Ultrasound bioeffects and safety

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Abstract: The main mechanisms by which ultrasound can induce biological effects as it passes through the body are thermal and mechanical in nature. The mechanical effects are primarily related to the presence of gas, whether drawn out of solution by the negative going ultrasound pressure wave (acoustic cavitation), a naturally occurring gas body (such as lung alveoli), or deliberately introduced into the blood stream to increase imaging contrast (microbubble contrast agents). Observed biological effects are discussed in the context of these mechanisms and their relevance to ultrasound safety is discussed.

Keywords: ultrasound safety, ultrasound bioeffects, thermal effects, acoustic cavitation, diagnostic ultrasound

1 INTRODUCTION

There is no doubt that the passage of ultrasound through tissue disturbs the cells in its path. Whether or not this leads to structural or functional changes depends to a large extent on the energy transmitted in the beam, its frequency, and the environment in which the cells find themselves. In the field of ultrasound, the term bioeffect is usually used in the pejorative sense, implying that it is unwanted, and may lead to harmful effects. In reality, bioeffects fall into two categories, those that are beneficial (reversible or irreversible) and may be used to therapeutic advantage, and those that lead to tissue damage that may be hazardous to the organ or individual exposed.

In considering the safety of medical ultrasound exposures, it has been conventional to divide bioeffects into groups determined either by the physical mechanisms producing them (mechanical or thermal) or to describe them in terms of effects occurring at the cellular or intact tissue levels. Both approaches have their own merits and accompanying disadvantages. It is necessary to build an overall picture that allows assessment by users of the safety issues arising from any particular ultrasound application, as the onus now lies with them to provide an accurate diagnosis using conditions that present as low a risk as possible. In making this assessment, it is necessary to consider the hazards presented by the ultrasound exposure and the associated risk. Here, the discussion presented by Duck [**1**] is useful. In ISO 14971 [**2**], an international standard addressing the application of risk management to medical devices, 'hazard' (defined as a possible source of harm) is distinguished from 'risk' (the probability of occurrence of harm, and its severity). Thus, a busy road presents a hazard, for which the risk to an individual is zero until he chooses to cross it, and then the risk varies according to whether or not he chooses to use a crossing, and the traffic density.

For ultrasound, the hazards arise predominantly from the heating caused by the absorption of the sound energy in tissue, from the mechanical effects arising from the presence of gas, and from radiation pressure. It is in terms of these mechanisms that reported bioeffects are discussed next.

2 LIMITATIONS OF EXISTING BIOEFFECTS LITERATURE

There is now a considerable ultrasound bioeffects literature, covering a wide range of biological models and ultrasound exposure regimes. It is this breadth that makes it difficult to distil the most relevant reports when considering diagnostic ultrasound safety. A problem in assessing low-level effects is

the inability to prove a negative. A null finding may be either because no effect exists, or because the assay used is insufficiently sensitive to detect it. This latter explanation is more likely to hold for the early literature, where available biological and functional assay tools were less sophisticated than modern ones. Another limitation of many early studies is the type of ultrasound exposure conditions used. From a diagnostic safety viewpoint, effects arising from short, high-amplitude ultrasonic pulses at high repetition rates are most relevant to clinical practice. In the main, however, bioeffects research has until recently focused on continuous-wave or long-tone-burst exposures. It may be argued that the experimental exposure regime is unimportant if the physical mechanism by which an effect is induced is known, as the likelihood of these mechanisms occurring during clinical applications can then be assessed. However, this highlights another concern with available experimental studies. Many basic studies have been conducted using cell exposures *in vitro*, with the cells being either maintained in suspension culture or grown as monolayers. Whereas these models allow careful study of effects on cell membranes and organelles under well-defined conditions, the way in which ultrasound interacts with these cells in an aqueous environment is different from the interaction with cells in intact tissues. It is likely that in these *in vitro* studies, the predominant mechanisms inducing biological effects will be non-thermal in origin, most probably acoustic cavitation and/or streaming. When cells are exposed to ultrasound *in vivo*, thermal mechanisms often become more important than mechanical ones, and in addition the body's normal physiological responses (e.g. an increase in local blood flow in response to a temperature rise) come into play. A final problem with the interpretation of many published studies lies with scaling. Investigations of effects in pregnant mice using a clinical diagnostic ultrasound beam, for example, can involve whole-body exposures of the foetus, whereas in the human only a small proportion of the foetal total volume is exposed. In addition, unless suitable provision is made, the attenuation of the beam by the tissues overlying the target of interest is considerably less in these circumstances than that in human exposures. This can be accounted for if the relevant tissue properties are known.

