Radiation Stress and its Bio-effects – Safety Aspects (update 2013)

Introduction

The mechanisms producing ultrasound bio-effects have been commonly classed as either thermal or cavitational. However there are a small number of reports in the literature of bioeffects where heating and cavitation are unlikely to be contributing factors. Radiation stress is the most probable mechanism occurring in these circumstances, since low level radiation stresses are exerted whenever an ultrasound beam passes through tissue. Useful reviews can be found in the literature (Duck, 1998; van Bavel 2007; BIR 2013). This tutorial examines aspects of radiation stress 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: another is the elevation of a water surface when exposed to ultrasound from beneath.

Radiation stress

Before considering the radiation stress experienced throughout a volume of tissue, a simpler situation will be discussed: that of an ultrasound beam reaching a surface. The surface could be, for example, a water surface, or in the body it could be an interface between soft tissue and bone, or tissue and air in the lungs. A force, or stress, is generated at the surface, which tends to push it away from the source of ultrasound. The strength of this push will depend on the shape and acoustic character of the interface, and on the power and angle of incidence of the beam.

The local stress is commonly called radiation pressure. It acts at every point on the surface within the acoustic beam. The radiation pressure depends on the ratio of the intensity to sound velocity. Hence the radiation pressure is greatest on the axis of the beam where the intensity is greatest, and lower towards the edges of the beam. The total force on a surface results from the summed radiation pressure, and it is proportional to the total acoustic power. Measurement of this force is a standard method of determining acoustic power.

The next situation to consider is the more complicated one of what happens within a volume of tissue or fluid when an ultrasound beam passes through it. Some of the energy absorbed from the beam generates an internal force acting in the direction of wave propagation, the radiation pressure gradient (or radiation stress gradient). For a plane wave, the radiation stress gradient is given by $2\alpha I/c$, where c is the speed of sound, I is the local intensity and α is the attenuation coefficient. It is greater at higher acoustic frequencies (because attenuation increases with frequency) and varies throughout the field as the intensity varies. So, for an unscanned beam (Doppler and M-mode) the radiation pressure gradient is greater at the focus and on the axis of the beam than elsewhere. In addition the radiation stress gradient can vary because of variation in the absorption coefficient due to tissue inhomogeneity or nonlinear enhancement (discussed below).

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

stress is proportional to the time-average intensity.

Acoustic Streaming

Acoustic streaming results from the radiation stress field in a liquid. The liquid moves away from the transducer as a result of the radiation stress gradient from absorption of acoustic energy. The flow velocity is proportional to the acoustic power and the attenuation coefficient. The maximum velocity reached in a fluid is limited by viscocity and by the geometric boundaries of the fluid space.
It is now recognised that low-level streaming always occurs when diagnostic ultrasound beams propagate through liquids. Measurements of streaming from commercial scanners (Starritt et al, 1989) reported a maximum streaming velocity in water of over 10 cm s^{-1} in pulsed Doppler mode. In imaging fields the streaming velocities were lower, of the order of 1cm s^{-1}. These studies also showed that streaming is established within about a second of the beam being switched on, well within the dwell time of clinical scanning. Streaming has also been observed in-vitro in blood, human serum albumin and amniotic fluid. Streaming at low acoustic powers and within restricted spaces has been investigated using a magnetic resonance imaging technique (Starritt et al, 1999). In water, streaming was observed in beams with acoustic powers as low as 1mW, at the lowest end of the power levels used by commercial ultrasound equipment. Streaming was also detected within the pores of a coarse sponge. Streaming is probably occurring, therefore, much more frequently during diagnostic ultrasound examinations than was previously appreciated. Although there is little information available in the literature, a growing number of clinical users are reporting observations of streaming. 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. There have also been some anecdotal reports of observations of streaming within a testicular abscess, and in the ventricles of an infant brain following haemorrhage. Streaming has also been observed during colour flow and power Doppler examinations of ovarian cysts.
In another EFSUMB tutorial the implications of acoustic non-linearity for safety are discussed (ECURS, 1994). One of the non-linear effects is an increase in the local absorption of acoustic energy associated with an acoustic shock. Since both radiation stress and acoustic streaming depend on absorption, both can increase in non-linear beams. Shocks can easily form in liquids such as urine and amniotic fluid in vivo, and therefore stress enhancement may be expected in fetal tissue when it is scanned behind these fluids.

