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Assessment of Myocardial Perfusion by Contrast Echocardiography – Ready for Clinical Practice?

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Increasing interest has been focused on myocardial contrast echocardiography (MCE) since latest ultrasound-specific imaging modalities allow the detection of ultrasound contrast agents within the myocardium after intravenous injection. Due to significant improvements in imaging technology MCE has become a valuable add-on tool for the diagnosis of coronary artery disease.

This review summarizes and estimates the clinical value of recent developments in myocardial contrast echocardiography, particularly with regard to the new real-time perfusion imaging, which allows simultaneous assessment of perfusion and wall-motion. *J Clin Basic Cardiol 2002; 5: 145–8.*

Key words: echocardiography, coronary artery disease, ultrasound contrast agent, myocardial contrast echocardiography, myocardial perfusion

The assessment of myocardial perfusion following intravenous injection of ultrasound contrast agents (USCAs) has been a major objective of research in the last two decades. In the 70s and early 80s, microbubbles of air found applications in the detection of intracardiac shunts and of valvular regurgitation [1–3]. A real breakthrough in contrast echocardiography was the discovery by Feinstein et al. [4] that sonicated human albumine led to small bubbles, which lasted much longer than any other microbubbles. Sonicated human albumin (Albunex®) was shown not only to enhance the right ventricle but also to be stable enough to pass the lung capillaries and achieve left ventricle opacification [5]. In the early 90s the third major discovery in the history of USCAs was the idea of replacing air by perfluorinated halocarbons, which are known to be well tolerated and to be exhaled unchanged, improving the resistance against collapse. Stabilization using variable shell materials, gases and coating substances improved the properties of USCAs. Four USCAs are approved and available for clinical use (examples see Table 1) [6–11].

Physical Properties of Ultrasound Contrast Agents

The physical properties of microbubbles are complex and depend on a number of factors, of which the most important is the applied acoustic power, measured by the mechanical index (MI). At low emission power, USCAs act as linear backscatter, increasing the signals received from blood, leading to the first intended clinical indication: Doppler signal enhancement.

In addition to these reflector properties, USCAs act as active sound sources, emitting nonlinear harmonic frequencies due to their radial oscillation when emission power is increased (acoustic pressure above 0.1 MPa; MI = 0.1–1.0) [12]. At high emission power (acoustic pressure above 1 MPa; MI > 1.0), USCAs can be destroyed, producing strong broadband frequency signals in a process known as stimulated acoustic emission [12–15].

Triggered Versus Real-Time Imaging

It has been shown that most USCAs are destroyed, at least partially, even at diagnostic emission power [16]. This effect may not be apparent in large vessels or in the cardiac cavities because there is a constant supply of fresh blood containing fresh microbubbles. However, in small vessels or in vessels with low flow such as a capillary bed, the bubbles can be destroyed before re-filling the vascular bed. As a consequence, visualization of USCAs in the microcirculation is difficult during real-time imaging [15].

To overcome this, intermittent imaging techniques that limit the time of exposure of microbubbles to the ultrasound beam have been invented [16, 17]. With this technique, individual single-frame images are obtained at designated points once every cardiac cycle up to triggering intervals every 15th cardiac cycle, allowing replenishment of the microbubbles between successive frames (Figure 1). Although the introduction of intermittent imaging has been a breakthrough in intravenous myocardial contrast echocardiography [16, 17], there are also disadvantages using this approach. Triggered imaging is technically demanding and requires a high level of expertise in acquiring images at the same scan plane for each triggered interval. Furthermore, simultaneous evaluation of wall motion cannot be performed.

Table 1. Ultrasound contrast agents for myocardial perfusion

Name	Manufacturer	Shell of the microbubbles	Gas	Approved in	Imaging modality
Levovist®	Schering (Germany)	Palmitate/ Galactose	Air	Canada, Europe	TRI
Optison™	Mallinckrodt (USA)	Albumine	Perfluoropentan	USA, Europe	TRI RTPI
Sonovue®	Bracco (Switzerland)	Phospholipid	Sulfurhexafluor	Europe	TRI RTPI
Definity™	Bristol-Myers Squibb former DuPont (USA)	Phospholipid	Perfluoropropan	USA, Canada	TRI RTPI

TRI = triggered imaging modalities; RTPI = real-time perfusion imaging

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Contrast Specific Imaging Modalities

Development in ultrasound imaging techniques recently provided a large variety of "contrast specific" imaging modalities (examples see Table 2), which improved the signal-to-noise ratio, allowing intravenous myocardial contrast echocardiography [14].

Harmonic B-mode imaging takes advantage of non-linear oscillation of microbubbles. During harmonic imaging, ultrasound is transmitted at a fundamental frequency of 1.5 to 2.0 MHz and received at twice this frequency. Using bandpass filters [18] the transmitted fundamental frequency is separated from the received signal allowing improved visualization of vascular beds containing USCAs. The signal-to-noise ratio during the presence of microbubbles in tissue is four- to fivefold higher at the harmonic compared with the fundamental frequency [19, 20].