Despite these limitations, understanding of the interaction of ultrasound with tissue is deepening, and many recommendations can be made for the appropriate use of ultrasound which minimize the risk associated with its use. It is clear that it is not possible to conduct all biological studies using clinical devices, and there are many areas for investigation that are still required. It is important in ongoing research to ensure that the most appropriate biological models and effects are addressed so that the implications of findings for current (and future) clinical practice may be understood.

In this regard, interpretation of the relevance of one exposure regime to another would be considerably simplified if bioeffects could be described in terms of units of 'dose'. This is an accepted concept in ionizing radiation, where exposure and dose have different units, but is very much more complex for ultrasound, where a number of different mechanisms of action are involved. Ultrasound exposures are usually described in terms of field parameters (pressure and/or intensity) measured in water. In order to describe the field in tissue it is necessary to know the attenuating effects of the intervening tissues. The amount of heating obtained depends in part on the intensity and the tissue absorption coefficient. The biological effects of tissue heating have been related to 'thermal dose'. This concept was introduced by Sapareto and Dewey [**3**] and includes both the temperature and the time for which it is maintained, thus incorporating the idea that high temperatures induce damage in a shorter time than lower ones. It is expressed in terms of the equivalent time at a reference temperature (usually taken as 43 °C) that produces the same effect.

3 MECHANICALLY INDUCED (NON-THERMAL) BIOEFFECTS

A recent publication has defined mechanically induced ultrasonic bioeffects as those resulting from exposures in which the temperature rises by less than 1 °C above normal physiological levels [**4**]; they are thus also known as non-thermal effects. These effects arise either directly from the interaction with the sound field (e.g. from the high shear stresses around an oscillating bubble) or as a consequence of this interaction (e.g. from the free radicals produced by bubble collapse during inertial cavitation). The mechanisms that have been identified include acoustic cavitation, radiation force, and acoustic streaming. It should be noted that for many ultrasound exposures, both thermal and mechanical effects will occur and are difficult to separate mechanistically, with, for example, a change in temperature affecting the threshold at which cavitation occurs.

The majority of mechanically induced bioeffects arise when the ultrasonic field interacts with gas in its path. The gas may take the form of naturally occurring gas inclusions, such as exist in the lung alveoli or bowel, deliberately introduced stabilized gas-filled microbubbles used to provide imaging contrast, or bubbles created during the rarefactional portion of the acoustic pressure cycle (acoustic cavitation).

Acoustic cavitation is a threshold phenomenon. In an ultrasonic field, gas is drawn out of solution at points of tensile weakness in the propagation medium (nucleation sites) only when the negative pressure exceeds a threshold amplitude. Once formed, the bubble can grow by rectified diffusion. At low-pressure amplitudes, the bubble will undergo linear oscillations with a radius–time curve that is approximately sinusoidal in shape. This is referred to as stable, or non-inertial, cavitation. As the pressure amplitude is increased, these oscillations become non-linear, and the radius may remain at its maximum amplitude for times longer than a half acoustic cycle, remaining at values less than equilibrium only for a very brief time. This behaviour can rapidly lead to collapse because during bubble shrinkage the momentum of the surrounding fluid overcomes the internal bubble pressure. This is inertial, or collapse, cavitation. A resonant bubble size exists at which a small increase in acoustic pressure amplitude results in a large increase in amplitude of radial oscillation. The magnitude of the pressure amplitude required (usually referred to as the cavitation threshold) depends on a number of factors such as the availability of nucleation sites, temperature, and ultrasound frequency. In a pure liquid containing cavitation nuclei, the threshold is ~ 0.2 MPa at 1 MHz for a 1 μs pulse [**5**], whereas in tissue without pre-existing nuclei the threshold has been shown to be greater than 4 MPa for a similar exposure regime [**6**]. Cavitation thresholds are usually determined experimentally on the basis of characteristic acoustic emissions from the driven bubbles [**7**]. Typically, broad band noise, subharmonic, and superharmonic signals are monitored. It is only in the inertial cavitation regime that high-frequency broadband signals are emitted, and this is therefore used as the marker for such events. The accuracy of threshold determination is critically dependent on the sensitivity of the detection system. Signals arising deep within tissue are more highly attenuated than those from the surface and are thus harder to detect. Cavitation threshold determination in tissue is therefore very difficult. The introduction of ultrasound microbubble contrast agents into the blood pool provides gas bubbles whose exposure may also give rise to biological effects.

