REVIEW ARTICLE

Contrast Echocardiography for Myocardial Perfusion Imaging Using Intravenous Agents: Progress and Promises

R. Amyot1, M.-A. Morales2 and D. Rovai2

1Hôpital du Sacré-Cœur, Montréal, Canada; 2CNR, Clinical Physiology Institute, Pisa, Italy

Aims: This article is a convenient overview to assist the interested echocardiographist towards acquiring his own experience in the field of myocardial perfusion imaging using intravenous contrast agents. This goal is now pursued in many centres, since contrast echo holds the advantages of cardiac ultrasound (non-invasiveness, high spatial and temporal resolution, wide availability, use of non-ionizing radiation), and because a variety of trans-pulmonary agents — together with a spectrum of imaging modalities — are becoming available.

Methods and results: Many technical considerations need to be addressed for optimal myocardial perfusion imaging: characteristics of the contrast medium (air-filled or perfluorocarbon filled and/or encapsulated agents), modality of administration (bolus injection or continuous infusion) and interaction between microbubbles and ultrasound (dependency on power output). Moreover, intermittent harmonic imaging, intermittent harmonic power Doppler, pulse inversion and amplitude modulation imaging have all been developed to enhance microbubble detection over myocardial tissue. These new acquisition modalities also yield specific artifacts impacting on myocardial perfusion assessment. Finally, acute myocardial infarction and chronic ischaemic heart disease (at baseline and during stress) are the most studied clinical models for perfusion imaging with contrast echo, and are reviewed in this article.

Conclusion: Perfusion imaging with intravenous contrast agents has never been as close to widespread clinical use as it is today, but many methodological issues remain unsettled before the wish of the contrast echocardiographist comes true: that is, a cheap, user-friendly and widely available technology that would disclose new information in echocardiography.

Key Words: contrast; echocardiography; imaging; myocardium; perfusion.

Introduction

From the early 80s, experimental and clinical studies provided support for the use of contrast agents to assess myocardial perfusion by echocardiography[1–10]. However, the need for intracoronary injection, safety concerns and unstable agents restricted their use to research settings. A recent boom in the field of contrast echo is due to its potential for imaging myocardial perfusion following intravenous contrast injection. To this end, many centres are now looking for the optimal acquisition modality, as myocardial perfusion imaging holds the same advantages that also favoured the widespread diffusion of echocardiography: a non-invasive approach, high spatial and temporal resolution, widely available technology and use of ultrasound instead of ionizing radiation. For the investigators exploring this field a variety of contrast agents with different characteristics are becoming available, as well as a spectrum of imaging modalities developed in the past few years. This article is a convenient overview to assist the interested
echocardiographist in acquiring his own experience in the field of myocardial perfusion imaging using intravenous contrast agents.

**Transpulmonary Agents: the Task of Sizing and Stabilizing**

Myocardial contrast enhancement using the intravenous route necessitates that both transpulmonary contrast passage and microbubbles persist long enough in the circulation to allow ultrasound examination. Bubble size is obviously of paramount importance, though not the only factor. Microbubbles larger than the capillary lumen are trapped in the pulmonary microcirculation, while air-filled bubbles small enough to cross the lung capillaries collapse within a few seconds due to surface tension, surrounding pressure and gas diffusion from bubbles into the blood\(^{[11,12]}\). To overcome the instability of air-filled microbubbles and allow them to reach myocardial circulation, two main strategies were initially adopted. A substance with surfactant-like properties (palmitic acid) has been included in the formulation of the agent Levovist\(^{[13]}\) (Schering AG, Germany) to reduce surface tension\(^{[14]}\), while a protein shell has been used to encapsulate the bubbles of the contrast agent Albunex\(^{[15]}\) (Mallinckrodt Medical Inc, U.S.A.), thus limiting outward gas diffusion\(^{[14]}\).

