Clinical Experience with SonoVue in Myocardial Perfusion Imaging

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Ultrasound-enhancing agents have the potential to evaluate myocardial perfusion, adding a new dimension to echocardiography. This article summarizes the clinical studies involving SonoVue, a new intravenous ultrasound contrast agent, in assessing myocardial perfusion. Safe and well tolerated, SonoVue coupled with echocardiography has the capability to identify perfusion abnormalities, as confirmed by scintigraphic imaging. While the optimal modalities for ultrasound perfusion assessment are not yet determined, numerous technical advances have been introduced: continuous infusion or slow intravenous administration of the agent, harmonic intermittent imaging, pulse inversion, background subtraction, color coding, and others. SonoVue is a promising new agent in the booming field of myocardial contrast echocardiography. (ECHOCARDIOGRAPHY, Volume 17, No. 6, Part 2, August 2000)

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The assessment of myocardial perfusion by ultrasound-enhancing agents has been tested in different experimental and clinical settings, potentially adding a new dimension to echocardiography. Likely applications would include bedside evaluation of the area of myocardium at risk for necrosis,[1-4] response to thrombolysis,[3-5] identification of no-reflow phenomenon (for risk stratification and therapeutic interventions),[6-8] assessment of viability (whether stunning or hibernation),[9-14] adjunct to stress testing to detect reversible myocardial ischemia,[15] and appraisal of collateral circulation.[16]

This approach was initially attempted using intracoronary injection of free air bubbles obtained by hand agitation or sonication of a variety of substances. Today, contrast microbubbles are industrially produced, and two ultrasound contrast agents have been approved by the FDA: Albunex and Optison (Molecular Biosystems, San Diego, CA, USA). The first agent is a solution of air-filled microspheres, produced by sonicating 5% human serum albumin; these air-filled microspheres have a limited stability and duration of contrast effect.[17] The second agent is based on perfluorocarbon-filled albumin microbubbles; this contrast agent is more stable than Albunex and has been approved for improvement of endocardial border delineation during echocardiography.[18]

SonoVue (Bracco, Italy) is a microbubble preparation that is stable, resistant to pressure, and specifically designed for use as a contrast agent for ultrasound imaging.[19-20] Stored in the form of a lyophilized powder, it can be reconstituted by addition of physiologic saline followed by hand agitation for 30 seconds. The resulting microbubble suspension is stable for 6 hours at room temperature. The microbubbles contain sulfur hexafluoride (SF6), a poorly soluble and totally innocuous gas, which is eliminated through the lungs. SonoVue solution is isotonic to human plasma and does not contain any protein-based material. This article focuses on the early clinical experience with this agent in myocardial perfusion imaging.

Clinical Studies with SonoVue

Six Phase I studies with this agent were completed in a total of 111 healthy volunteers.[21-26] Based on the safety profile and the preliminary efficacy profile of the agent, further clinical investigations have been completed or are ongoing. As of December 1999,

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more than 1700 subjects had received SonoVue in completed clinical studies for both cardiac and noncardiac indications. In these studies SonoVue appeared to be safe and well tolerated. The majority of adverse events was mild in intensity and resolved without sequelae.

Three Phase II clinical trials were conducted to evaluate the use of SonoVue for the assessment of myocardial perfusion. The first study (BR1-021) enrolled 15 patients with a known perfusion defect based on a prior SPECT study.[27] The view that best delineated the defect on the SPECT study was the only view assessed during myocardial contrast echocardiography. All patients were studied using power Doppler harmonic imaging following intravenous contrast administration. The agreement between myocardial contrast echocardiography and SPECT in the detection of perfusion defects by slow bolus injections of SonoVue (2-3 ml over 20 seconds) was assessed by using a 5-segment matching model. The concordance between the two modalities for the presence or absence of the defect was 93%. A high agreement was also obtained on the location of the defects (96%, 93%, and 87% for the anteroseptal inferoposterior and apical regions, respectively). The results of this study documented the potential of SonoVue to determine the presence of resting perfusion abnormalities.

