New technology in echocardiography II: imaging techniques

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Intravascular techniques

Intravascular ultrasound (IVUS) imaging of coronary arteries has become possible due to improvements in the miniaturisation of ultrasound transducers. Intravascular B scan imaging consists of cross sectional imaging of vessels by miniature ultrasound transducers mounted on wires which are contained within a catheter sheath (fig 1). The scanning beam is directed at right angles to the axis of the wire and sweeps through 360° (fig 2). In addition to imaging of structures related to the vessel wall, efforts are being made to classify the tissues present with a view to predicting the success of interventional procedures. Few commercial companies produce such systems. Three

approaches to the generation of an ultrasound image have been reported.¹

- A single transducer element is rotated directly by the drive shaft.
- A single element is fixed and the ultrasound beam swept through 360° by reflection of the beam from a rotating acoustic mirror.
- Array of elements are arranged in a circle around the catheter tip.

In this last approach typically 32 elements are used in present systems and the beam is rotated in a circle by firing groups of elements in turn. This is technically demanding and it is difficult to generate a narrow beam with a relatively small number of elements. With mechanical scanners geometrical distortion of the image may occur as a result of changes in the angular rotational speed of the drive wire. One advantage of the array systems is that sweeping of the beam is electronically controlled and such distortion will not occur.

The ultrasound beam characteristics determine the spatial resolution of the intravascular image which in turn determines the ability to perceive detail in the image. Measurements of the spatial resolution characteristics of a single 30 MHz element intravascular scanner have been reported, where it was noted that considerable deterioration of the lateral spatial resolution occurs with increasing depth.² The limited space available in general makes it difficult to incorporate the advanced beam focusing techniques found in external transducers. Prototype single crystal catheter scanners have been described operating at frequencies as high as 60 MHz.

Three dimensional imaging

3D ultrasonic techniques for visualisation of the heart have been reported for 20 years.^{3,4} With the ever increasing speed and storage capacity of computers, 3D manipulation of ultrasonic images has in recent years become feasible on a commercial basis; this requires the transfer of a complete set of 2D images to the computer. Several approaches are possible for acquisition of the 2D ultrasound images. One common approach is to acquire a set of transoesophageal 2D ultrasound images using a multiplane probe.⁵ The transducer is mechanically rotated in steps through 180°, and sequential scans are acquired and stored by the computer. The multiplane probe has been used to acquire a set of B scan images of the left ventricle.⁶ Automatic algorithms may be employed to trace the edges of the left ven-

Figure 1 Catheter scanners. (A) Rotating transducer, drive shaft (1), window (2), transducer (3); (B) rotating mirror, drive shaft (1), window (2), transducer (3), mirror (4); (C) circular electronic array, preamplifiers (1), transducer elements (2), guide wire (3). (Reprinted by permission of Kluwer Academic Publishers from Bom N, ten Hoff H, Lancee CT, Gussenhoven WJ, Bosch JG. Early and recent intraluminal ultrasound devices. *Int J Cardiac Imaging* 1989;4:79-88.)

Figure 2 Pulse-echo B mode image of diseased artery walls obtained with a rotating 30 MHz transducer.

tricle, and a display program allows visualisation of the reconstructed left ventricle from any selected view. This system has recently become commercially available (TomTec, Germany). 3D imaging has potential in the display of ventricular wall motion, valve structure, ventricular blood volumes, and ventricular myocardial mass (fig 3), but has yet to be fully compared with conventional 2D imaging. Its main role may prove to be in perfusion studies using ultrasonic contrast agents.

Research is being conducted on the reconstruction of 3D intravascular images in the coronary arteries. This requires collection of a set of 2D images at equidistant points along the coronary artery, and is carried out by moving the catheter a known distance between each B scan image^{7,8} (fig 4). The technique has potential in the detailed exploration of the characteristics of plaque and in the assessment of the coronary artery post-angioplasty.

