Detection of Resting Myocardial Perfusion Defects by SonoVue® Myocardial Contrast Echocardiography

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Background: SonoVue® is a new microbubble contrast agent containing sulfur hexafluoride. We assessed the efficacy of SonoVue® myocardial contrast echocardiography (MCE) to detect resting perfusion abnormalities. Methods: Nineteen adult patients with a wall motion abnormality in a screening echocardiogram were studied. Each patient received up to four bolus injections of 2.0 mL SonoVue® (Bracco Diagnostics, Inc.) during echocardiographic examination using either B-mode (n = 12) or power Doppler (n = 7) imaging. Each patient also had SPECT nuclear perfusion imaging performed. Segmental assessment of myocardial perfusion from SonoVue® MCE images were compared with corresponding SPECT nuclear images. Results: Using B-mode imaging, the mean number of views obtained with a single SonoVue® injection ranged from 1.4 to 1.9, with 2 or 3 injections required for a complete examination. Ninety-four percent of segments were scored as diagnostic. Agreement between B-mode and SPECT images was 72% for segments with a perfusion defect, 86% for normal perfusion, and 80% for segments with either perfusion defect or normal perfusion (all views combined). Using power Doppler imaging, the mean number of views obtained with a single SonoVue® injection ranged from 1.0 to 1.3, with 2 to 4 injections required for a complete examination. Sixty-eight percent of segments were scored as diagnostic. Agreement between power Doppler and SPECT images was 67% for perfusion defects, 53% for segments with normal perfusion, and 59% for segments with either perfusion defect or normal perfusion (all views combined). Conclusions: SonoVue® MCE has the potential to assess myocardial perfusion at rest. B-mode imaging was more accurate than power Doppler imaging when compared with SPECT nuclear imaging. (ECHOCARDIOGRAPHY, Volume 20, August 2003)

SonoVue, myocardial perfusion, myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) using newer microbubbles has shown promise in the clinical setting to delineate normal and abnormal myocardial perfusion. It has also been demonstrated that high mechanical index (MI) triggered MCE using can be used to detect perfusion defects in patients with coronary artery disease (CAD).[1] SonoVue® (BR1; Bracco Diagnostics, Inc., Princeton, NJ, USA) is a new microbubble contrast agent currently being evaluated for cardiac and other vascular ultrasound applications.[2-5] It consists of sulfur hexafluoride-filled microbubbles in a phospholipid shell. Sulfur hexafluoride (SF_6) is a poorly soluble, totally innocuous gas that does not undergo metabolism and is eliminated in expired air.[6]

The purpose of this study was to evaluate whether SonoVue® MCE is able to detect resting myocardial perfusion defects.

Methods

Study Population

Nineteen patients were enrolled sequentially in two groups: the first group of patients was evaluated using B-mode imaging (n = 12) and the second group using power Doppler imaging (n = 7). Patients were eligible for the

study if they were at least 18 years of age, had a history of ischemic heart disease, had a discrete left ventricular wall motion abnormality (ie, two consecutive segments graded as hypokinetic, dyskinetic, or akinetic) on a noncontrast echocardiogram performed within 7 days prior to SonoVue® administration, and were clinically indicated for a radionuclide perfusion study. Exclusion criteria included a technically inadequate imaging window on screening noncontrast echocardiogram, severe congestive heart failure, unstable angina, severe arrhythmia, a right-to-left circulatory shunt, pulmonary hypertension, or pregnancy and lactation. The study protocol was approved by the institutional review board, and written informed consent was obtained from all patients prior to enrollment.

Study Agent Administration

Patients received up to four intravenous bolus injections of SF_6 microbubbles (SonoVue®) at a dose of 2.0 mL each, in accordance with the prespecified phase II protocol. The bolus was administered over 30 seconds followed by slow 5-mL normal saline flush. The number of injections each patient received was determined by the need to obtain a complete MCE examination. SonoVue® was provided by Bracco Diagnostics Inc. as a sterile, pyrogen free, lyophilized powder. A white, milky suspension of SF_6 microbubbles was obtained by adding 5 mL of physiologic saline (0.9% sodium chloride) to the powder, using standard clinical aseptic techniques followed by hand agitation. After reconstitution, bubble concentrations are in the range of 1 to 5×10^8 microbubbles per milliliter. SonoVue® microbubbles range in diameter from 1 to 10 μm (mean diameter, 2.5 μm; $90\% < 8 \mu$m).