More recently, different companies used high-molecular-weight gases (mainly fluorocarbons) with low solubility in blood to produce microbubbles with greater stability than the first generation, air-filled agents\(^{[15]}\). Optison\(^{[16]}\) (Mallinckrodt Medical Inc, U.S.A.)\(^{[17]}\), EchoGen\(^{[18]}\) (Sonus Pharmaceutical, U.S.A.)\(^{[17]}\), SonoVue\(^{[19]}\) (Bracco, Italy)\(^{[17]}\), Definity\(^{[20]}\) (DuPont Inc, U.S.A.)\(^{[19]}\), Sonazoid\(^{[21]}\) (Nycomed-Amersham, Norway)\(^{[20]}\) and PESDA\(^{[21]}\) are some examples of agents commonly referred to as ‘second generation’. Both first and second generation agents microbubbles which are smaller than the capillary lumen, although presenting different stability and resonance properties. In order to assess myocardial perfusion, imaging modality and system settings should be adjusted according to the particular agent in use, since imaging techniques based on bubble disruption seem more adequate in conjunction with ‘fragile’, air-filled agents, while those based on bubble resonance are preferable in combination with second generation agents.

The use of a long half-life deposit contrast agent (i.e. with trapping of most bubbles in the microvasculature) permits a stable myocardial enhancement, allowing the more time-consuming three-dimensional\(^{[13]}\) data acquisition\(^{[22]}\). At present, a major disadvantage of these deposit agents is the impossibility of performing intravenous injections for myocardial imaging.

**Contrast Administration: the Different Modalities**

Contrast dosage to optimize myocardial perfusion imaging varies from agent to agent. For each contrast agent and imaging modality, the ideal blood concentration of microbubbles is confined within tight limits: high concentration of the agent induces far-field attenuation artifacts, while suboptimal concentration results in low signal-to-noise ratio.

The ideal mode of administration (whether bolus injection, continuous infusion or slow intravenous injection) depends in part on the agent. Each mode of administration has its advantages and disadvantages\(^{[15]}\). Intravenous bolus injection, followed by a saline flush, is certainly the easiest way to administer a contrast agent; however, the contrast effect is short-lived and quantification of perfusion, as well as the comparison of baseline and stress studies, is difficult. Furthermore, the ideal concentration range is reached only briefly during myocardial wash-in and wash-out phases, while concentration is often too high at peak contrast enhancement, precluding imaging because of saturation, attenuation and blooming artifacts. Continuous infusion — although more complex to perform — avoids the need to repeat bolus injections for dose titration and image acquisition, confers steady-state microbubble concentration facilitating the echo examination, and results in less far-field attenuation\(^{[23]}\). Accordingly, contrast infusion is preferable when rest and stress conditions are compared. Slow bolus injection is a compromise between these two approaches.

**Interaction Between Microbubbles and Ultrasound**

Gaseous microbubbles in a liquid medium demonstrate a unique behaviour when submitted to an ultrasound field, displaying different scattering patterns depending on the acoustic transmit power\(^{[13]}\). At low emission power, contrast microbubbles are exposed to a low incident pressure and their volume remains constant over time. The echo signal enhancement is therefore proportional (in theory and within certain limits) to the number of bubbles. This response devoid of significant resonance phenomenon is termed *linear backscatter*\(^{[24,25]}\). At higher output power, the microbubbles produce *non-linear backscatter*, characterized by the emission of harmonics. This second mechanism takes advantage of the high compressibility of the gaseous content of microbubbles: when exposed to ultrasound (i.e. pressure oscillations), the bubbles vibrate in a rapid succession of expansion-compression cycles. The amplitude of the bubble volume change is maximal at a definite frequency, called resonant frequency. When microbubbles are insonated at their resonant frequency, ultrasound scattering includes emissions at rates (harmonics) that are multiples of the incident (fundamental) frequency\(^{[26–29]}\). Consequently the contrast agent is imaged more selectively, since it is more likely to produce harmonics than the surrounding tissues, thereby increasing signal-to-tissue ratio in contrast echocardiography. Finally, when subjected to critical ultrasound
power, the contrast microbubbles resonate so intensely that they are destroyed and produce a transient, high amplitude signal with a broad spectrum of frequencies in addition to harmonics. Bubble disappearance does not occur instantly, but over a period of time depending on the bubble shell and gaseous content properties.