A second Phase II study was conducted in 58 patients with perfusion abnormalities, knowing the results of the myocardial scintigraphy.[28] Myocardial contrast echocardiography was performed using not only power Doppler harmonic imaging, but also harmonic gray scale imaging using qualitative and quantitative (video intensity) assessment of the contrast activity. In addition to analysis of raw online images, B-mode images were digitally processed and color coded. The results of this study suggest that SonoVue appears to have potential clinical utility as a contrast agent for enhanced detection of myocardial perfusion defects at rest during intermittent, harmonic B-mode echocardiography and intermittent, harmonic power Doppler echocardiography. The agreement with SPECT varied with the dose, administration modality (bolus or infusion), and pulsing interval.

In both the aforementioned pilot studies, the investigator knew the results of the myocardial scintigraphy prior to SonoVue administration, and only one echocardiographic view was examined. Therefore, a third Phase II study was designed, which included 19 patients, to more closely represent clinical practice for the use of contrast agents in echocardiography.[29] The patients were enrolled based on the presence of ventricular wall-motion abnormalities at rest, and multiple echocardiographic views were recorded in each patient. The investigator did not know the results of the SPECT study until after echocardiographic assessments were completed. Two to three contrast injections were required to complete the contrast perfusion study in four views using B-mode echocardiography. Combining all the views in B-mode imaging, the agreement between myocardial contrast echocardiography and SPECT was 72% for segments indicating the presence of a perfusion defect, 86% for segments indicating normal perfusion, and 80.2% for segments with perfusion defect or normal perfusion. This study demonstrated that the use of repeated bolus doses was effective in obtaining different echocardiographic views, allowing completion of a myocardial perfusion examination.

These clinical studies provided the basis for pursuing a comprehensive Phase II dose-finding study (BR1-038). This study was designed to assess the dose-response relationship for a slow intravenous administration of SonoVue for myocardial perfusion based on the extent of qualitative enhancement and contrast duration during harmonic B-mode and harmonic power Doppler imaging. This assessment was based on an apical four-chamber view. An offsite comparison was performed between contrast echo images and corresponding radionuclide perfusion images for detection or exclusion of perfusion defects. In a subset of patients, angiographic findings were compared to radionuclide perfusion study and myocardial contrast echocardiography for the purpose of assessing coronary artery disease. This study was international, with sites in Europe and the United States. The study was recently completed and the results are under evaluation.

Representative Case

The following example is the case of a patient enrolled in the BR1-038 study. A 59-year-old man was admitted to the hospital 40 minutes after the onset of acute chest pain resistant to sublingual nitrates. The electrocardiogram showed ST segment elevation in DI, avL, and from V2 to V6 (maximal ST elevation was 0.3 mV). To proceed to primary PTCA, the patient underwent coronary angiography. The angiography showed occlusion of the left anterior de-

scending artery (LAD) in its middle third and a tight stenosis at the origin of the first diagonal branch; the circumflex and the right coronary arteries displayed only minor luminal irregularities. The patient successfully underwent PTCA plus stenting on the LAD lesion and PTCA on the diagonal branch. At the time of hospital discharge (7 days postrevascularization) transthoracic two-dimensional echocardiogram (Fig. 1) showed severe hypokinesia and reduction of systolic thickening of mid-anterior septum and apical septal and lateral segments. To evaluate myocardial perfusion, slow intravenous SonoVue injection was performed under harmonic intermittent power Doppler imaging. Figure 2 illustrates contrast echocardiography during the infusion of 4 ml of the agent completed over 1 minute 20 seconds. A definite perfusion defect is clearly appreciated in apical septal and lateral segments. SPECT imaging with thallium-201 at rest demonstrated a severe uptake defect involving the anterior septum and the apex with prevalence of necrosis in these walls.

This case illustrates the substantial agreement between myocardial contrast echo and radionuclide perfusion imaging that both reflect the state of myocardial microcirculation with different modalities. Of notice, the information on myocardial perfusion abnormalities cannot be predicted neither by coronary anatomy (showing a patent infarct-related artery) nor by regional wall-motion assessment (demonstrating more extensive regional contractility abnormalities).