The action of an ultrasound wave on a bubble will give rise to small-scale circulation in the fluid surrounding it (microstreaming). If a bubble is close to a cell, the localized shear stresses induced can lead to changes at the cell membrane [**8**]. The absorption of the ultrasound wave by the bubble leads to a radiation force. This may cause the bubble to move at high speed (~ 10 m/s), creating high shear along its path, or may attract cells and particles to itself, forming local aggregates. Such cell clumping may damp the bubble oscillation.

Collapsing (inertial) bubbles have a highly destructive effect on cells nearby. Shock waves may be produced, leading to high stresses locally, which can distort and lyse cells. Extremely high temperatures are also produced, and this can lead to chemical dissociation of water and the formation of the short-lived free radicals $^{\bullet}$H and $^{\bullet}$OH. On recombination, hydrogen peroxide may be formed, and this is thought to be the mechanism for production of the DNA strand breaks seen *in vitro* [**9**]. Free radical production has never been proven *in vivo*, however, in part possibly because their effects have extremely short range and would therefore be difficult to detect. It has proved extremely difficult to induce genetic mutations in cells *in vitro*, even at very high-pressure amplitudes [**10**].

The situation when a gas inclusion lies in the ultrasound beam is somewhat different. Here, the gas body may be too large to oscillate in response to the pressure wave. The organ in which this is most important is the lung, but large gas bubbles may also occur in the bowel. Lung haemorrhage (or more accurately, capillary extravasation) has been observed following ultrasound exposure of rodent, swine, and monkey lungs [**11–16**]. Raeman *et al.* [**17**] showed that the presence of ultrasound microbubble contrast agents did not increase the amount of lung haemorrhage seen. While such effects have never been reported in adult or neonatal human lung following ultrasound exposure, their biological consequences are unclear. A small amount of extravasation may be seen, for example, after a bout of coughing. Church and O'Brien [**18**] have demonstrated that mechanical index (MI) is a poor predictor for the threshold for this effect and have proposed a lung-specific index instead. Vascular damage has also been reported at the intestinal wall in mice (threshold 1 MPa, 0.7–3.6 MHz [**19**]). In an extensive discussion of the mechanisms of action

responsible for the lung haemorrhage seen, Church *et al.* [**20**] suggest that it is caused by direct mechanical stresses associated with ultrasonic propagation in the lung, and the alveolar response to the compressional and tensional waves. The mechanism is thus believed to rely on the presence of gas bodies and so is not of concern in the fluid-filled foetal lung.

In the absence of gas, an ultrasonic wave can generate a radiation force in tissue. This arises from the absorption of acoustic energy along the propagation path, which leads to a non-zero time-averaged force per unit volume. The force, F_{rp}, is given by

$$F_{rp} = 2\alpha I/c \quad (1)$$

where α is the absorption coefficient, I is the intensity, and c is the speed of sound. At an intensity of $1\,W/cm^2$ this gives the very small force of $\sim 1.3\times10^4\,N/m^3$ in a typical soft tissue ($\alpha = 10\,Np/cm$; $c = 1500\,m/s$). A pulsed ultrasound exposure may thus create a pulsatile force at the pulse repetition frequency (prf) of the ultrasound beam. This may result in an audible signal, which may be responsible for the reported increases in foetal movements *in utero* [**21**–**23**]. Radiation forces may also set up macroscopic streaming patterns in fluids. This has not been shown to produce adverse effects, but has been used diagnostically to differentiate between solid and fluid-filled cysts.

A number of biological effects have been attributed to the mechanical mechanisms discussed above. Cavitation has been shown to be the major mechanism involved in lysis of cells exposed to ultrasound *in vitro* [**24**–**26**]. Increasing the cell concentration decreases the proportion of lysed cells [**27**], probably because of the increased oxygen consumption and associated carbon dioxide production from the larger number of cells. This would reduce the amount of cavitation activity [**28**]. Cells in mitosis appear to be more affected by cavitation events than those in other stages of the cell cycle [**29**]. Some ultrastructural and functional changes have also been attributed to non-thermal mechanisms. Changes in cell membrane permeability resulting from exposure regimes typical of ultrasound therapy (1–2 MHz, $\sim 1\,W/cm^2$, ms pulses) have been attributed to streaming. These effects are of particular interest in the field of drug delivery and sonoporation [**30**].