Since measuring peak incident pressure is difficult in vivo, an index of the mechanical work applied to a microbubble during a single ultrasound half cycle is displayed on the screen. This ‘mechanical index’ can be adjusted by modifying acoustic depth and output power settings. Schematically, linear backscatter occurs at low mechanical index (<0·1), bubble disruption is the rule with default settings (mechanical index >1·0), and non-linear backscatter without massive bubble disruption occurs at intermediate mechanical index values. Due to mechanical index heterogeneity in the ultrasound beam (higher in the centre of the sector and at the focal zone) and variability in ultrasound attenuation by various tissues, these three different backscattering behaviours are not sharply demarcated, but rather coexist over a wide range of acoustic power. Furthermore, they also vary according to the echo scanner and contrast agent. For example, less stable agents may demonstrate bubble disruption even at low output power. Moreover, in every contrast agent the microbubbles display a significant diversity in size, and the transducer transmits ultrasound over a broad range of frequencies. The random encounter between a variety of bubble sizes and a spectrum of ultrasound frequencies allows more bubbles to find their resonant frequency. This phenomenon provokes harmonic emission from the majority of contrast agents using commercially available ultrasound systems.

**From Bubbles to Images**

The challenge of myocardial perfusion assessment with intravenous contrast agents goes beyond mere blood opacification within the cardiac chambers: it consists of rendering detectable the small amount of blood in the myocardial microvasculature despite the strong scatter produced by the surrounding solid structures (clutter). To reach this goal, several imaging modalities have been proposed over the past few years.

**Harmonic Imaging**

As stated before, if a microbubble is insonated at its resonant frequency and with appropriate (intermediate) incident pressure, the bubble starts to vibrate. These changes in bubble volume are asymmetrical, since the bubble compressed by the ultrasound becomes stiffer and resists further reduction in size, while an expanding bubble becomes less rigid and enlarges more easily. These asymmetrical oscillations are the basis of harmonic emission. In Figure 1, the agent Levovist is insonated at a frequency of 3-7·5 MHz and the back-scattered echo signal displays two main peaks on the frequency spectrum: at 3·75 MHz (fundamental frequency) and at 7·5 MHz (second harmonic). Moreover, ultraharmonics are obtained beyond the second peak and subharmonics below the fundamental frequency.

Using second harmonic imaging, the ultrasound system receives and analyses backscattered signals at a frequency that is twice the emitted (fundamental) frequency, allowing an improved detection of the vibrating contrast agent and a lesser visualization of the surrounding tissues. In harmonic B-mode imaging, resonating bubbles and tissue are displayed in shades of grey, as in conventional B-mode imaging. An adequate real-time myocardial perfusion imaging is difficult to obtain in humans using harmonic B-mode imaging.

**Intermittent Imaging**

With the usual diagnostic settings, the ultrasound beam destroys contrast microbubbles. Thus, intermittent imaging reduces microbubble exposure to the ultrasound field, producing better myocardial enhancement than continuous imaging. The combination of second harmonic imaging (to enhance microbubble detection) with intermittent imaging and intermediate acoustic power (to reduce bubble disruption), in conjunction with a second generation agent, permits visualization of myocardial perfusion in humans, as shown in Figure 2.

