GUEST EDITORIAL

Safety: The heart of the matter

Abstract  An integral part of evaluation of cardiac disease in modern day medicine is echocardiography. It has made great strides since the initial collaboration of Dr Helmut Hertz and Dr Inge Edler. In its modern day form, echocardiography maintains a legacy of a bedside utility while adopting many of the technologic advances ushered in by the digital era. As a result, it boasts a broad and growing spectrum of application including routine use in primary cardiac diagnosis and screening, therapeutic assessment, and guidance of interventional and surgical procedures. With the advent of ultrasound contrast agents it is now arguably the most complete 'one-stop' investigational tool to assess cardiac structure, function and perfusion. However, has it maintained its safety profile? The familiar and oft quoted dictum in medicine of "first do no harm" is of great importance for any diagnostic tool and patient safety should remain a primary consideration for any new investigational technique. In this issue Cosyns’ et al. have examined whether some of the theoretical and in vitro experimental concerns surrounding myocardial injury during and following contrast echocardiography result in any detectable change in cardiac function.

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Please see page 238 for the article by Cosyns et al. (doi: 10.1016/j.euje.2005.03.002) to which this editorial pertains.

Cosyns’ et al. chose tissue Doppler imaging (TDI) to try to identify any changes in left ventricular (LV) function. In many ways TDI is an ideal tool due to its ability to assess longitudinal function, TDI enables measurements of atrioventricular annular and regional myocardial velocities, and is more sensitive than conventional echocardiography in detecting minor abnormalities of LV systolic and diastolic dysfunction. Tissue Doppler, strain, and strain rate echocardiography are real time ultrasound techniques that provide an accurate measure of myocardial function. They offer an objective means to quantify global and regional ventricular function and improve accuracy and reproducibility above conventional 2D echocardiography.¹,²

Radial and longitudinal ventricular function can be assessed by the analysis of myocardial wall velocity and displacement indices, or by the analysis of wall deformation using the rate of deformation of a myocardial segment (strain rate) and its deformation over time (strain). A quick and easy assessment of left ventricular ejection fraction is obtained by mitral annular velocity measurement during a routine study, especially in patients with poor endocardial definition or abnormal septal motion. Strain rate and strain are less affected by passive myocardial motion and tend to be uniform throughout the left ventricle in normal subjects. The improved accuracy and ease of quantification of markers of LV systolic and
diastolic function make it ideal for assessment of sub-clinical changes in function.

The study of myocardial perfusion with echocardiography involves the intravascular injection of contrast agents that can scatter ultrasound. Myocardial contrast echocardiography (MCE) utilizes acoustically active gas filled microspheres (microbubbles) which have rheology similar to that of red blood cells. Ultrasound contrast agents consist of microbubbles with a diameter of <5 μm, containing a high molecular weight gas encapsulated by a stabilizing shell. These agents are able to traverse the pulmonary vasculature and concentrate in the myocardium reflecting the relative myocardial blood volume within the myocardial microvasculature. Due to their acoustic properties, microbubbles considerably enhance the backscattering capabilities of blood, thereby allowing the capillary bed to be imaged with ultrasound. It is now well established that contrast microbubbles can be destroyed by acoustic pulses used in the frequency and intensity range of diagnostic cardiac ultrasound. Because microbubbles are compressible, they alternately contract and expand in the acoustic field, a phenomenon often referred to as cavitation. At low acoustic pressure, microbubbles usually grow and shrink rhythmically and symmetrically around their equilibrium size, this is known as stable or non-inertial cavitation. At higher acoustic pressure, however, the expansion and contraction of microbubbles usually become unequal and markedly exaggerated, leading to their destruction. This second form of activity is known as inertial cavitation.

Because of safety considerations, the possible interaction between ultrasound and tissue has received much attention. It has been shown in animal studies that in organs containing air or in the presence of strong cavitation nuclei, such as contrast agents, ultrasound exposure may induce significant tissue damage, particularly to the microvasculature. There is also accumulating evidence that the mechanism by which tissues are being damaged is the process of inertial cavitation. During this process, microbubbles experience extreme variations in their size, which may culminate in their physical destruction. Locally, inertial cavitation can produce temperature and pressure changes, which by themselves may damage tissue. It may also generate free radicals, cause sonoluminescence, microstreaming and shear stress secondary to the collapse and/or rapid translation movements of the microbubbles. In an in vitro study by Ay et al., they showed that in isolated rabbit hearts exposed to microbubble contrast and ultrasound there was a transient rise in coronary perfusion pressure, and decrease in contractile function. There was also an associated rise in measured lactate levels, implying that the likely mechanism of LV dysfunction relates to transient ischaemia caused by microvascular damage, as a result of inertial cavitation, leading to increased coronary perfusion pressures resulting in myocardial ischaemia.

However, several factors have to be considered before the findings can be extrapolated to the clinical setting. Firstly, the maximum number of microvessels ruptured per ultrasound exposure was extremely low (0.015%) and therefore may be clinically irrelevant. The transducer and tissue were separated by Ringer’s solution, so ultrasound attenuation was practically negligible. In the clinical setting, tissue attenuation is responsible for a decrease of 0.3 dB cm⁻¹ in the amount of ultrasound energy that reaches the focal point of the transducer. Also the concentration of contrast used in this study was far greater than is used in clinical studies in humans. The interspecies differences in terms of tissue vulnerability are also very important. For example, although lung haemorrhage has been observed with ultrasound in rodents no such effect has been observed to date in humans exposed to similar ultrasound energies. Studies performed thus far in thousands of patients with ultrasound contrast agents have failed to document any clinically detectable adverse events.

The study from Cosyns et al. examined the effects of MCE on LV systolic and diastolic dysfunction in humans using TDI. They clearly demonstrated a lack of any clinically significant change in TDI parameters before, and during MCE examination using a high mechanical index (MI) technique. In a study by Soman et al. where haemodynamics were evaluated in patients with heart failure who had undergone MCE using SonoVue, no significant changes in cardiac haemodynamics were observed before, during and 1 h after SonoVue administration. This is reassuring and underpins the hypothesis that despite animal data, clinically relevant effects are unlikely to occur with MCE.

As myocardial tissue is inherently excitable, a variety of stimuli can cause premature ventricular complexes (PVCs). Although PVCs have been reported in human beings subjected to strong ultrasound fields, there have been no such report with regard to the use of diagnostic ultrasound. In diagnostic ultrasound the energy level is several orders of magnitude lower and is well below the threshold for induction of PVCs. The postulated precipitant to PVCs in contrast echocardiography is again thought to be related to inertial cavitation.
resulting in capillary endothelial dysfunction, microvessel rupture and transient ischaemia. There is a concern that microbubble contrast agents, which can act as the nuclei of inertial cavitation at lower MI, may initiate PVCs within the clinical range of diagnostic ultrasound. There are only limited studies which have examined this in humans; one study by van der Wouw et al. 15 (10 patients, 9 controls) demonstrated that contrast echocardiography performed with AIP101 (ultrasound contrast agent) induced an increased number of PVCs, they found MI, dose of contrast agent and infusion versus bolus injection all increased the frequency of PVCs. Other studies have not demonstrated any such adverse effects. A more recent study16 of 135 patients from the POINT investigators found that there was no increase in PVCs observed following myocardial contrast echocardiography. The machine settings, concentration of contrast used and the patient characteristics most closely reflected those used in clinical practice.

Thus, overall, the risk of serious adverse reactions is small if not negligible. In this regard, the large clinical experience accumulated so far in several clinical trials17–19 and in routine clinical practice of more than two million patients is particularly reassuring.

References


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