Ultrasonic radiofrequency (RF) signals backscattered from the myocardium

To date, methods for ultrasonically assessing global or regional myocardial function have largely been centred on the analysis of time sequences of images acquired from an ultrasound scanner. Whether this analysis is performed qualitatively by visually interpreting the grey-scale images or quantitatively is largely dictated by the information required from the study and the resources available for subsequent image manipulation and analysis. Quantitative analysis of regional myocardial function may be evaluated either from an assessment of the regional contractility of areas during a stress-echo protocol or alternatively by a relatively new technique involving the monitoring of the variation of integrated backscatter from myocardial segments. Since ultrasonic machines for cardiac applications are optimised to enhance ventricular and valvar dynamics rather than changes in the low-level backscatter signals scattered from within the myocardium, this latter technique requires

access to the ultrasound data earlier in the processing path before signal manipulation. Unfortunately in many instances gaining access to the ultrasound data early in the ultrasonic processing path is dependent on the goodwill of the ultrasound manufacturer. In addition, some of the larger ultrasonic manufacturers work with the analogue signal till late in the signal path, necessitating access to a high-speed digitiser and concomitant computer facilities to capture and store the data. Alternatively a method which bypasses all this off-line analysis has now been implemented on-line by one company (Hewlett Packard, USA) which permits a region-of-interest (ROI) to be interactively chosen and the real time variation of integrated backscatter (IB), a parameter calculated from the RF data, to be continuously displayed on the ultrasound screen.

Without access to the RF data, the image sequence can be digitised at the end of the signal-processing path using a frame-grabber connected to the scanner video output and the variation in grey-scale intensity over a ROI calculated using standard software image analysis packages.⁹⁻¹¹ In some instances, for an individual machine application and set-up it may be possible to use test phantoms to measure and compensate results for the effect of some of the non-linear processes which occur within the ultrasound machine. Because differences in processing paths occur not only between machines from individual manufacturers but also between different models and application set-ups, this can prove to be a time-consuming exercise.

Figure 5 illustrates several of the non-linear processes which occur within an ultrasound machine and which result in the dynamic range of the echo signals being compressed from 100 dB to 20 dB. These processes are time gain compression (TGC), logarithmic compression, demodulation, and scan conversion compression.

ANALYSIS OF RF BACKSCATTER FROM THE MYOCARDIUM

A parameter calculated from the backscatter reflected from the myocardium has been shown to be a discriminator between normal and infarcted myocardium.¹² The parameter, integrated backscatter, is the ratio of the energy backscattered in the acoustical signal arising from the tissue volume of interest divided by that from a reference reflector. For cardiological application, no obvious choice of an anatomical reference reflector exists, although several authors have used the magnitude of the pericardial echo,^{13,14} the magnitude of echoes from the blood pool,¹⁵ or some external source of reference echo.^{16,17}

It has been reported that the magnitude of integrated backscatter measured from normal canine myocardium varies in a predictable manner throughout the cardiac cycle (fig 6)¹⁸ with minimal values at end systole and maximal ones at end diastole. This cyclic variation has been confirmed clinically in the left ventricular posterior wall and the interventricular

Figure 3 Photographs of displays of 3D scans of the left ventricle and valve apparatus (A) and tricuspid valve (B). The images can be rotated on the display to provide an appreciation of the third dimension.

septum in patients with normal ventricular function when imaged from the standard precordial long or short axis scanning positions. In addition, an overall increase in the magnitude of integrated backscatter has been noted from ischaemic or infarcted myocardium¹⁹⁻²² with a concomitant reduction or complete absence of cyclic variation also associated with these regions.²³ In addition upon reperfusion of myocardial regions which had suffered an ischaemic insult, the recovery of this end diastolic to end systolic variation seemed to be an earlier and more sensitive indicator of future

Figure 4 Photographs of a display of a 3D scan of an artery. Rotation of the image provides an appreciation of the third dimension (Courtesy of J Gardener.)

tissue integrity than the dynamics of wall thickening.²⁴⁻²⁷ In dilated or hypertrophied cardiomyopathies an increase in the magnitude of integrated backscatter was also observed²⁸⁻³¹ and a reduction in the normal cyclic variation of integrated backscatter.³²