The ideal triggering time during the cardiac cycle is still an open question. Although coronary blood flow is higher during diastole than during systole, many investigators agree that a systolic triggering is preferable as left ventricular cavity is smaller and the myocardium thicker, thus rendering myocardial perfusion more easily detectable.
When imaging modalities based on bubble destruction are utilized in conjunction with continuous contrast infusion, pauses in ultrasound transmission are necessary for contrast refilling of the myocardial microvasculature. Because of the slow velocity of blood in the microcirculation (in the range of millimetres per second), pauses from one to eight cardiac cycles may be necessary for microvascular contrast replenishment. Assuming total microbubble disruption with every ultrasound sweep, changes in the pulsing interval provide information on myocardial blood flow velocity, as the hypoperfused areas require longer pulsing intervals to fill with microbubbles, and even longer intervals are needed to define absence of perfusion. Moreover, myocardial signal intensity is mainly related to myocardial vascularity or intramyocardial blood volume. The product of plateau myocardial intensity (reflecting myocardial vascularity) and rate of intensity rise (reflecting blood flow velocity) allows estimation of myocardial blood flow in experimental animals.

**Harmonic Power Doppler Imaging**

With this imaging modality, the ultrasound signal is also generated at one frequency and received at twice that frequency, but the signal is processed according to Doppler algorithms. Conventional Doppler maps the velocity of targets in the blood stream, but is not sensitive enough to detect any signal from intramyocardial vessels (as blood flow velocity is too low, in the range of millimetres per second). Power Doppler does not reflect the velocity of scatterers in the myocardial microcirculation, but rather the intensity (or power) of the backscattered Doppler signal, and displays it in a colour code. Although harmonic power Doppler further improves detection of microbubbles over tissue as compared to harmonic B-mode imaging, it does not allow myocardial perfusion imaging in real time.

**Intermittent harmonic power Doppler** (also known as power angio or energy imaging) generates multiple pulses sent in rapid succession along each scan line of the image and, consequently, several trains of echoes are received. The output power of the transducer is set high enough to provoke bubble resonance and disruption. In the presence of microbubbles, the first train of backscattered echoes contain a strong signal (caused by bubble disruption), while the following ones contain a weaker signal (only the background tissue signals since the bubbles have disappeared). The subtraction of these signals from each line provides a strong signal related to the presence of disrupting bubbles. This approach minimizes background tissue signals and may be considered a line-by-line subtraction method. Thus, intermittent harmonic power Doppler illustrates the spatial distribution of microbubbles in myocardial microcirculation, reflecting myocardial vascularity or intramyocardial blood content.

Even at high output power, bubble disruption is not instantaneous. The ideal time interval between two consecutive pulses (the inverse of pulse repetition frequency) depends on the agent: shorter with ‘fragile’ air-filled contrast agents and more prolonged with ‘more stable’ second generation agents. Thus, pulse repetition frequency should be maximized with air-filled microbubbles and reduced with second generation agents. However, reducing pulse repetition frequency induces tissue motion detection. Thus, air-filled agents seem preferable in association with intermittent harmonic power Doppler. At present, myocardial perfusion assessment using this approach is under validation in many centres. A representative example in a patient with recent myocardial infarction is shown in Figure 3.
produces a signal, reflecting the presence of the bubble.

**Pulse Inversion Imaging**

This recent innovation is aimed at more effectively suppressing echoes received from tissue and more selectively enhancing the microbubble signal. Pulse inversion imaging consists of emitting in rapid succession two pulses that are identical, with the exception of inverted polarity. Therefore, the backscattered signal generated by motionless structures contains pairs of pulses that are identical, yet opposite in phase; the sum of these two echoes abolishes the signal (c=0). The echoes reflected from a resonating microbubble are asymmetrical, due to changes in bubble volume between the two pulses. The sum of these two different echoes produces a signal, reflecting the presence of the bubble.