Using harmonic B-mode imaging, harmonic frequencies generated gradually as the ultrasound wave propagates through the tissue have to be taken into account [21]. Although tissue reflection generates very little harmonic energy compared to USCAs, these tissue harmonics have to be removed by background subtraction methods for quantitative assessment of myocardial perfusion [14].

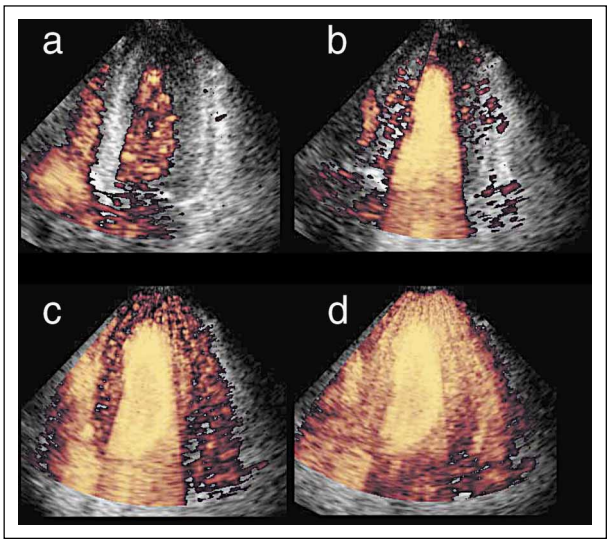

Figure 1. Different degrees of myocardial contrast using harmonic power Doppler imaging (four chamber view) during continuous infusion of Levovist®: Arrival of the contrast agent in the right ventricle (a) and complete left ventricular opacification shortly after (b) using triggered imaging every heart cycle (1:1). Complete left ventricular myocardial opacification using higher trigger intervals every 3rd (c) and every 5th (d) cardiac cycle.

Table 2. Imaging modalities for assessment of myocardial perfusion

	MI	Real-time imaging	Residual myocardial tissue signals	Need for background subtraction	Endocardial border delineation
Harmonic B-mode	0.6	No	Yes	Yes	Poor
Power Doppler	> 1.0	No	Few*	No	Good
Pulse inversion	0.3	No	Yes	Yes	Moderate
Power pulse inversion	< 0.15	Yes	No	No	Good
Power modulation	< 0.15	Yes	No	No	Good
Coherent imaging	< 0.15	Yes	No	No	Good

MI = mechanical index; * = wall motion artifacts can be minimized with proper machine settings

Harmonic power Doppler imaging (H-PDI) has been introduced into echocardiography as a contrast-specific imaging modality that encodes, in different hues of a color map, the power of the color Doppler signal after wall filtering. H-PDI bases on the detection of strong non-linear signals generated by the microbubbles at the time of their destruction (stimulated acoustic emission), resulting in a phase shift of received ultrasound waves. Because no Doppler signals are present in the myocardium prior to injection of USCAs, H-PDI was recently proposed as a method for quantitative analysis of myocardial blood flow without the need for background subtraction [22–24].

Pulse inversion imaging utilizes characteristics specific to non-linear microbubble oscillation to subtract rather than to filter out the fundamental signal. This technique works by sending two successive ultrasound pulses of the same frequency, waveform and focusing, but with opposite polarities. The ultrasound system sums the returning fundamental as well as the harmonic components, resulting in a cancellation of the fundamental signals, whereas the harmonic components are combined and reinforced. Although pulse inversion imaging lead to increased sensitivity to contrast and produces images with very high spatial resolution, tissue motion artefacts may still be a problem [18, 25, 26].

The latest developments in contrast specific ultrasound instrumentation are *power pulse inversion, power modulation* and *coherent imaging* that can be performed at low emission power (MI < 0.15) [27–29]. A sequence of normal and inverted pulses is transmitted, detecting harmonic signals from USCAs along with fundamental signals. These signals are mathematically combined to provide detection of a pure harmonic signal from the microbubbles allowing complete cancellation of the fundamental signals without conventional filters that would remove valuable signals from USCAs. Using these low-power technologies the destruction of the microbubbles is reduced allowing real-time imaging (> 20 frames/s). Even the amplitude of tissue signals can be minimized, thus myocardial contrast signals can be analyzed without background subtraction.

Application of Myocardial Contrast Echocardiography

A large body of experimental and clinical work with intracoronary and aortic root injections of USCAs in the 80s and 90s has shown that myocardial contrast echocardiography (MCE) can be used to assess risk area and infarct size [30, 31], or to evaluate the presence of collaterals [32]. Besides, intracoronary MCE can be utilized to evaluate viable myocardium after acute infarction [33], to delineate reperfusion reflow zones [34, 35], or to predict prognosis and functional discovery after revascularization [36]. Due to its invasive character, intracoronary MCE is only of minor clinical significance.