B-Mode and Power Doppler Echocardiography

Images were obtained using a commercially available echocardiographic machine ATL 5000 (Bothell, WA, USA). The frequencies of the probe used for harmonic imaging were 1.8-MHz transmit and 3.6-MHz receive. Instrument settings were optimized prior to SonoVue® administration. For B-mode imaging, MI ranged from 0.7 to 1.2 for all patients. For power Doppler imaging, MI ranged from 0.7 to 1.3, while pulse repetition frequency (PRF) ranged from 500 to 2100. The optimal PRF for SonoVue® was not established at the time of this study. Hence the optimal PRF was selected for each patient based on minimal motion artifact and best myocardial contrast effect.

A screening noncontrast B-mode examination was performed for assessment of wall motion abnormalities within 7 days prior to administration of SonoVue®. Echocardiographic views for assessment of wall motion were selected from the following six views: apical four-chamber (A4C), apical two-chamber (A2C), apical long-axis (APLAX), parasternal mid-short-axis (SAX-PM), parasternal apical-short-axis (SAX-AP), and parasternal long-axis (PLAX) views. SonoVue® MCE imaging began with the echocardiographic view most likely to reveal a myocardial perfusion defect based on the wall motion abnormality seen in the screening noncontrast echocardiogram. A second echocardiographic view was selected that anatomically complemented the first view (ie, the view that illustrated the same defect or an additional defect in the same territory). Additional views were imaged if they were deemed essential to detect the perfusion abnormality in a given patient.

For each injection of SonoVue®, echocardiographic imaging (B-mode or power Doppler) began 30-seconds prior to SonoVue® administration (minimum of three frames acquired). Following administration of SonoVue®, triggered images that were gated to an electrocardiogram at end-systole, at every cardiac cycle (1 : 1) and every fourth cardiac cycle (1 : 4), were obtained. At least three evaluable frames were obtained for each pulsing interval in one view before switching to the next view. Imaging continued after each injection until virtual disappearance of the contrast effect from the left ventricle and myocardium. All images were recorded on SVHS videotape.

Radionuclide Perfusion Imaging

The ^{99m}Tc-sestamibi single-photon emission computerized tomography (SPECT) imaging was done in each patient within 4-weeks prior to or 1-week after administration of SonoVue®. A standard image acquisition protocol was used 1-hour after administration of ^{99m}Tc-sestamibi. The reconstructed data set was reformatted to yield horizontal long-axis views, vertical long-axis views, and a series of SAX views from apex to the base of the left ventricle. No percutaneous or surgical coronary interventions were done in any of the patients between the SPECT and MCE studies.

Efficacy Assessment

A single reader blinded to the results of the SPECT study interpreted all of the echocardiographic images. For each patient, the reader recorded the number of SonoVue® injections required for a complete examination, i.e., sufficient to determine whether or not a perfusion defect was present (additional injections, not to exceed a total of four, may have been administered at the investigator's discretion). For each bolus injection, the reader recorded the number of assessable views and pulsing intervals. Segmental assessments of myocardial perfusion were made from the selected echocardiographic views. Each segment in the chosen view was scored as follows: 0 = normal perfusion; 1 = possible perfusion defect; 2 = definite perfusion defect; AF = artifact; IC = insufficient contrast; AT = contrast attenuation; and NV = segment not visualized. Artifacts were defined as those which precluded the visualization of the myocardium, such as lung or rib shadows and calcific or prosthetic materials. When contrast was the cause of suboptimal visualization of the myocardium, such as those from excessive contrast in the near field or a papillary muscle shadow, it was assigned the score of AT. Normal, possible, and definite perfusion defects were prospectively defined as homogenous opacification, inhomogenous opacification not due to AT, AF or IC, and lack of opacification, respectively.

The SPECT nuclear images were oriented to produce views consistent with images generated from the echocardiographic evaluations. Each segment was assessed using the scale as for SonoVue® MCE images, excluding segments with insufficient contrast (IC) and contrast attenuation (AT).