Despite the large amount of clinical data which is currently available, of which a few are cited above, integrated backscatter as an indicator of tissue viability is still largely not used as a routine clinical tool. Several factors contribute to this. Firstly, cyclic variation within the myocardium has almost exclusively been observed only from the precordial long and short axis views.³³ In a recent study, however, cyclic variation from the myocardium was shown to be present when measured from the apical two and four chamber precordial views of the heart, although in these views the maximum in integrated backscatter is not always coincident with end diastole nor the minimum with end systole.³⁴ Clinical trials are currently underway to establish whether this variation also changes with abnormal left ventricular function. If so, then it will be possible to measure changes of integrated backscatter from all myocardial regions of the left ventricle. Secondly, as stated previously, until recently access to the ultrasonic RF data has generally been restricted to a few research centres. With ultrasound companies giving wider access to this data, it will soon be possible to quantitate changes in myocardial signatures independently of the control settings of the ultrasound scanner.

Myocardial contrast echocardiography

CONTRAST AGENTS

Contrast agents, in particular those that depend on the extremely high scattering prop-

Figure 5 Stages of compression of the dynamic range of echo signals in a conventional ultrasonic scanner.

Figure 6 Variation of integrated backscatter echo signal over a cardiac cycle.

erties of microbubbles, have been extensively used to enhance the power of Doppler signals from blood. Myocardial contrast echocardiography is a relatively new method for studying myocardial perfusion.³⁵ It has the potential to provide information on myocardial perfusion

which perfectly complements the anatomical, functional, and haemodynamic information derived from routine echo studies.

This technique was first described with intra-aortic and intracoronary injections of contrast microbubbles to demonstrate myocardial perfusion.³⁶ When the microbubbles enter the myocardium they cause an increase of backscattered ultrasound energy (power) and hence raise the myocardial grey level intensity in the image (fig 7).

Early contrast agents were derived by agitation of solutions such as indocyanine green, saline, dextrose, hydrogen peroxide, and blood to produce free gas bubbles of air.³⁶ Unfortunately these bubbles that are not encapsulated have a wide range of diameters and the gas diffuses back into the liquid too quickly to allow widespread distribution in the body. Free gas bubbles cannot pass through the lungs so no opacification of the left heart can be achieved unless a right-to-left shunt is present.

Techniques have been devised to create encapsulated bubbles which have a longer life and can survive passage through the lungs. For example, a sonication technique produced microbubbles in human serum albumin (HSA) with diameters less than 10 μm .^{37, 38} Sonication is a technique which produces small microbubbles in a fluid by exposing it to very high intensity ultrasound, typically 20 kHz. Cavitation occurs causing small microbubbles to be produced in the fluid. The process of sonication is illustrated in figure 8. There is at present considerable commercial research and development related to microbubble contrast agents. Some products which are undergoing trials are described below and in the table.

Albunex, marketed in Europe as Infuson (Nycomed, Norway) is made from sonication of 5% HSA and has a shelf life of 6 months. Injections range from 0.025 to 1.0 ml/kg. It is an isotonic, ready to use suspension of $5 \times 10^8/\text{ml}$ air-filled microspheres with diameters of 4 to 10 μm .⁴⁰ At room temperature the suspension remains stable for up to 20 weeks.⁴¹ Nycomed is currently developing a more stable agent called NUS, which will be marketed as a myocardial perfusion agent. This agent is also sonicated human serum albumin but the shell is degraded synthetic polymer.

