Current perspectives

Non-invasive assessment of myocardial perfusion by intravenous contrast echocardiography: state of the art

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Many technical problems, related to both imaging instrumentation and contrast agents, have to be taken into account before attempting non-invasive evaluation of myocardial perfusion by intravenous contrast media injection.

Potentials and pitfalls of first generation contrast agents (i.e. Levovist®, Schering AG, Berlin, Germany) using intermittent harmonic angio imaging and of second generation contrast media (i.e. SonoVue™, Bracco SpA, Milan, Italy) using real-time perfusion imaging in the non-invasive assessment of myocardial perfusion were described and discussed.

We still need more solid data before introducing intravenous myocardial echocardiography into the clinical arena. However, convincing data from several research laboratories are paving the way for the widespread use of this new method in clinical practice.

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After many years of study and research, the non-invasive assessment of myocardial perfusion by echocontrast agents has become a clinical reality[1-11]. The use of some first and second generation contrast agents (Levovist® and Optison®) in humans has recently been approved in Europe and the United States. The fast technological progress of echocardiographic imaging explains the growing interest in this new methodology. However before starting this scientific journey, it is necessary to have the greater number of information in order to avoid all the pitfalls previously observed with other perfusion techniques. A number of technical details relating to both imaging instrumentation and contrast agents should be borne in mind in order to achieve an appropriate myocardial opacification by intravenous contrast media injection.

Echocardiographic imaging: harmonic angio or harmonic power Doppler

Visual assessment of myocardial perfusion by means of gray scale images is limited because of the poor signal-to-noise ratio and the limited ability of the human eye to discriminate between shades of gray. The raw signal enhancement provided by contrast is relatively low (about 20-30 dB) owing to the substantial decline in the signal intensity from the cavity to the myocardium.

Harmonic angio imaging overcomes these limitations since only the transient scattering due to microbubble destruction is detected[12,13]. Irvine et al.[14] have recently shown, using a perfusion tube model under zero-flow conditions, that the backscatter produced from the unencapsulated microbubbles is the only factor responsible for the generation of the power Doppler signal. Thus, the harmonic angio signal originates from exploding microspheres and not from the red blood cells that move too slowly within the capillaries (1-2 mm/s) to be detected by the system.

The higher the transmitted power, the more bubbles are destroyed. This results in a sudden increase in the amplitude of the returning signal. The faster the bubbles disappear, the easier it is to distinguish this effect from that of cardiac motion which also produces a changing signal. Several parameters affect microbubble dissolution, including their composition and the amplitude and frequency of insonation[15,16]. To ensure com-

plete microbubble destruction after a single ultrasound sweep during continuous contrast media infusion and to avoid motion artifacts, it is necessary to increase the amount of ultrasound exposure by increasing the frame rate and mechanical index. Thus, the medium angio packet size should usually be used, the two-dimensional depth should be as shallow as possible and the angio box as narrow as possible. Angio gain and wall filters should be adjusted so that no motion artifacts are displayed in the harmonic angio mode without contrast. The two-dimensional received gain should be decreased so that the tissue remains dark before contrast injection. The compression must be higher (> 70) in order to increase the "dynamic range". One should initially focus on the mitral leaflet level; when necessary it has to be moved towards the apex to reduce false apical contrast defects. To further ensure artifact-free contrast imaging, the multiple frame trigger may be activated. With this software, three consecutive frames starting at the trigger point are acquired and displayed in a dual screen format. The first new frame at the trigger delay shows the "contrast flash" into the myocardium representing bubble destruction. If the setting is correct, the following two frames should appear empty (void of contrast). Images have to be acquired into loops and reviewed frame-by-frame for quality control. Further, since the frequency of insonation affects the dissolution rate and in order to shorten tissue motion artifacts, the maximum pulse repetition frequency (PRF, between 3.2 and 6.2 KHz) should be used.