Safety Assessment

Physical examination was performed prior to SonoVue® administration and within 1- to 24-hours after the last dose of SonoVue®. Vital signs were obtained at 1-minute prior to and 5-minutes after each injection, and at 10-minutes, 15-minutes, 24-hours, and 72-hours after the last dose. Standard clinical laboratory tests were performed prior to administration of SonoVue® and at 24- and 72-hours after the last dose. Patients were monitored for adverse events up to 72-hours after the last injection of SonoVue®.

Methods of Analysis

Descriptive statistics were used to summarize all parameters. Data obtained from B-mode and power Doppler assessments were analyzed separately. For assessment of echocardiographic images, the frequency of each distinct myocardial perfusion score and the corresponding percentage of the total number of segments evaluated were determined based on all echocardiographic views obtained. The percentage of segments with scores indicating diagnostic images (i.e., scores of 0, 1, or 2) was also determined. Agreement between echocardiographic and SPECT images were analyzed by matching each echocardiographic segment to the corresponding SPECT segment within the same view for which there was a diagnostic score. Percent agreement between echocardiographic and SPECT images was determined for each view and combined across views. If both examinations identified a perfusion defect, they were considered to agree regardless of whether the score was a "1" (i.e., possible perfusion defect) or a "2" (i.e., definite perfusion defect).

In addition to segmental assessment of agreement between echocardiography and SPECT, agreement was also assessed at the coronary territory level. For each patient, the occluded vessel believed to be responsible for the observed perfusion defect was identified using a 14-segment model for vessel mapping (Fig. 1). Agreement was defined as the same vessel or the same combination of vessels identified with both SPECT and echocardiography.

Results

Patient Characteristics

Ten of 19 patients studied were male, and nine patients were female. Ages ranged from 41 to 93 years old (mean age 70.4 years old). Eleven patients had a history of previous myocardial infarction, ten patients had a history of congestive heart failure, and eight patients had history of hypertension. Nine patients had prior remote cardiac surgery or percutaneous transluminal coronary angioplasty.

Number of SonoVue® Injections Required

With B-mode imaging, complete examinations were obtained with two or three SonoVue® injections (4 and 8 patients, respectively). The mean number of views obtained per injection
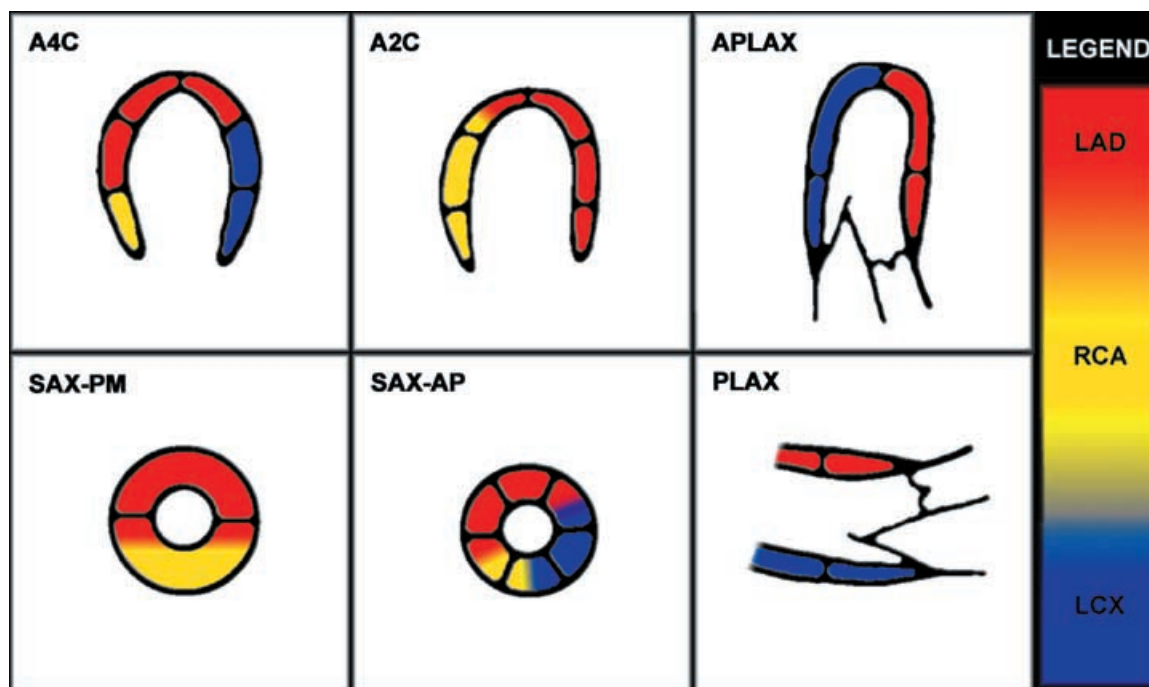
Figure 1. *Schema of assignment of the 14 echocardiographic segments in standard views to coronary artery territories. Overlapping colors signify overlapping coronary territories. Abbreviations: A4C = apical four-chamber view (horizontal long-axis view on SPECT); A2C = apical two-chamber view (vertical long-axis view on SPECT); LAD = left anterior descending; PLAX = parasternal long-axis view; RCA = right coronary artery; SAX-PM = short-axis view, papillary muscle level (mid-SAX tomograms on SPECT); SAX-AP = short-axis view, apical level (apical-SAX tomograms on SPECT); SPECT = single-photon emission computed tomography.*