All living tissues exposed to ultrasound contain blood vessels and so effects on the vasculature have been the subject of considerable study. This is of particular importance as ultrasound microbubble contrast agents (UCAs) are carried by the blood to the sites of interest. The filtration of impurities from blood by the body reduces the probability of the existence of cavitation nuclei and renders it difficult to produce damage to whole blood *in vivo* [**31**–**34**]. In experiments *in vitro* erythrocyte haemolysis and platelet activation have been seen in the presence of cavitation [**35**–**37**].

Dalecki *et al.* [**33**] were able to produce a small, clinically insignificant degree of haemolysis in mice exposed to ultrasound through the chest wall. The pressure amplitude required to induce this was reduced in the presence of UCAs, but the threshold was still considerably above that usual from commercial diagnostic scanners [**38**–**41**]. There is now a large body of information about haemolysis resulting from ultrasound exposures in the presence of UCAs. The amount of haemolysis produced appears to be strongly frequency dependent [**42**–**44**], but the MI does not prove to be a good predictor of this effect because the magnitude of the effect decreases with frequency much more rapidly than the inverse square root of frequency characteristic of MI. There is, however, a good correlation between the amounts of haemolysis and inertial cavitation detected [**43**, **45**–**47**].

Dalecki *et al.* [**48**] reported haemolysis in tissue adjacent to foetal bone in the absence of UCAs (10 μs, 100 Hz prf, 3 min, 1.2 MHz, peak positive pressure 4 MPa, peak negative pressure 2.5 MPa). The shearing motion of the soft tissue against the rigid bone was thought to account for this, although Bigelow *et al.* [**49**] have also postulated a thermal mechanism.

Gross *et al.* [**50**] were unable to detect acoustic cavitation at pressure amplitudes up to 0.7 MPa ($16\,W/cm^2$, 0.5–1.6 MHz) in canine aortas, or up to 5.5 MPa ($1\,kW/cm^2$, 0.75–1.45 MHz) in canine left ventricular blood. Ivey *et al.* [**39**] were able to generate bubble boluses using 15 ms pulses of 1.8 MHz ultrasound at 23 MPa ($19\,kW/cm^2$). Hwang *et al.* [**51**] used a 'passive cavitation detector' to study cavitation induced by 6.5 MPa pulses (500 cycle, 1 kHz prf, 1.17 MHz) in rabbit ear veins. No cavitation was seen at 3 MPa, but in the presence of UCAs, the threshold fell to 1 MPa.

Miller and Quddus [**52**] reported an increase in petechiae in the intestines and abdominal muscles of mice (2.5 MHz, 610 ns pulse, 3.6 kHz prf) following injection of UCAs. The threshold was 0.64 MPa for muscle and 1 MPa for intestine.

Endothelial cell damage has been observed in rat mesentery when exposed to ultrasound using a 1.8 MHz phased array transducer [**53**, **54**]. In the presence of UCAs, the threshold for damage was

reduced from 0.82 MPa in their absence, to 0.14 MPa in their presence. As UCAs are most frequently used in echocardiology, the heart has been the subject of considerable study. Li *et al.* [**55**, **56**] described both microvascular leakage and petechiae following ultrasound exposure of rat hearts using a 1.7 MHz diagnostic ultrasound scanner. The threshold for microvascular leakage was 1 MPa and that for petechiae was 0.4 MPa. Red cell extravasation and damaged cardiomyocytes were seen on histology, with microlesions scattered throughout the tissue. These had resolved to small fibrous regions within six weeks [**57**].

Glomerular capillary haemorrhage has been reported when rat kidneys subjected to contrast-enhanced ultrasound scanning were studied histologically [**58**, **59**]. The threshold at 4 MHz was 2 MPa. In a later study [**60**], the effects of the blood in the Bowman's space were examined following intermittent exposure of the rat kidney using 1.5 MHz diagnostic ultrasound at MI values up to 1.5 for 1 min. They found statistically significant haemorrhage and haematuria for $MI > 0.65$. While the majority of erythrocytes were washed out over a 24 h period, some nephrons remained blocked and there was some evidence of tubular epithelium degeneration. The authors propose that care should be taken when exposing elderly patients with diabetic or other types of renal disease to contrast-enhanced ultrasound.