**Real-time Perfusion Imaging**

To allow myocardial perfusion imaging in real time, two technologies were recently proposed and are still under evaluation. These very sensitive and selective modalities for echographic contrast imaging are based on the use of low output power (mechanical index <0·1), limiting microbubble disruption and avoiding the need for intermittent imaging. Since these technologies are based on non-linear microbubble oscillations without disruption, they are used in conjunction with second generation contrast agents and not air-filled microbubbles. The great potential of these new approaches is their ability to combine cardiac function and myocardial perfusion information at the same time.

To further improve detection of resonating microbubbles and suppress signals from moving tissue, pulse inversion technology is used in combination with power Doppler in power pulse inversion\(^{[43]}\). The method is similar to pulse inversion imaging, except that a sequence of more than two pulses is transmitted in alternating phases. The echoes from successive pulses are recombined to eliminate the effects of tissue motion. This method allows suppression of tissue movement without disrupting microbubbles. Recent data suggest that real-time assessment of myocardial perfusion is possible during dobutamine echocardiography using power pulse inversion at a very low mechanical index\(^{[44]}\).

In power or amplitude modulation two pulses are generated by the transducer, the second pulse having half the power of the first signal (for example, mechanical index 0·1 and 0·05, respectively). In the presence of tissue with a linear response, the first backscattered signal displays the full intensity and the second echo half of that intensity. By doubling the received low intensity signal and subtracting one signal from the other, they cancel out. In the presence of a resonating microbubble, the intensities of the two backscattered signals are not linearly related; therefore, scaling and subtracting them does not cancel the signal, selectively enhancing the non-linear microbubble behaviour (Fig. 5).

In order to quantify myocardial perfusion with both power pulse inversion and amplitude modulation, a burst of high power ultrasound is first transmitted to destroy the bubbles, followed by continuous imaging at low mechanical index to display refilling of the myocardium with microbubbles in real time. In short, both power pulse inversion and power modulation are multiple pulse technologies allowing real-time perfusion imaging: the first modulates the phase, while the latter varies the amplitude of the emitted pulse in order to favour imaging of non-linear backscatter.

**The Impact of Artifacts in Perfusion Imaging**

The study of myocardial perfusion by intravenous contrast administration is affected by a variety of artifacts that must be taken into account to prevent an erroneous interpretation of the images. In contrast echocardiography, knowledge of the possible artifacts is as important as being updated on the available technologies and agents. The blooming effect occurs when signal intensity in the left ventricular cavity is too high, due to excessive agent dosage or gain setting, or to improper contrast administration\(^{[45]}\). The left ventricular cavity signal becomes saturated and myocardial enhancement is not
due to tissue perfusion, but to the strong scattering of bubbles in the ventricular cavity (Fig. 6). This artifact can produce false negative results, as myocardial perfusion defects may go undetected during blooming. To identify this artifact, one should remember that myocardial enhancement physiologically follows left ventricular contrast effect, while the two effects are simultaneous in the presence of blooming. To obtain reliable images, the operator should either wait for spontaneous bubble dissolution or reduce contrast dosage, infusion rate or gain setting during a subsequent administration.

An excessive concentration of microbubbles can also produce shadowing artifacts, characterized by attenuation of the ultrasound beam and inability to visualize far-field structures. As for the blooming effect, the operator should either wait for spontaneous bubble dissolution or repeat contrast administration more properly. Because of contrast-induced attenuation, apical views are preferable in myocardial perfusion imaging. Attenuation artifacts are located in the left atrium in apical views, while they may involve the posterior wall of the left ventricle if the heart is imaged in parasternal views. For the same reason, apical segments show more contrast enhancement than basal segment even in normally perfused hearts. Poor contrast enhancement of entire walls, as the lateral wall in the apical four-chamber view, may occur because of attenuation of the ultrasound beam by structures located between the probe and the heart (as ribs or lungs), as illustrated in Figure 7. The latter artifact should be identified before...
injecting the contrast agent, as it affects fundamental echo as well.