Properties of some common left heart contrast agents

Left heart agent	Manufacturer	Type of agent	Capsule	Gas	Bubble size	Dose/concentration*
Albunex (Infuson in Europe)	Nycomed (Europe) Mallinckrodt (USA)	Encapsulated bubble	Albumin	Air	Range (4–10 μm), mean 4 μm	0.025–1.0 ml/kg
Levovist	Schering	Encapsulated bubble	Palmitic Acid	Air	Range (2–8 μm), median 3 μm	17 ml of 200 mg/ml 11 ml of 300 mg/ml 8 ml of 400 mg/ml 5 $\mu\text{l/kg}$
Aerosomes	ImaRx	Encapsulated bubble	Lipid	C, F ₈	Mean (2 μm)	
Quantison	Andaris	Encapsulated bubble	HSA	Air	Mean (3.2 μm), range (< 2% > 6 μm)	20–200 $\mu\text{l/kg}$
Echogen	Sonus Pharmaceuticals	Phase-shift	N/A	Perfluoropentane	Range (2–5 μm)	0.1 ml/kg

HSA = human serum albumin.
*Particles/ml solution.

Figure 7 Enhancement of the echogenicity of the myocardium by a microbubble contrast agent. (A) Before and (B) after intra-aortic injection of Levovist in an open-chested pig study.

A saccharide-based agent, SHU 508A Levovist (Schering AG Laboratories, Berlin), has diameters ranging from 2 to 8 μm .⁴² The Levovist product comes in a vial containing granules and a low concentration of a physio-

Figure 8 Sonication process with a low frequency ultrasonic horn source of kHz ultrasound.

logical fatty acid. The granules are mixed vigorously with sterile water, creating a milky suspension of galactose microparticles. The rough surfaces of these galactose microparticles act as origin and adherence sites for bubbles stabilised by a monolayer shell of fatty acid. The microbubbles are of a limited size, about that of an erythrocyte. After injection of the suspension, the galactose microparticles dissolve within seconds to release the bubbles into the blood stream. Such bubbles can last for as long as 5 minutes, recirculating many times. Concentrations of between 200 and 400 mg/ml are used. Another example of a saccharide-based agent is SHU 454 Echovist (Schering AG Laboratories, Berlin). It has bubble diameters of 5 to 15 μm and does not pass through the lungs to a significant extent. SHU 454 is used for right heart applications.

Aerosomes (ImaRx Pharmaceutical, Tucson, Arizona) are lipid-coated microbubbles containing fluorocarbon gas (C_3F_8).^{43 44} There are on average 6 to 7 $\times 10^8$ bubbles/ml with a mean diameter of 2 μm . The recommended dose is 5 $\mu\text{l/kg}$. The agent is reported to be able to withstand pressures up to 300 mmHg, an important consideration in myocardial imaging. The gas is exhaled from the body and does not seem to have toxic effects.

Quantison (Andaris, Nottingham) is another HSA gas encapsulated agent with microbubbles of a mean diameter of 3.2 μm with less than 2% having diameters greater than 6 μm . The thickness of the shell of this agent can be varied between 100 and 200 nm to enable it to withstand high pressure. Andaris are also currently developing another agent, Quantison Depot and marketing this as a myocardial perfusion agent.

A third type of agent in addition to free and encapsulated bubbles is the phase-change agent which is injected into the body as a liquid and at body temperature converts into microbubbles.^{45 46} The agent (Echogen, QW3600) developed by Sonus Pharmaceuticals (Bothell, Washington, USA) is a perfluoropentane emulsion which vaporises to give bubbles with diameters of 2–5 μm . After intravenous injection, it clears from the blood stream in 30 to 40 minutes but attaches to the endocardium giving prolonged enhancement. The recommended dose for humans is 0.1 ml/kg. The above examples of contrast agents are quoted to illustrate the types known to be under development. There are at least 12 contrast agents in the preliminary stages of evaluation. An intravenous agent for myocardial perfusion has still to reach a stage of common acceptance.

TECHNOLOGY FOR CONTRAST STUDIES
Although much effort has been expended on the development of contrast agents, there has unfortunately been little progress on the development of ultrasound technology for the detection of myocardial contrast. Several dedicated computer systems for myocardial contrast echo have been described^{47–49} and used with intra-aortic injections.

Figure 9 Wash-in and wash-out perfusion curves of a microbubble agent (Albunex) in the myocardium before and after angioplasty (PTCA).