Despite these devices, some problems about the correct insonation of the left wall in four chambers and of the anterior wall in two chambers persist. The shortened ultrasonic energy in the distal portion sector can be inadequate for successful microbubble breaking. It is very important to reposition the transducer and to center the walls in the sector. Further, a contrast overplus in the left ventricle or an harmonic angio gain too much higher can determine prolonged signal persistence (blooming effect) and mask a perfusion defect.

Contrast agents for intermittent imaging

To obtain a reliable myocardial opacification by this method, a contrast agent with a thin shell and a low persistence gas should be used. The reduced solubility and the high molecular weights of gases used for "second generation" contrast agents makes it harder to differentiate them from tissue when a microbubble destruction imaging technique is used. For this reason, we used Levovist® (Schering AG, Berlin, Germany), which is a galactose-based echo-enhancing "first generation" contrast agent highly responsive to ultrasound. When mixed with water, it forms microbubbles of air covered by a thin layer of palmitic acid. By using a multiple frame trigger as a quality control, we found that almost all microbubbles within the myocardium were "acoustically destroyed" by a single sweep of ultrasound resulting in a high and rapid Doppler signal. The microbubble infusion rate should be optimized to obtain complete bubble destruction with a single sweep of ultrasound thus avoiding the blooming effect, and to obtain a satisfactory myocardial opacification without significant shadowing. For this purpose, we use continuous pump infusion of this agent prepared in the standard manner (a solution of 400 mg/ml, 2 ml bolus followed by an infusion of 300 ml/hour)[17,18].

The concentration of microbubbles in tissue is also strictly dependent on the rate of tissue replenishment[19]. Since, in the infarct area, the myocardial blood flow should be reduced, the rate of destruction of contrast may exceed its replenishment in this zone if a shorter intermittent imaging technique is used[19]. For this reason, the end-systolic trigger intervals increased from 1:4 to 1:8. One should ensure that the trigger point be placed just behind the end-systole during the isovolumetric relaxation time and that motion artifacts are reduced to a minimum. During these prolonged trigger intervals, particular attention should be paid to maintain the same scan plan by reducing the patient's breathing. Using different trigger intervals, the severity of coronary stenosis may be assessed[19-21]. In figure 1 the formula used for the quantitative assessment of myocardial blood flow is depicted.

The clinical value of quantitative analysis is still under discussion. Several factors may affect the rise and the peak of signal intensity in different myocardial segments including: a) systo-diastolic changes in contrast intensity, b) fiber orientation, c) different ultrasound energy in the lateral field, and d) motion artifacts. Further, quantitative studies require a tedious and time-consuming off-line analysis with a frame by frame re-alignment of the region of interest. For all these reasons, with the commercially available softwares, quantitative analysis should be limited to experimental studies.

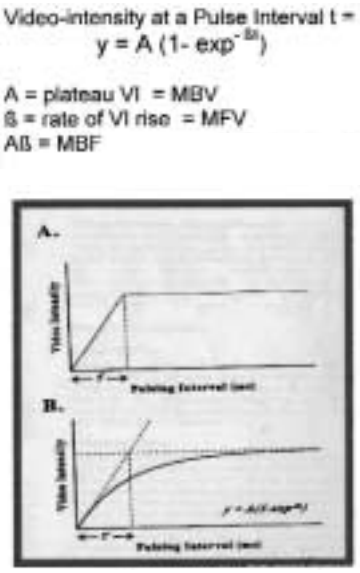


Figure 1. *Scheme of replenishment curves. MBF = myocardial blood flow; MBV = myocardial blood volume; MFV = myocardial flow velocity; VI = videointensity.*

Echocardiographic imaging: real-time perfusion

To correctly visualize myocardial perfusion using harmonic angio or harmonic power Doppler, intermittent imaging is required. This is one of the most important limitations of this technique since simultaneous imaging of perfusion and contraction is not possible. Further, as previously underlined, the flow velocity into the capillaries is extremely slow. Thus, the replenishment time may in some cases be longer than the imaging time. It has been hypothesized that using low ultrasound energy and a moderate frame rate in gray scale harmonic imaging, bubble destruction may be reduced and a continuous perfusion imaging may be obtained.