Wall motion artifacts appear during harmonic power Doppler when pulse repetition frequency is too low, allowing detection of heart movements. These artifacts manifest as coloured ventricular walls already visible before contrast administration. As stated before, pulse repetition frequency should be increased at the maximal value, which allows the detection of bubble disruption for each agent. Motion artifacts can also be caused by patient or transducer movement during imaging. To facilitate probe holding, flash echo has been proposed. It consists of continuous imaging at low output power (facilitating probe holding), interrupted by intermittent bursts of high power images (causing bubble disruption for perfusion imaging).

Finally, heterogeneity of the ultrasound beam within the sector should be considered. The mechanical index is lower in the lateral portions of the sector than in its centre. To compare the different walls under similar acoustic conditions, each wall should be transiently moved toward the centre of the sector during data acquisition. The mechanical index is also higher in the focal zone. If the focus is moved away from the transducer (in the left atrium), a beam overlapping can occur in the near field, favouring bubble disruption and appearance of false apical perfusion defects. Moving the focus toward the transducer eliminates artifactual perfusion defects at the apex by reducing proximal beam overlapping.

**Offline Analysis and Display Modalities**

To facilitate visual assessment of myocardial contrast enhancement, several strategies have been employed: digital subtraction of background from contrast images, colour-coding instead of grey-scale imaging and functional imaging. In pre-contrast background images, the reflectivity of the ventricular walls is heterogeneous secondary to several factors: the relation between orientation of myocardial fibres and the ultrasound beam, the attenuation phenomenon and the combination of linear and non-linear scatterers in the same image[46]. This uneven background interferes with myocardial perfusion measurement during myocardial contrast echocardiography. With background subtraction, pre-contrast baseline images are digitally eliminated from contrast pictures by off-line image processing[47]. Although this procedure enhances the small contrast-induced increment in myocardial signal intensity, it may introduce artifacts due to image misalignment or to the physiological beat-to-beat variability in cardiac volume and ejection fraction.

Colour-coding of grey-scale images simply exploits the fact that the human eye can distinguish only a few
shades of grey, while perceiving thousands of hues of colour. At present, a variety of colour maps are proposed by different companies, but standardization (as achieved for colour Doppler) is still lacking. Finally, in functional imaging a single image is derived from the analysis of a sequence of images. With this modality, signal intensity reflects the behaviour of a functional parameter (for example time to peak intensity, mean transit time, etc.) in the myocardium.

Clinical Models

Although more arduous in terms of organization and feasibility, myocardial perfusion imaging is easier to interpret in acute myocardial infarction than in chronic ischaemic heart disease. In acute infarction, myocardial perfusion resembles a black and white situation where a perfusion defect is present downstream to the acute occlusion (in the absence of collateral circulation) and disappears completely, or partially, after reflow. In the presence of coronary stenoses, post-infarction scars or hibernating myocardium, myocardial perfusion is often reduced at baseline and/or during stress, and contrast echocardiography may fail to identify subtle reductions in coronary blood supply. Other clinical models appear very interesting from the physiological point of view (for example, syndrome X, hypertensive and diabetic heart disease, hypertrophic and dilated cardiomyopathies), yet are still virtually unexplored by contrast echocardiography.

Myocardial Perfusion in Acute Infarction

In the early hours of infarction, the pattern of myocardial perfusion depends on artery patency at the time of contrast agent injection: persistent coronary occlusion or vessel recanalization. During occlusion, the lack of opacification in the downstream, non-perfused myocardium may be clearly outlined by contrast echo. In this setting, contrast echo is superior to the study of ventricular wall motion by two-dimensional (2D) echocardiography, since detection of an impaired regional function provides only indirect assessment and tends to overestimate the extent of the jeopardized myocardium.