ranged from 1.4 to 1.9. With power Doppler imaging, complete examinations were obtained with two (2 patients), three (3 patients), or four (2 patients) SonoVue® injections. The mean number of views obtained per injection ranged from 1.0 to 1.3.

Assessment of Accuracy for B-Mode Images

For patients imaged using B-mode ($n = 12$), 94.4% of segments assessed (204/216) were scored as diagnostic (i.e., score of 0, 1, or 2). The rate of agreement (for segments indicating the presence of a perfusion defect on SPECT, segments indicating normal perfusion on SPECT, and all segments with either perfusion defect or normal perfusion on SPECT) between B-mode and SPECT images is illustrated in Table I. For all echocardiographic views combined, the percent agreement between B-mode and SPECT was 72% for all three perfusion categories. The A4C and SAX-AP views provided the highest rates of agreement (81% to 91%) for all three categories.

Assessment of Accuracy for Power Doppler Images

For patients imaged using power Doppler ($n = 7$), 67.6% of all segments (46/68) were scored as diagnostic. IC was the most frequent nondiagnostic score (30.9% of all segments). As depicted in Table I, percent agreement with SPECT was 66.7% for segments indicated as perfusion defect on SPECT, but only 52.6% for segments with normal perfusion on SPECT. The parasternal short-axis mid-view provided the highest agreement between power Doppler and SPECT for all perfusion categories.

Coronary Territory Agreement

Using SonoVue®-enhanced B-mode imaging, specific coronary territory disease could be identified for 11 of 12 patients. The remaining patient had left circumflex coronary artery (LCX) and right coronary artery (RCA) disease identified with SPECT. Nine of 12 patients had agreement between SPECT and B-mode with

TABLE I

Agreement Between SonoVue® MCE and SPECT Evaluation of Segmental Perfusion

Perfusion Category	Echocardiographic View	B-mode		Doppler	
		Number*	Agreement†	Number*	Agreement†
Perfusion defect	Apical four-Chamber	7	81.3% (13/16)	6	66.7% (12/18)
	Apical two-chamber	11	62.9% (22/35)	1	66.7% (2/3)
	Parasternal short-axis: mid	10	75.0% (15/20)	3	71.4% (5/7)
	Parasternal short-axis: apical	6	85.7% (6/7)	1	50.0% (1/2)
	All views combined	12	71.8% (56/78)	7	66.7% (20/30)
Normal perfusion	Apical four-chamber	8	90.6% (29/32)	7	54.2% (13/24)
	Apical two-chamber	9	87.1% (27/31)	1	0.0% (0/3)
	Parasternal short-axis: mid	10	80.0% (32/40)	3	63.6% (7/11)
	Parasternal short-axis: apical	8	90.9% (10/11)	0	—
	All views combined	12	86.0% (98/114)	7	52.6% (20/38)
Perfusion defect or normal perfusion	Apical four-chamber	8	87.5% (42/48)	7	59.5% (25/42)
	Apical two-chamber	11	74.2% (49/66)	1	33.3% (2/6)
	Parasternal short-axis: mid	10	78.3% (47/60)	3	66.7% (12/18)
	Parasternal short-axis: apical	9	88.9% (16/18)	1	50.0% (1/2)
	All views combined	12	80.2% (154/192)	7	58.8% (40/68)