Following these concepts a new technique, called real-time perfusion imaging has recently been introduced[22,23]. To be able to maximize microbubble signals and minimize tissue signals, either the phase or amplitude of the pulse packets may be modified. In the phase inversion approach, the phases of two successive pulses are inverted, while in the power modulation approach, the acoustic power of the two successive pulses is modified. Any stationary linear target that responds equally to positive and negative pressures will be canceled whereas asymmetric bubble oscillation will be enhanced. In this way, the fundamental components of the echoes will be subtracted without filtering whereas the harmonic components will be added. Unfortunately, when the tissue being evaluated is moving, the fundamental signal is not completely cancelled and motion artifacts result. In case of increased sensitivity, tissue artifacts may be removed by transmitting a longer sequence of inverted pulses. In conventional harmonic imaging, the bandwidth is restricted in an attempt to reduce the overlap between the transmitted signal and that of received harmonics. Real-time perfusion imaging technology avoids these bandwidth limitations by subtracting rather than filtering out the fundamental signal. In this way, a larger bandwidth may be used with a higher resolution and an increased sensitivity to contrast agents.

In real-time perfusion imaging, three or more sequences of normal and inverted pulses are transmitted. Harmonic and fundamental signals from tissue and contrast are received while stationary and tissue components are filtered out. This allows detection of a pure harmonic signal from the contrast agent. Operating at a low mechanical index, bubble destruction is reduced together with tissue harmonic components.

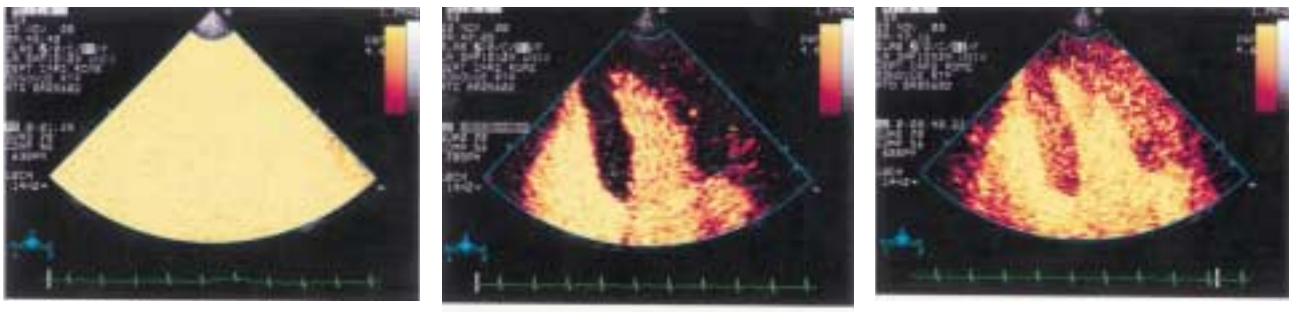
Advantages and disadvantages of real time perfusion as compared to intermittent imaging are summarized in table I.

Several echo labs are now testing this new technology to assess the potential of real-time perfusion in clinical practice. In particular, it is still unclear which families of contrast agents are more suitable for this method, if bolus or continuous infusion should be used and finally, if using flash to destroy bubbles, territories with reduced coronary reserve may be easily delineated.

Our preliminary experience with SonoVue™ (Bracco SpA, Milan, Italy), a new second generation contrast agent, has shown a constant and repetitive myocardial opacification using both bolus or continuous infusion. The extent of the contrast defect was clearly defined in real time (Figs. 2 and 3).