Contrast echo performed shortly after attempted reperfusion not only identifies successful from failed reperfusion, but also provides additional information on the state of the coronary microcirculation. In the case of rapid coronary reopening in the absence of significant residual vessel narrowing, reactive hyperaemia yields a brighter downstream contrast effect in experimental animals. In contrast, in the presence of a flow-limiting stenosis or if the agent is administered after the hyperaemic phase, no significant difference in the opacification of the reperfused myocardium is generally apparent. Despite achievement of an adequate coronary recanalization and flow at angiography, trivial or absent enhancement in the downstream myocardium proved to be associated with no- or low-reflow. This phenomenon was reported in 18%–25% of patients undergoing intracoronary contrast injections after primary PTCA. The incidence is even higher in studies using intravenous contrast administration.

Data from trials having used intracoronary contrast injection were recently confirmed in a study by Porter et al. The authors evaluated myocardial perfusion in 45 patients in the early post-infarction period using intravenous administration of a second generation agent (PESDA). The subjects were classified in three groups: TIMI 3 flow and no contrast defect, TIMI 3 flow but presence of a perfusion defect, and TIMI 0–2 flow. Follow-up transthoracic echocardiography at 9 weeks showed significant deterioration in end-systolic volume and wall motion score index in the patients with TIMI 0–2 flow and in those with TIMI 3 and no-reflow by contrast echo. In contrast, TIMI 3 patients with contrast reflow demonstrated significant improvement of these values. Interestingly, in patients with TIMI 3 flow, the no-reflow by contrast echocardiography was not predicted by Q waves on the ECG, TIMI frame count or residual stenosis in the culprit vessel.

In another study, Kamp et al. assessed myocardial perfusion in acute infarction using intravenous injection of a second generation agent (NC100100, Sonazoid, Nycomed-Amersham, Norway) and intermittent harmonic imaging with intermediate output power. Contrast was injected immediately prior to, and 1 h and 24 h after coronary angioplasty in 60 acute infarction patients. A reduction in the extent of the contrast defect from pre- to immediately post-angioplasty imaging was observed in 73% of patients with baseline abnormalities, paralleling improvement from baseline TIMI 0–2 to post-procedure TIMI 3 flow. Importantly, these data underline the regional variability in assessing perfusion defects: in patients with TIMI 0 flow, myocardial contrast echocardiography showed a defect in 100% of anterior infarctions but in only 28% of inferior infarcts.

Of note was that the size of the perfusion defect by myocardial contrast echocardiography performed 24 h after reperfusion in anterior infarcts proved the strongest independent predictor of left ventricular function recovery at 4 weeks. Finally, inter- and intra-observer agreement was higher in evaluating myocardial perfusion in anterior infarctions by contrast echo than in assessing wall motion abnormalities by 2D echocardiography. Although these studies are afflicted by several limitations (small sample size, highly selected patients, various methodologies, occasional high drop-out rate), general consistency in their results is very reassuring.

Myocardial Perfusion by Contrast Echocardiography in Chronic Ischaemic Heart Disease

In several studies, myocardial perfusion assessment by contrast echo was compared to nuclear imaging. Porter et al.
et al.[50] studied 28 patients comparing intravenous PESDA in conjunction with intermittent harmonic imaging at rest and following dipyridamole to rest thallium and Technetium-99m sestamibi dipyridamole. Assessment of perfusion by contrast echocardiography was accomplished by measuring background-subtracted peak myocardial videointensity. Correlation between the two imaging modalities was high at rest (r=0.84) and following stress (r=0.88). The overall sensitivity and specificity of myocardial contrast echocardiography in detecting nuclear defects were 92% and 84%, respectively.

Similarly, Kaul et al.[52] compared myocardial contrast echocardiography to Tc-99 sestamibi SPECT at baseline and following dipyridamole injection in 30 ambulatory patients. Contrast echocardiography was performed with intravenous FS-069 (Optison®), Mallinckrodt Medical Inc, U.S.A. and acquired with harmonic intermittent imaging. Background-subtracted grey-scale images were colour-coded for interpretation. Overall agreement between contrast echocardiography and SPECT on a segment-by-segment analysis of perfusion was 92%. Concordance of the two modalities in classifying segments and vascular territories as normal, fixed or reversed was 92%. However, intra-observer agreement for contrast echocardiography ranged from 67% to 88% and inter-observer agreement from 63% to 66%.