Qualitative Versus Quantitative Assessment of Myocardial Perfusion

Myocardial echo contrast enhancement may be assessed both qualitatively and quantitatively. Although it would be highly desirable to be able to obtain quantitative information on tissue perfusion by contrast echocardiography, the exact measurement is affected by several limitations. A major one regards the relation between microbubble concentration and intensity of ultrasound signal. As a matter of fact, several studies have demonstrated that this relation is not linear over a wide range of contrast concentrations.[30-31] To overcome this limitation, the utilization of a very limited range of contrast concentrations, where this relation is assumed to be linear, has been proposed.[30] However, the concentration of microbubbles following a bolus contrast injection is often above this "linear range."

To overcome this limitation and to quantify myocardial blood flow, Wei et al.[32] proposed a continuous infusion of second generation echo contrast agents during intermittent harmonic imaging. Using this approach, a steady state may be achieved where microbubble concentration is constant. In this situation, the concentration of microbubbles is proportional to the fraction of blood volume, while the rate at which microbubbles enter different organs is related to their velocity. Concerning utilization of contrast echocardiography in routine clinical practice, a slow administration of SonoVue, as shown in Figure 2, seems to be an acceptable

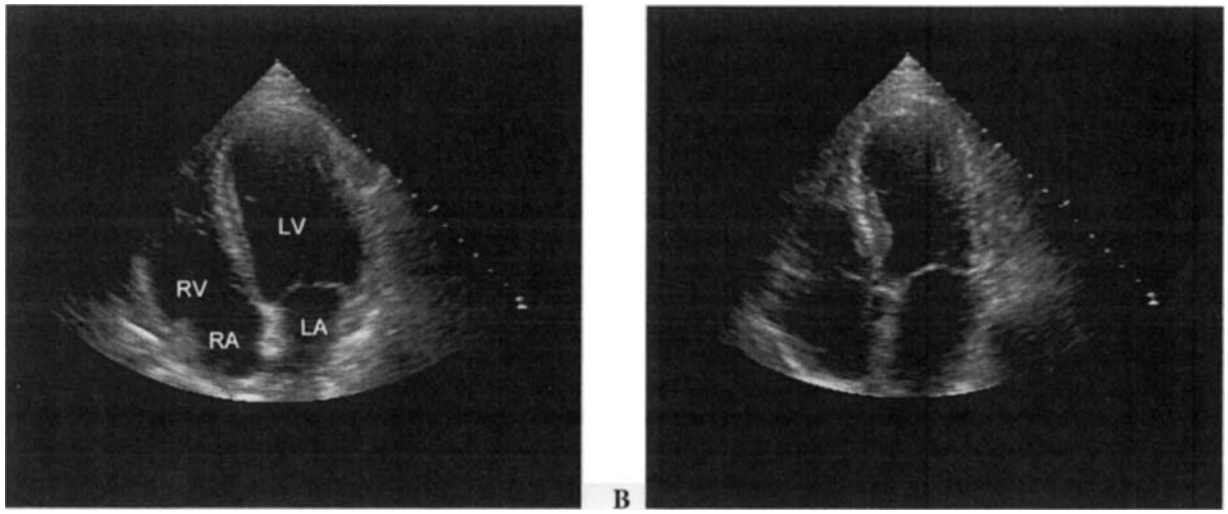

Figure 1. *Two-dimensional echocardiographic images in the apical 4-chamber view, corresponding to end-diastole* **A** *and end-systole* **B.** *A reduction in systolic thickening can be appreciated in mid-anterior septal, apical septal, and lateral segments.*