Trans-cranial Doppler is used for diagnostic examinations in the brain. The effect of ultrasound exposure in the presence of contrast agents has therefore been studied in some detail, in part also because there is some interest in using UCAs to aid dissolution of thrombus in stroke patients. Hynynen *et al.* [**61**] found vascular wall damage, haemorrhage, and occasional necrosis at pressure amplitudes greater than 6.3 MPa (1.5 MHz, 10 μs, 1 kHz prf, 20 s,), well above the amplitude currently used for trans-cranial Doppler examinations.

Neuronal migration has recently been studied in embryonic mice [**62**]. Unanaesthetized pregnant mice (day 16 gestation) were exposed to several sessions of diagnostic levels of 6.7 MHz ultrasound (0.2 ms pulse length, I_{SPPA} 1 W/cm^2, I_{SPTA} 0.48 W/cm^2, I_{peak} 1.31 W/cm^2). No changes in brain size or in gross cortical cytoarchitecture were found ten days after birth. A highly significant, dose-dependent increase in neuronal dispersion was, however, found in animals that had been exposed for a total of 30 min or more. The majority of bromodeoxyuridine (BrdU) labelled cells had reached cortical layers II and III in control animals, whereas for exposed animals, there were fewer cells in these layers, and more in the lower layers and the subcortical white matter. There are some questions about the experimental methodology in these studies as maternal restraint can affect neuronal migration; however, even if this is a real ultrasonically induced effect, its functional significance is not clear [**63**]. Similar effects can be caused by other factors. In addition, it is not obvious that these results can be extrapolated directly to humans because of the problems of scaling discussed above.

4 THERMALLY INDUCED BIOEFFECTS

As an ultrasound beam travels through tissue, its energy is attenuated owing to absorption and scatter. The tissue energy absorption results in heating. The temperature rise may be calculated, provided that the thermal and acoustic properties of tissue are known and the acoustic field is well characterized.

In considering thermal bioeffects, it is important to know both the duration of the exposure and the temperature achieved. Heat is a well-known teratogen. In an effort to aid understanding of heat-induced cellular damage and to provide a method of predicting what effects may be expected from a given thermal exposure, the concept of thermal dose has been introduced [**3**]. The following equation is used in this context

$$t = t_{43} R^{(T-43)} \tag{2}$$

where t is the time required at temperature T to produce an effect of the same magnitude as would result from heating at 43 °C for a time t_{43}. It is derived from consideration of activation energies and from Arrhenius analysis. R is 0.5 for temperatures above 43 °C and 0.25 for those below this value. Thermally induced bioeffects thus increase linearly with increasing heating time and exponentially with temperature difference. Using this equation, any heat exposure can be related to an equivalent heating time at 43 °C. This temperature was chosen as there appears to be a break point in the Arrhenius plot ($1/T$ versus $\ln(t)$) at this temperature for many biologically determined endpoints (e.g. inactivation rates, enzyme activation, cell death, tumour necrosis, and teratogenesis).

Many experimental animal models used for thermal biology studies have core temperatures that are different from that of the human. There has been

some discussion as to whether it is the temperature rise or the absolute temperature that is the most important factor in determining the magnitude of any effect seen, and therefore how safety-related recommendations should be couched. This is important, e.g. when the safety of scanning a pregnant mother who has a mild fever is being considered.

Miller *et al.* [**64**, **65**] have studied the relevance of the thermal dose concept for the induction of birth defects in the rat foetus. They demonstrated that the thermal dose to the embryo, rather than the mother, was the defining factor in inducing effects, and that it was the temperature rise above the core level that was important.

The main concern about thermal effects arising from diagnostic ultrasound exposure is in obstetric applications as the embryo and foetus are known to be thermally sensitive, especially during organogenesis. The central nervous system (CNS) is of particular concern. It is well accepted that elevated maternal temperatures (whether from fever or other causes) can lead to birth defects [**66**–**72**]. It has not been possible to obtain temperature measurements in the ultrasonically exposed human foetus *in utero* for a number of reasons, mainly related to the ethics of such a study. Estimates of temperatures that may be achieved therefore come from theoretical modelling, measurements in tissue mimicking phantom materials, and animal models *in vivo*.