Recent developments in microbubble technology and ultrasound imaging techniques improved the discrimination of microbubble signals within the myocardium following intravenous injection. In animal models triggered intravenous MCE (using increasing trigger intervals at high emission power) has been validated as a technique for quantifying myocardial blood flow and assessing the degree of coronary stenosis [37–39]. These animal studies led to

the first comparative studies in humans. Kaul and others [40] demonstrated that MCE could detect myocardial perfusion at rest and during dipyridamole stress in humans. The location and physiological relevance of perfusion defects were similar to that provided by Tc-99m sestamibi SPECT, with interobserver agreement between the two techniques exceeding 90 %. The study was performed using harmonic B-mode imaging, therefore the images had to be digitally subtracted and color coded before visual analysis of perfusion was performed.

The first multicenter clinical trial of MCE was reported in 1998, studying the ability of a second-generation perfluorcarbon USCA to identify perfusion defects in postmyocardial infarction patients [41]. The results of this trial demonstrated limitations in the ability of MCE to provide data of comparable accuracy to radionuclide scintigraphy for this application. On the other hand, this multicenter study demonstrated that in less experienced hands, the interpretation of myocardial perfusion with these advanced ultrasound techniques may not be as good as in the original pilot studies [18, 42].

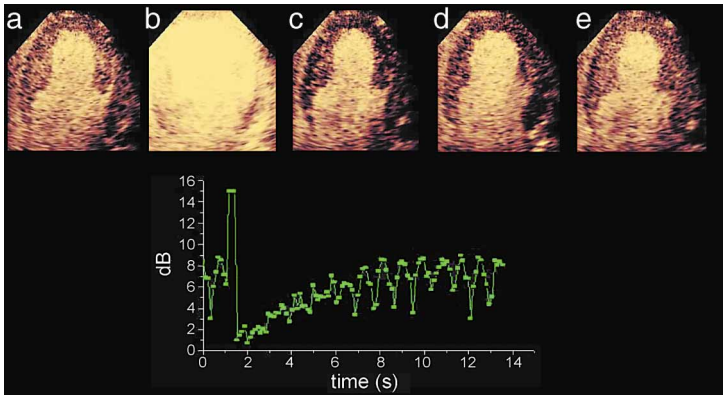

Figure 2. Negative bolus destruction reperfusion study using power pulse inversion imaging. First, continuous infusion of a contrast agent is adjusted to achieve full myocardial opacification using real-time imaging at very low emission power (a) (MI = 0.09). After destruction of the microbubbles by a short period of high power imaging (b) (MI = 1.3) myocardial contrast replenishment is recorded at low emission power (c–e) (MI = 0.09). A region of interest (ROI) is placed in the septum and repeated measurements are made at the endsystolic frames. The graph shows the reperfusion curve for this ROI, fitting well to the monoexponential function.

This is one of the reasons why none of the introduced high-power imaging technologies could be established as a standard for clinical use, primarily because of the practical limitations of triggered imaging. Technical problems include transducer and cardiac translation motion during long triggering intervals and the inability to simultaneously assess wall motion and perfusion.

The introduction of a new generation of contrast specific imaging technology in 1999 was promising for future clinical use of intravenous MCE [25, 27]. These low-power technologies (MI < 0.15) significantly reduce destruction of the microbubbles, approaching real-time assessment of myocardial perfusion at frame rates up to 30 Hz (real-time perfusion imaging; RTPI). Furthermore, simultaneous evaluation of wall motion is possible. The clinical benefit of this approach has been demonstrated by Porter et al., using power pulse inversion imaging [29]. This study was performed in 117 patients during dobutamine stress echocardiography by using bolus injections of Optison™ or Definity™. Overall agreement between quantitative coronary angiography and myocardial contrast enhancement on a territorial basis was 83 %, as compared with 72 % for wall motion assessment alone. Contrast defects were observed in 17 territories subtended by > 50 % diameter stenoses that had normal wall motion at peak stress. However, the knowledge of both wall motion and perfusion seems to be of synergistic value [29, 43]. Moreover, wall motion analysis may serve as a "back up" if the perfusion study is not diagnostic [43].

Even quantitative assessment of myocardial perfusion, that was primarily used in research rather than in clinical settings, seems to be practicable using low-power technologies. Recently, Wei and colleagues described a technique for quantitative assessment of myocardial perfusion during continuous intravenous infusion of USCAs, based on the ultrasound-induced destruction of microbubbles and the assessment of their replenishment [39, 44]. The mathematical model used for non-linear curve fitting to analyze replenishment parameters was originally defined for intermittent imaging using increasing trigger intervals at high emission power. Recent animal studies demonstrated that this model could be applied to real-time perfusion imaging as well. Using low power techniques, a brief pulse of higher mechanical index ("flash", MI > 1.0) is transmitted to clear the myocardium of microbubbles. Returning immediately to low power real-time imaging, reperfusion may be visualized, further offering the opportunity to quantify the flow velocity and the blood volume at the level of microcirculation non-invasively (see Figure 2) [45, 46].

Conclusion

Perfusion abnormalities develop earlier than abnormalities of the wall motion in the region subtended by a significant coronary stenosis. Thus, MCE provides valuable additional information approaching the pathophysiologic substrate of ischaemia. The clinical application of MCE in daily routine depends on additive diagnostic information compared to conventional stress echocardiography. Outcome-studies have to demonstrate the prognostic relevance of MCE findings in order to establish this new method.

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