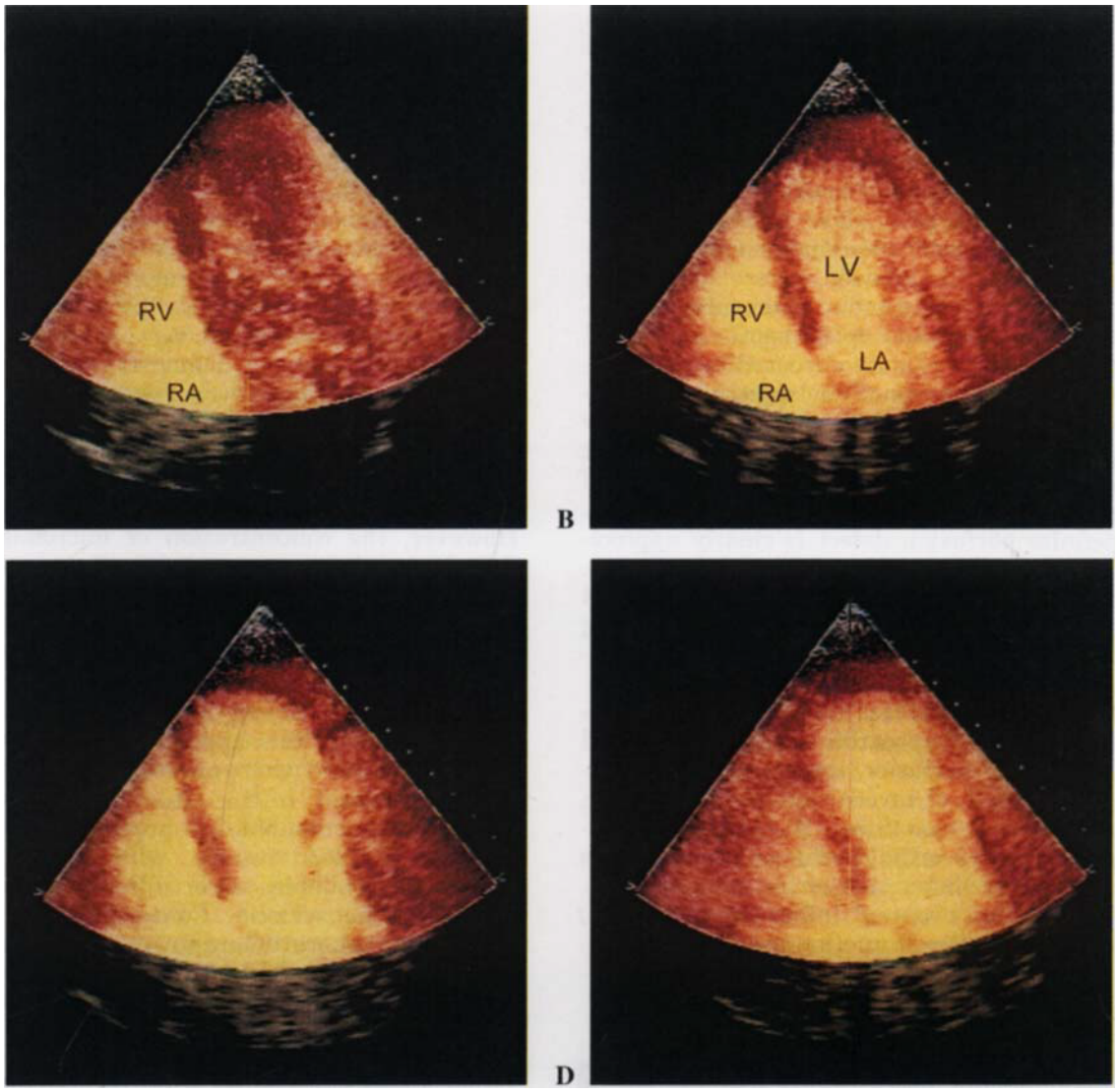

Figure 2. *Myocardial contrast echo study during the infusion of SonoVue.* **A.** *corresponds to contrast enhancement of right heart cavities;* **B.** *to the enhancement of left ventricular cavity and* **C, D** *to myocardial contrast enhancement. A perfusion defect can be appreciated in lower panels in apical septal and lateral segments.*

compromise that can be easily and routinely performed in different clinical settings.

Before contrast administration, normal ventricular walls show different degrees of myocardial intensity. This heterogeneity in myocardial background is mainly due to the angle between incident ultrasound beam and myocardial fibers, a phenomenon commonly referred to as anisotropy.[33,34] An heterogeneous background intensity is also present in patients with previous infarction, whose infarcted walls often show an intensity higher than normal myocardium, likely due to the presence of fibrotic or scar tissue. This heterogeneous background may affect the measurement of myocardial perfusion when digital subtraction is performed. Due to these reasons, it would be desirable to eliminate background intensity in contrast echocardiography, as partly done using power Doppler[35] or pulse inversion technology.[36,37]

Indicator dilution theory assumes that the changes in signal intensity following the administration of a tracer into the blood stream reflect its passage through the circulation.[38] This is true if the tracer is purely intravascular (as contrast microbubbles) and if it is stable enough. First generation contrast agents are

sensitive to pressure and to contact with blood, so that the changes in myocardial contrast intensity are due both to the passage of microbubbles through the coronary circulation and to their in vivo decay. This limitation is less obvious with second generation agents, such as SonoVue, which are characterized by a greater stability in vivo.