Most systems developed in individual centres have used small micro-computers and video frame grabbers. These acquire analogue video data from the video output on the ultrasound scanner. Once a series of echocardiographic frames have been stored in the computer memory then an area of interest may be established on the image and changes in grey level as a result of contrast injection evaluated using video densitometry. Unfortunately, as noted earlier, there is a large amount of distortion and compression of ultrasound data by the imaging system.

This data distortion has meant that quantitative analysis is difficult because a non-linear relation exists between back-scattered ultrasound intensity and grey level display. Furthermore, the comparative low contrast resolving power of current imaging systems means that the small changes in backscatter echo intensity from the myocardium that occur as a result of intravenous contrast injection are not detectable.

To facilitate quantitative analysis of perfusion, temporal changes in myocardial contrast enhancement have been analysed. An area of interest may be positioned over any portion of the image and changes in the grey level values plotted against time. This provides a contrast wash-in and wash-out curve. These curves have been analysed in a number of different ways and parameters such as the peak grey level, wash-out half-time, area under curve and wash-in time have been utilised by several authors.⁵⁰⁻⁵⁴ An example of a perfusion curve is shown in figure 9.

Methods based upon backscatter signal intensity and grey level data seem adequate for intracoronary injections of contrast where changes in signal amplitude are relatively large. However, as previously mentioned, they appear insensitive for the detection of the very small quantities of microbubbles appearing in the myocardium after intravenous injection of transpulmonary agent. In addition, they have only been tested in experimental situations where image quality was optimum.^{55 56}

Analysis of the unprocessed radiofrequency ultrasound signals, returning from the imaging transducer to the ultrasound system, may provide a sensitive method of detecting any small changes in backscattered signal amplitude. The radiofrequency signal may be analysed

Figure 10 Variation of integrated backscatter and mean frequency of the ultrasound signals from the left ventricular chamber and myocardium after injection of a microbubble contrast agent (Albunex). Each frame corresponds to one cardiac cycle: frames are triggered from the R wave of the electrocardiogram.

not only for changes in backscattered amplitude, but also for any changes in its frequency spectrum that might have occurred as a result of interaction with contrast microspheres.⁵⁷ From an instrumentation point of view, it may be technically easier to create methods for analysis of small changes in frequency than small changes in amplitude. The backscatter from Alunex is frequency dependent and its resonant frequency appears to be within the bandwidth of cardiac diagnostic imaging transducers. Therefore, it is not surprising that significant changes in the mean frequency of the scattered signal may be seen after Alunex injections.⁵⁸

Figure 10 illustrates the variation in myocardial integrated backscatter and the shift in mean frequency of the backscattered signal after Alunex was given to one patient. Frames correspond to cardiac cycles, frame acquisition being triggered from the R wave of the ECG. An increase in myocardial integrated backscatter is seen, together with a fall in mean frequency of the backscattered signal. This latter phenomenon is thought to result from resonant absorption of certain parts of the transmitted ultrasound spectrum,⁵⁸ which causes a net shift in the backscattered signal.

Pulse-echo grey shade and colour Doppler flow imaging techniques are being developed to extract information from the second harmonic of the backscattered signal from microbubbles.⁵⁹ The second harmonic occurs at twice the frequency of the normal backscattered signal and is due to non-linear oscillation of the bubbles. A second harmonic component is not present in the backscattered signal from tissue and hence by examining it the microbubble signal is more clearly seen. Second harmonic imaging is expected to enhance the signal from bubbles in blood vessels by a factor in excess of 20 dB.

Echocardiography has now been largely accepted as the gold standard for the evaluation of valvar heart disease, congenital heart disease, cardiomyopathies, pericardial disease, and left ventricular function. However, the technique has yet to make a significant impact upon the management of patients with ischaemic heart disease and most patients seen in any adult cardiology centre have ischaemic heart disease. The advent of myocardial contrast echocardiography should extend the role of echocardiography significantly into the assessment of ischaemic heart disease.

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