*Number of patients with at least one segment scored as diagnostic (ie, score of 0, 1, 2) by SPECT and for which one corresponding segment (same view and segment) was assessed by echocardiography.
†Number of segments in agreement divided by the total number of SPECT segments indicating perfusion defect, normal perfusion, or perfusion defect or normal perfusion (×100%).
Abbreviations: MCE = myocardial contrast echocardiography; SPECT = single-photon emission computed tomography.

respect to vessel disease identification (all views combined). The highest agreement rates were for the parasternal short-axis apical view (8 of 9 patients) and apical four-chamber view (6 of 8 patients).

With SonoVue®-enhanced power Doppler imaging, 6 of 7 patients had specific vessel disease identified. The remaining patient had LAD and RCA disease identified with SPECT. Five of 7 patients had agreement between SPECT and Doppler with respect to vessel disease identification (all views combined).

Safety and Tolerability

Only one adverse event (intravenous infiltration) was reported. There were no clinically significant changes in physical examination findings or vital signs. There were no clinically meaningful trends in hematology, serum chemistry, or urinalysis parameters. Abnormalities in laboratory values were infrequent and generally attributable to underlying conditions or medications.

Discussion

Data from this study reports that intravenous SonoVue® is an efficacious and safe agent for MCE. SonoVue® bolus intravenous injection, when combined with B-mode high-MI triggered imaging, is superior to power Doppler imaging with respect to visualization of both normal and abnormal myocardial perfusion.

High-MI triggered techniques can use either single or multiple pulse transmission methods.[7] B-mode and power Doppler imaging would be an example of the former and the latter, respectively. Single-pulse transmission technologies also utilize the conventional B-mode pathway to process the returning signals so that the resultant image is of high resolution. Power Doppler imaging utilizes the Doppler pathway and the resultant images are of inferior resolution than the B-mode images. But the microbubble disruption caused by the multiple pulses in the power Doppler method elicits a superior microbubble signal that can be displayed as a color overlay over the background gray scale image. Single-pulse transmission, even at MI > 1.0, causes less microbubble disruption than

the power Doppler imaging method. Also, tissue harmonics cause the myocardium to be brighter, especially at higher MIs, thus confounding visualization of the microbubble signals.

We obtained superior results with B-mode triggered imaging in almost every respect with SonoVue® MCE. More views per injection and more myocardial segments were analyzable. Agreement rates for perfusion abnormalities in the power Doppler images when compared to SPECT nuclear matched B-mode agreement rates in only in the SAX-PM view. For normal myocardial perfusion and overall perfusion assessments the agreement rates to SPECT images were even worse when compared to B-mode triggered images. When using power Doppler imaging, deficient destruction of microbubbles due to depth dependent attenuation in transmitted ultrasound power can produce a region of the myocardium in which little or no color is seen. This artifactual "dropout" is especially common in the distal field of imaging and can be misinterpreted as a perfusion defect. The lack of wall motion information in the triggered images makes this even harder to differentiate. The inferior detection rates of perfusion defects may be the result of blooming artifacts resulting from high contrast concentration, a problem especially related to bolus injections. Furthermore, distal attenuation due to excessive contrast is more pronounced with power Doppler imaging than with B-mode imaging (Fig. 2). Because power Doppler is based on assigning color

to changes in the field caused by bubble disruption, cardiac motion can result in color signals. This could result in erroneous interpretation of normal myocardial perfusion. In this study we used a maximum triggering interval of 1 : 4, which was not significantly affected by motion artifacts, but even this required obtaining images during breath holding in three patients. Clearly, longer triggering intervals and dyspneic patients pose a problem for carefully excluding motion artifacts when using power Doppler imaging.