While the human eye can discern only a few shades of gray (on average 16), it can discriminate between thousands of hues of color. The main advantage of color over gray scale images is that the perception of differences in myocardial signal intensity is easier. This has been extensively used in nuclear cardiology, where perfusion images are usually color-coded. This advantage can also be utilized in myocardial contrast echocardiography to make the subjective identification of perfusion abnormalities easier.[31,39]

Studies have shown that pulsed imaging as compared to continuous imaging can minimize the destruction of microbubbles.[40] Accordingly, triggered imaging was employed in these studies to maximize the assessment of myocardial perfusion following intravenous administration of SonoVue. Changes in triggering interval (time interval between two consecutive frames) can produce several positive effects. Using the adequate dose of contrast agent and acoustic pressure, a single sweep of ultrasound can destroy all microbubbles within the sector. If this is achieved, myocardial intensity in the next frame reflects the number of microbubbles entering the myocardium in the ultrasound field during the pulsing interval. According to this approach, varying this interval allows to explore different flow velocities, because normally perfused ventricular walls are replenished by microbubbles at low pulsing intervals (e.g., one beat), while hypoperfused areas can require very prolonged pulsing intervals (up to 8 beats or even more) to fill the myocardium.[32]

Using continuous intravenous infusion of SonoVue at pulsing intervals of 1, 3, and 8 cardiac cycles Lindner et al.[28] demonstrated that relative perfusion defects at rest are best discerned at long pulsing intervals. At rest, when the heart rate is normal, plateau myocardial intensity in normal myocardium is usually reached at pulsing intervals of 5 to 6 cardiac cycles. Background-subtracted myocardial intensity at a pulsing interval of every 8 cardiac cycles, therefore, represents relative myocardial blood volume in different myocardial beds. Better representation of relative myocardial blood volume in normal and infarcted beds at a pulsing interval of 8 cardiac cycles should provide better assessment of relative perfusion. A good correlation was found between relative perfusion defects by SPECT and by myocardial contrast echocardiography using a pulsing interval of 8 (correlation coefficient $r = 0.73$). This correlation was not as good when myocardial contrast echocardiography was performed with pulsing intervals of 1 and 3.

Significance of Myocardial Echo Contrast Enhancement

Myocardial contrast intensity is heavily affected by biological factors: mainly changes in coronary blood flow and alterations in myocardial blood volume. These factors influence contrast intensity in opposite directions. Moreover, the transit time of microbubbles through the coronary circulation is inversely related to coronary blood flow, but directly related to myocardial vascularity and blood volume.[41] Therefore, an increase in coronary flow not accompanied by an increase in myocardial vascularity and blood volume is achieved by a faster transit of microbubbles through the coronary circulation. Conversely, an increase in coronary blood flow mediated by augmented myocardial vascularity and blood volume will increase myocardial contrast enhancement and lengthen microbubble transit. The analysis of still frames as shown in Figure 2 more likely reflects changes in myocardial vascularity among different ventricular walls, while changes in signal intensity using different triggering intervals should mainly reflect changes in blood flow velocity.[32]

Advantages of Myocardial Contrast Echocardiography over SPECT

Despite the previously mentioned limitations, myocardial contrast echocardiography offers several potential advantages over radionuclide perfusion imaging. The relatively lower cost of ultrasound equipment permits MCE to be more readily available to community health care facilities, and its portability allows bedside evaluation of critical care patients. In addition, there is no delay in diagnosis with MCE: images may be assessed in real-time. Myocardial contrast echocardiography also has several safety advantages compared to SPECT: there is no exposure to radioactivity for patients or health care personnel, and there is no additional expense for radioactive waste disposal.

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