 83  
 Shear waves, 16  
 Soft tissues, 4, 8, 96, 138  
 Souvenir scanning, 151  
 Spatial peak, pulse-average intensity, 137  
 Spatial-peak temporal average intensity ( $I_{\text{spta}}$ ),  
     10, 47, 137  
 Specific heat, 15  
 Spectral pulsed Doppler, 138  
 Standing wave, 6  
 Streaming, 83  
 Surface waves, 16

## T

Tactile sensation, 87  
 Temperature increases, 46, 47, 49, 51, 63  
 Temperature rise, 50, 138, 139  
 Temperatures, 14  
     tissue, 22, 23  
     transducer face, 18, 23, 32  
 Temperature thresholds, 57  
 Temperature-time profiles, 59  
 Teratogenic effects, 46, 54  
 Thermal, 81  
 Thermal bio-effects, 49  
 Thermal conduction, 16  
 Thermal dose, 56, 60, 61  
 Thermal effects, 13, 46, 147  
 Thermal exposures, 60  
 Thermal index, 2, 60, 134, 137, 138, 145, 149  
     bone thermal index (TIB), 23, 37, 38, 42  
     cranial thermal index (TIC), 23, 37, 38, 42  
     definition, 23  
     soft tissue thermal index (TIS), 23, 37, 38, 42  
 Thermally induced biological effects, 55  
 Thermally induced teratogenic effects, 53  
 Thermal phantom, 31, 41  
 Thermal safety, 135  
 Thresholds, 58

TI. *See* Thermal index  
 TIB, 138  
 TIC, 138  
 Time-averaged acoustic intensity, 15  
 TIS, 138  
 Tissue heating, 15  
 Tissue perfusion, 15  
 Total acoustic power, 4  
 Track 1, 137  
 Track 3, 137, 138, 143  
 Transducer heating, 147  
 Transducers, 15, 50  
 Transducer self-heating  
     measurement of, 31  
     surface temperature, 31  
     temperature limits, 23, 30  
     temperature rise, 31  
 Transducer surface temperatures, 134  
 Transmission, 7  
 Trans-vaginal probe, 136  
 Transverse/shear wave, 5

## U

Ultrasound contrast agents (UCA), 69, 70, 72,  
     75, 76, 150  
 Ultrasound dosimetry, 2  
 Ultrasound heating, 48  
 Ultrasound safety, 125, 126, 131  
 Ultrasound wave propagation, 5  
 Ultrastructural changes, 93  
 Unscanned beam, 10, 82  
 Unscanned transducer, 139

## V

Vasculature, 96

## W

Wavelength, 5, 6  
 Wave propagation speed, 6  
 WFUMB Safety Committee, 143–146  
 Worst case values, 31, 34–36, 41