Aside from the tissue acoustic and thermal properties, the local blood supply will have an important effect on the temperature reached, as significant cooling may be provided. In two studies in which the temperature rise in the brains of live and dead foetuses was compared for identical exposure conditions, the maximum temperature achieved in sheep foetuses was 30–40 per cent higher after death [**73**] and 10 per cent higher in guinea pig foetuses [**74**]. In guinea pigs this difference was only seen in late gestation, once the cerebral vessels were well developed [**75**]. In the human, there is no circulation during the early stages of gestation, it is only at 10–11 weeks that the embryonic and maternal circulations connect [**76**]. Abramowicz *et al.* have summarized experimental data addressing temperature rise from ultrasound exposures (260 mW, I_{SPTA} 2.9 W/cm^2, 120 s, pulsed, 3.2 MHz) in a number of experimental foetal models [**77**]. They report the measured temperature rise in foetal guinea pig brains. The highest temperatures were found close to bone, with the increase correlating well with gestational age (and therefore degree of bone mineralization). The temperature rise was 1.2 °C at 30 days' gestation and 5.2 °C at 60 days (120 s, I_{SPTA} 2.9 W/cm^2 , 3.2 MHz). Normal gestation for the guinea pig is 66–68 days. These exposure conditions are approximately four times higher than those currently allowed by the US Food and Drug Administration (FDA) for diagnostic use. In studies of heating of the brain of neonatal pigs, it was found that vascular perfusion had no effect on the final temperature achieved when a narrow focused beam was used, whereas in a region where the beam was broad, perfusion could reduce the temperature by up to 20 per cent [**78**]. This is to be expected as it is the high temperature gradients at the edge of the focused beam that will dominate the heat transport in these circumstances.

5 MECHANICAL AND THERMAL INDICES

It is clear from the discussion above that, in assessing the risk presented by a particular ultrasound examination, it is instructive to be able to judge the probability of occurrence of thermal and/or mechanical effects in the exposed tissue. To this end, the FDA has introduced an output display standard (ODS) [**79**].

The ODS defines safety-related on-screen indices to be displayed in real time to aid the user in making an informed judgement about the benefit–risk ratio of an examination. The thermal index (TI) is calculated as the ratio of the output source power to the output required at the same location to produce a 1 °C temperature rise using the same scanner settings. Three different thermal indices have been defined: TIS, the TI relevant for homogeneous soft tissue; TIB, the TI relevant when bone lies at the focus, and TIC, the cranial index for use when bone lies close to the transducer front face. For obstetric scanning, TIS is the appropriate index until bone mineralization takes place, after which time TIB becomes more relevant. None of the thermal indices takes account of potential transducer self heating, which may be the greatest source of temperature rise in tissues near the surface. The MI is designed to inform the user about the possibility of mechanical damage in tissue arising from the presence of gas bodies. Originally based on an analysis of the pressure required to initiate inertial cavitation in a cloud of gas-filled bubbles in water [**80**], the index takes the form

$$\mathrm{MI} = p_{\mathrm{r}} f^{1/2} \tag{3}$$

where p_{r} is the peak rarefactional pressure and f is

the centre frequency of the ultrasonic pulse. The ODS specifies that equipment must be capable of displaying indices if values can exceed 1.0 under any operating conditions. Such equipment must display values that exceed 0.4.

Both indices have their drawbacks and limitations. For example, for the TI a single value of soft tissue attenuation of 0.3 dB/cm per MHz is assumed. This is considerably lower than most measured values [**81**]. Another limitation is the assumption that acoustic propagation is linear. This is inappropriate, especially when measuring diagnostic acoustic pressure amplitudes in water. In addition, these indices do not provide the user with any indication as to where in space the indices are valid. This information is especially important in obstetric scanning as any judgement about risk versus benefit must take into account the sensitivity both of the tissues of interest, and of other structures in the beam path that are exposed incidentally.