Visual assessment of myocardial opacification is an evaluation of myocardial blood volume.[8] In this study, using SonoVue® bolus injections, we were able to demonstrate that such a qualitative assessment of MBV was efficient in the detection of normal perfusion from perfusion defects. Incorporating the changes in regional myocardial signal intensity over time, by looking at the 1 : 1 and 1 : 4 triggered images enhanced the ability to differentiate normal from abnormal perfusion patterns (Fig. 2). In those with regional wall motion abnormalities and myocardial infarction, merely evaluating the peak myocardial opacification, in other words peak MBV, may be sufficient to detect abnormalities. Eleven patients in this study had a history of myocardial infarction. But in those with residual flow in the region of wall motion abnormality, change in peak opacification over time helped to assess residual microvascular flow.[9,10]
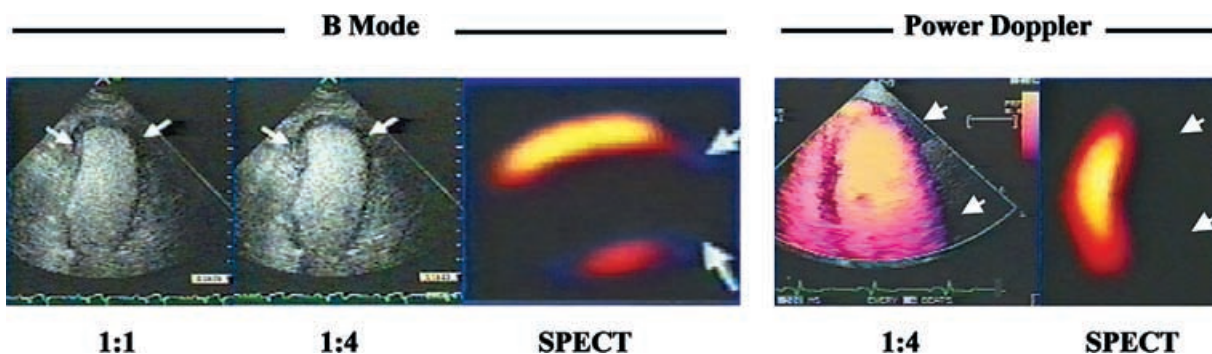

Figure 2. *Examples of B-mode and power Doppler high-MI triggered MCE and corresponding SPECT images. The B-mode MCE is an apical two-chamber view illustrating an apical perfusion defect (arrows), and the power Doppler MCE demonstrates a lateral wall perfusion defect (arrows). The mid to basal anterior wall abnormalities seen on B-mode and power Doppler high-MI triggered MCE are most likely an attenuation artifact. The images depicted also demonstrate a lateral wall defect. This region is commonly associated with a high rate of false-positives, however, in this patient it is a true defect as confirmed by SPECT. Abbreviations: MCE = myocardial contrast echocardiography; MI = mechanical index; SPECT = single-photon emission computed tomography.*

Limitations

The entire population was a small number of carefully selected patients and hence caution should be exercised in extrapolating the results of this study to a larger population. Although high-MI triggered power Doppler imaging was done with due attention to all the technical details as B-mode, it did not fare as well as B-mode. For many reasons outlined in the discussion section, a bolus-based study may have disadvantaged the power Doppler imaging modality. Using a microbubble infusion strategy, Heinle et al.[11] had better results with power Doppler imaging in the detection of myocardial ischemia. A maximum of 1:4 triggering interval was used and hence it can be argued whether peak myocardial opacification was indeed achieved. But in the setting of normal heart rate and cardiac output, we would expect peak myocardial intensity to be reached between four and six cardiac cycles. Lastly, this study only compares two high-MI triggered modalities and does not provide any information on the newer real-time, low-MI MCE techniques. However, high-MI triggering still produces maximal signals for any given concentration of microbubbles than any of the low-MI techniques.

Conclusions

MCE using intravenous SonoVue® is safe and efficient in the detection of myocardial perfusion abnormalities in patients with resting wall motion abnormalities. Furthermore, when compared with SPECT, B-mode high-MI triggered imaging yields better agreement rates than power Doppler imaging. Additional SonoVue® MCE studies are needed to assess its performance with low-MI real-time techniques, and the ability to detect inducible ischemia.

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