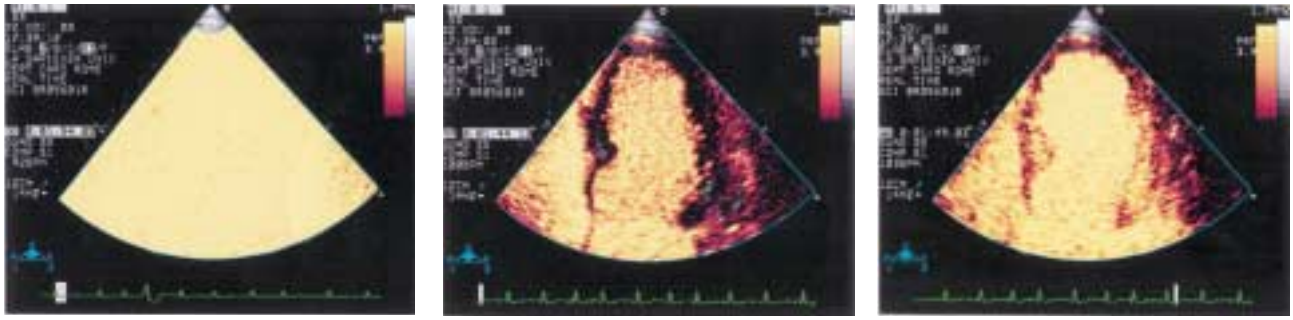
Table I. Real-time perfusion imaging versus intermittent imaging.

Advantages	Disadvantages
Simultaneous assessment of perfusion and function	Less mechanical index, less signal
Frame rate-real time 10-20 Hz	More bubbles are required (5-8 times higher than intermittent imaging), more attenuation
Frame rate-intermittent imaging > 30 Hz	Adequate myocardial opacification 60% of intermittent imaging
Rapidity of data acquisition (8 s vs 10 min)	Most bubbles behave similarly after destruction
Less duration of data acquisition, less motion artifacts	Resonation dependent on shell, gas and bubble characteristics
Image alignment is not required	



A **B** **C**

Figure 2. *Real-time perfusion imaging: example of a patient without coronary artery disease showing a normal myocardial opacification after i.v. bolus injection of 1 ml of SonoVue™ (Bracco).* A: *high signal intensity during bubble destruction using a high mechanical index (1.7);* B: *no myocardial enhancement soon after bubble destruction using a low mechanical index (0.1);* C: *homogeneous myocardial opacification after a few seconds at a low mechanical index (0.1).*



A B C

Figure 3. *Real-time perfusion imaging: example of a patient with an acute myocardial infarction showing an apical contrast defect after i.v. bolus injection of 1 ml of SonoVue™ (Bracco).* A: *high signal intensity during bubble destruction using a high mechanical index (1.7);* B: *no myocardial enhancement soon after bubble destruction using a low mechanical index (0.1);* C: *apical defect with homogeneous myocardial opacification of the mid and basal portions of the left ventricle after a few seconds at a low mechanical index (0.1).*

Conclusion

Many parameters have to be taken into account before trying to evaluate myocardial perfusion non-invasively. Several laboratories are now working to assess the reproducibility and accuracy of this method in different clinical settings. Unfortunately, no data are yet available from multicenter studies and, to date, different modalities of contrast injection or imaging cannot be recommended. However, in our experience, independently of the contrast agent used, continuous infusion is mandatory for quantitative analysis using real-time imaging whereas bolus injection is recommended for contrast defect assessment. On the contrary, using intermittent imaging, continuous infusion at different trigger intervals is mandatory for both qualitative and quantitative analysis.

Regardless of the injection modality, the rate of injection and the amount of contrast used should suffice to obtain a strong signal (input function) whilst avoiding shadowing and/or blooming effects. For this purpose, the power gain should be higher in real time than in intermittent imaging. There are no objective rules, but the personal experience of any laboratory is the most important pre-requisite to obtain an adequate myocardial opacification.

We have still much to discover. However, the combined efforts of the pharmaceutical industry and technological research are moving us closer to the line of this fascinating hurdle race.

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