When the ODS was first introduced, it was assumed that users would be educated in the importance of these indices [**82**] and thus the transfer of the onus to them for assessing scan safety would be appropriate. However, a recent survey has revealed that many obstetric users pay no heed to the indices while scanning and are only poorly informed as to their meaning [**83**]. In a survey carried out in the UK, in which sonographers were asked to record the indices they used for a variety of scans carried out during the course of one day, it was reassuring to discover that the vast majority of examinations conformed to the British Medical Ultrasound Society (BMUS) guidelines for exposure times at a given TI or MI value [**84**, **85**]. In a survey of MI values observed during neonatal cardiac scanning in the UK, however, average MIs of 1.1 ± 0.3 for B-mode and 1.3 ± 0.3 for colour/pulsed wave Doppler mode were found [**86**]. These are at a level for which the current National Council on Radiation Protection and Measurements (NCRP) advice is that a risk–benefit analysis is important ($MI > 0.5$) and the BMUS guideline advises that for $MI > 0.3$ the exposure time should be reduced as far as possible [**85**, **87**]. The maximum values recorded were 1.6 in B-mode and 1.7 in Doppler mode.

6 ADVICE AND SAFETY STANDARDS

International professional medical ultrasound societies have their own safety committees, and the International Electrotechnical Commission (IEC) is producing standards relating to the safety of diagnostic ultrasound scanners. Perhaps the most important IEC standard in this context is IEC 60601-2-37, which specifies the maximum surface temperatures for transducers run in air (50 °C, temperature rise 27 °C) and in contact with skin (43 °C, temperature rise 10 °C) [**88**]. This is important because transducer self-heating can often be the main cause of temperature rise, albeit superficially. For transducers used internally the maximum allowed temperature rise is 6 °C. IEC 61157 specifies the information that manufacturers must supply about the acoustic output of their scanners [**89**]. The list was drawn up from safety considerations.

The FDA regulates the acoustic output from ultrasound scanners [**90**]. The most commonly used route for approval is that known as Track 3. Devices must conform with an upper limit of *in situ* spatial peak intensity I_{SPTA} (720 mW/cm^2), spatial peak pulse average intensity I_{SPPA} (190 W/cm^2), MI of 1.9, and TI of 6.0. TI may exceed 6.0 provided the level can be justified. Either MI or I_{SPPA} must conform to these limits. For ophthalmology, the poor vascularization of the eye leads to caution owing to the possibility of thermal effects, and lower limits have been set (I_{SPTA} 50 mW/cm^2, MI 0.23, TI 1.0 (I_{SPPA} not specified)).

The American Institute of Ultrasound in Medicine (AIUM) [**91**] and European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [**92**] have published documents designed to explain the rationale for these safety indices. The World Federation of Ultrasound in Medicine and Biology (WFUMB) has published statements about thermal effects and the safety of contrast agent usage [**93**]. EFSUMB has also produced tutorial articles on safety-related subjects, designed to be accessible to the non-specialist ultrasound user [**92**].

7 DISCUSSION AND CONCLUSIONS

It is clear from what has been presented in this paper that the passage of ultrasound through tissue can result in a number of bioeffects that arise from interaction mechanisms which are both thermal and mechanical in origin. When scanning, therefore, the user (on whom the onus for safety now rests) needs to be confident that any benefit outweighs the risk to the patient. Information about the probability of effects arising from these mechanisms is available in the form of real-time on-screen indices (MI, TI). It appears that the usefulness of this approach is limited, however, owing to lack of effective user education and the form these indices take. They

appear to be largely ignored during scanning. If some visible or audible alert were available when appropriate levels are exceeded, more notice might be taken of the indices.

Thermal effects are likely only to be of any significance when ultrasound examinations are carried out using a stationary transducer over bone (such as is used in trans-cranial Doppler examinations). The amount of heating is likely to be small in early pregnancy, as there is no mineralization and so little absorption. Acoustic cavitation is unlikely to occur in tissue at diagnostic output levels in the absence of contrast agents.

Human epidemiological studies have failed to show any causal relationship between diagnostic ultrasound exposures and adverse effects, although it must be remembered that all surveys have involved individuals exposed *in utero* using ultrasound scanners that are now over 10 years old, and typically had lower output than those available today [**94**, **95**]. The overall picture of diagnostic ultrasound is that there is no real cause for concern about safety for techniques in common clinical use at this time. Caution must be exercised, however, when high output regimes (such as pulsed Doppler) are used in obstetrics. Given the difficulty in establishing thresholds for biological effects, good practice would be to use scanner outputs that are as low as reasonably achievable (ALARA) while still acquiring the required diagnostic information. Unnecessary (non-medical) examinations, especially during pregnancy, are inadvisable given the large number of unknowns that still exist.

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