Radiation stress on fluids and tissues

In fluids and cell suspensions, fluid displacement occurs as a result of acoustic streaming. It is unlikely that the process of gently stirring either amniotic fluid or urine will present a biological hazard. Shear will occur at the boundary of a stream but it is unlikely to cause damage to cells in suspension. Acoustic streaming has been shown to be the mechanism responsible for 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. 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. A number of papers report observations of non-thermal non-cavitational effects on soft tissues. These may be grouped into two categories, as either physical effects or sensory 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 stress 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. The fetal 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.

Bone healing

Low intensity pulsed ultrasound (LIPUS) has recently gained popularity for therapeutic purposes in tissue regene-ration. The sound levels of LIPUS are of the same order of magnitude as those used in US diagnosis, or lower. LIPUS has practical potential, commercial equipment is available and patients are able to perform the therapy themselves,at home. Typical exposure parameters are: f=1.5 MHz, pulse length 200 µs, repetition frequency 1 kHz, intensity 30 mW/cm^2, and 20 minutes sonification/day over the period of treatment.

LIPUS may increase the extent of fracture healing as well as its rate, especially in case of fresh fractures and nonunions (Xuedong et al.2010). Siska et al. (2008) summarized prospective, randomized, double-blind, placebo-controlled clinical studies and found a statistically significant increase of the rate of healing between 53% and 69% in comparison to the controls in 5 of 7 investigations.

It appears that only damaged cells are sensitive to the effects of ultrasound, healthy tissue is not changed. The mechanisms of the ultrasound bioeffects are not fully understood. However, it is assumed that non-thermal, non-cavitational effects play a role. Most researchers agree that primarily the major locus of the bone effects is primarily the osteoblasts (Li et al. 2002). Mechanical perturbations serve as extracellular signals. Rocca (2009) provided an overview of published literature on this subject. LIPUS stimulates the cellular attachments to the surrounding matrices, the intracellular signaling cascades and gene expression for chondrocyte- and osteocyte-specific proteins. Tang et al. (2006) presented detailed results obtained in vitro with rat osteoblasts and found that ultrasound stimulates the COX-2 (enzyme active in the prostaglandin synthesis) expression through the upregulation of cell membrane integrins, acitivation of FAK and other protein kinases. Li and Chang (2002) showed the influence of LIPUS on prostaglandin (PGE_2) secretion. Furthermore, LIPUS enhances the vascularity at the fracture site as demonstrated by Rawool et al. (2003) who conducted *in-vivo* experiments at dogs.

Other authors have shown that low intensity ultrasound (LIUS) has a positive effect also on cartilage tissue growth. The viability, proliferation and matrix protein synthesis of chondrocytes has been changed *in vitro* and LIUS has been applied in cartilage tissue engineering using mesenchymal stem cells *in vivo* (Byoung et al. 2007).

In contrast, Duda et al. (2004) conducted studies with tissue-engineered cartilage

and found that LIPUS has no accelerating effect on the maturation of the tissue implanted into mice.

Nerve regeneration

It is generally known that LIPUS also accelerates peripheral nerve tissue regeneration. This was recently confirmed by different groups working on the functional recovery of neurotometically injured sciatic nerves of rats (Crisci and Fereirra 2002, Chen et al. 2010). Other authors (Tsuang et al. 2010) have performed *in vitro* experiments and concluded that low intensity pulsed ultrasound exposure could promote Schwann cell proliferation, prevent cell death, and keep adequate phenotype presentation for peripheral nerve recovery. Alterations of the expression of different genes were also found (Zhang 2009).