On the contrary, Marwick et al.[53] studied 203 patients with previous myocardial infarction in a multicentre trial and disclosed different results. The contrast agent (NC100100, Sonazoid®, Nycomed-Amersham, Norway) was intravenously injected at rest and compared with rest Technetium-99m SPECT imaging. Myocardial enhancement was assessed under various conditions: harmonic vs. fundamental imaging, continuous vs. triggered acquisition, and injection of three different amounts of intravenous contrast medium. Intermittent harmonic imaging with the highest contrast dose displayed the greatest proportion of interpretable segments (72%). Using this technical setting, sensitivity and specificity of contrast echo for detection of perfusion defects identified by SPECT were 31 and 93%, respectively. As discussed by the authors — and underlined in an editorial comment[54] — disagreement between their study and the previous two trials may be explained by major methodological differences. Marwick et al. did not submit images to post-processing or videointensity analysis; their images were acquired and interpreted by cardiologists without a deep expertise in the field of myocardial contrast echocardiography; the fact that 70% of segments with severe defects on SPECT imaging had normal regional function by 2D echocardiography raises the question of false positive SPECT defects; finally, only a minority of patients were studied by intermittent harmonic imaging, the majority of them being investigated with fundamental imaging. These observations confirm the importance of expertise in interpreting contrast studies, optimal imaging modalities and the need for more data before myocardial contrast echocardiography becomes a widespread, routine procedure for perfusion assessment.

Recently harmonic power Doppler imaging of myocardial perfusion has been compared with Technetium-99 SPECT by Heinle in 123 patients with known or suspected coronary artery disease[55]. Images were obtained at baseline and during adenosine infusion. Overall concordance between contrast echo and SPECT was 81% for normal vs. abnormal perfusion. Agreement between the two methods varied with the involvement of the three coronary territories, being equal to 81% for the left anterior descending artery, to 76% for the right coronary artery and to 62% for the left circumflex artery. Discrepancies between the two techniques were more evident in the circumflex territory were fixed defects were observed in 33% by contrast echo, but in only 14% by SPECT. With the aim of obtaining the simultaneous assessment of myocardial perfusion and wall motion, a low mechanical index and frame rates of 10–20 Hz (accelerated intermittent imaging) have been utilized in patients undergoing dobutamine or exercise stress. An incremental benefit of myocardial perfusion versus wall motion analysis was found, especially during the pharmacological test[56]. Other investigators have shown that this approach is particularly accurate in the diagnosis of exercise-induced myocardial perfusion defects in the left anterior descending territory[57].

**Conclusion**

Progress in myocardial contrast echocardiography has advanced at an exponential rate in the last decade, thanks to growing interest from the pharmaceutical companies, the imaging industry and the medical community. Recent advances consisted in the introduction of safe and stable transpulmonary agents for left heart opacification. Moreover, better understanding of microbubble interaction with ultrasound has led to rapid evolution in imaging techniques and confirmed a potential for myocardial opacification with contrast echocardiography as routine testing in the near future. However, many methodological issues remain unsettled. In fact, perfusion imaging with intravenous contrast agents has never been as close to widespread clinical use as it is today, but a gap still persists before the wish of the contrast echocardiographer comes true: a cheap, user-friendly and widely available technology that would disclose new information for everyday cardiology.

**References**


[34] Porter TR, Xie F. Transient myocardial contrast after initial exposure to diagnostic ultrasound pressures with minute doses of intravenously injected microbubbles. Demonstration and potential mechanisms. Circulation 1995; 92: 2391–2395.


Intravenous Contrast Echocardiography for Myocardial Perfusion