Ren et al. (2010) published results on the LIPUS-induced elongation of neutrides in rat cortical neurons and explained it by the inhibition of one of the central regulator enzymes in the cytoskeletal-related signalling pathway.

As in case of the bone cells, the basic mechanisms for interactions between nerve cells and ultrasound are not yet fully understood. One hypothesis is that stretch-sensitive channels in neural membranes could serve to functionally modulate neuro-electric signals which are normally mediated by voltage-dependent channels (Mihran et al. 1990).

Ang et al. (2006) observed that ultrasound exposure from a B-scanner (f= 6.5 MHz, I_{SPTA}=1,5 mW/cm², total exposure time 30 min and longer) is able to influence neuronal migration in the proliferating brain of mice embryos. A statistically significant number of labeled neurons failed to acquire their proper position in the cortex. The authors interpreted the effects as being due to non-thermal, non-cavitational interactions. However, the transferability of the results to humans is not entirely clear, especially given the very different sizes of the imaged targets (Ang et al. 2006, Maršal 2010).

Sonothrombolysis

Ultrasound enhanced thrombolysis is a promising tool for facilitating therapies for stroke and other acute ischemic diseases. This is evidenced by an extensive literature in recent years (Atar et al 1999, Francis 2001, ter Haar 2007).

The mechanisms of thrombus dissolution vary with the mode of ultrasound delivery, i.e. frequency (20 kHz– MHz range) and intensity (0.2–2.0W/cm²), pulse regime, presence of microbubbles etc. (Atar and Rosenschein, 2004, Balucani and Alexandrov 2010). Many authors agree that the synergistic effect of ultrasound and thrombolytic substances is responsible for the dissolution of the clots and that cavitation phenomena are in many cases a major mechanism. The effects are clearly supported by the presence of gaseous contrast agents as used for ultrasound diagnosis. Microstreaming is assumed to increase the transport of the thrombolytic agents into the clots (Francis et al. 1995, Hitchcock and Holland 2007).

On the other hand, cavitation is not the only effective mechanism. Although Everbach and Francis (1999) suppressed cavitation in an experiment by applying high static pressure they found that the initial increase in thrombolysis was reduced by only 50%. Non-thermal, non-cavitational mechanisms may promote enzymatic reactions due to diffusion enhancement.

The use of transcranial Doppler and

transcranial colour-coded duplex for diagnosis and therapy represents a pioneering step in sonothrombolysis (Mikulik and Alexandrov 2006). In a large meta-analysis Tsivgulis et al. (2010) summarized the results of 6 randomized and 3 nonrandomized studies evaluating a total of 416 cases. They compared the thrombolytic effect of tissue plasminogen activator (tPA) in combination with ultrasound and gaseous ultrasound contrast agents (UCA). They also estimated the safety of the method on the basis of the occurrence of intracerebral hemorrhage in the brain tissue. It was found that recanalization of the occluded vessels and functional independence at 3 months are significantly improved by the synergistic effect of tPA and ultrasound. The presence of UCA provides a further increase. The application of high-frequency ultrasound was not associated with a significantly increased symptomatic intracerebral hemorrhage. In contrast, low frequency applications (300 kHz, 700 MW/cm²) seem to be of more critical concern for safety (Daffertshofer et al. 2005).

Conclusion

It is increasingly recognised that radiation force effects provide a possible explanation for ultrasound bio-effects which appear to be non-thermal and non-cavitational in nature. In adult tissue, the forces generated by radiation stress 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 which it develops in later fetal and adult life since the intercellular matrix has yet to develop. This period, particularly when cell differentiation and migration is occurring, could be one of particular vulnerability to mechanical stress. However there is insufficient evidence to know whether or not the passage of an ultrasound beam could exert sufficient radiation stress to cause permanent displacement of cells. 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.

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