Assessment of Myocardial Perfusion with Intravenous Contrast Echocardiography:

Comparison with ^{99}Tc-Tetrofosmin Single Photon Emission Computed Tomography and Dobutamine Echocardiography

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The aim of the study was to evaluate the accuracy of intermittent, harmonic power Doppler (HPD) during intravenous Levovist infusion in identifying myocardial perfusion abnormalities in patients with recent infarction. Fifty-five patients with first acute myocardial infarction, successfully treated by primary PTCA, were studied after 1 month by myocardial contrast echocardiography (MCE), ^{99m}Tc tetrofosmin single photon emission computed tomography (SPECT), and low dose dobutamine echocardiography (DE). Scoring myocardial perfusion as normal, moderately, or severely reduced; MCE and SPECT were in agreement in 71% of segments ($k = 0.414$). Discordance was mainly due to ventricular walls with normal enhancement by MCE and moderate perfusion abnormalities by SPECT. Scoring perfusion as present or absent, the agreement significantly improved up to 86% ($k = 0.59$). Sensitivity and specificity of HPD for identifying SPECT perfusion defects were 63% and 93%, respectively. The agreement between MCE and SPECT was higher (85%, $k = 0.627$) in patients with anterior infarction. An improvement in regional contractile function was noted after dobutamine in 79 dysfunctional segments. A normal perfusion or a moderate perfusion defect by MCE were detected in 71 of 79 of these segments, while a severe perfusion defect was observed in 59 of 85 ventricular segments without dobutamine-induced wall-motion improvement. Sensitivity and specificity by HPD in detecting segments with contractile reserve were 90% and 69%, respectively. Thus, intermittent HPD during Levovist infusion allows myocardial perfusion abnormalities to be detected in patients with recent infarction. This method has a limited sensitivity but a high specificity in detecting SPECT perfusion defects, and a good sensitivity but a limited specificity in detecting contractile reserve. (ECHOCARDIOGRAPHY, Volume 20, January 2003)

myocardial contrast echocardiography, Levovist, myocardial perfusion scintigraphy, dobutamine echocardiography

Myocardial echo contrast enhancement can be obtained combining the intravenous administration of contrast agents able to cross the lungs with new ultrasound technologies, as intermittent harmonic imaging[1–4] and intermittent, harmonic power Doppler (HPD).[5–8] The latter method relies on the detection of microbubbles disrupted by ultrasound and takes advantages from "fragile," air-based, first-generation contrast agents and a high mechanical index.[9] Thus, HPD can be regarded as a line-by-line subtraction method, illustrating the spatial distribution of microbubbles in myocardial circulation and reflecting myocardial vascularity or intramyocardial blood content. The accuracy of myocardial perfusion assessment in the human using intravenous contrast echocardiography varied widely in the different studies, ranging from quite limited[3,4,7] to good agreement with perfusion data obtained by myocardial scintigraphy.[1,2,6]

The aim of this study was to evaluate the accuracy of myocardial contrast echocardiography

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(MCE) (using intravenous Levovist [Schering AG, Berlin, Germany] administration and intermittent HPD) in identifying myocardial perfusion abnormalities in patients with recent infarction. To ensure a homogeneous patient population, only infarction patients successfully treated with primary percutaneous transluminal coronary angioplasty (PTCA) were admitted to the study. Myocardial perfusion by ^{99m}Tc tetrofosmin single photon emission computed tomography (SPECT) and low dose dobutamine echocardiography (DE) were selected as the criterion standards for myocardial perfusion and contractile reserve, respectively.

Methods

Study Population and Protocol

The study included 57 patients (48 men, 9 women, mean age 57 ± 10 years) with first acute myocardial infarction treated by primary PTCA with achievement of a thrombolysis in myocardial infarction (TIMI) III flow in each patient. The infarct related artery (IRA) was the left anterior descending (LAD) in 37 (64%) patients, the left circumflex (LCx) in 6 (11%), and the right coronary artery (RCA) in 14 (25%) patients. A single vessel coronary artery disease was present in 29 (50%) patients, a double vessel involvement in 19 (34%), and a triple vessel disease in 9 (16%) patients. Left ventricular ejection fraction on admission was 0.46 ± 0.06, range 0.27–0.57. Exclusion criteria included galactose diabetes, pregnancy, lactation, cardiogenic shock, inability to complete the protocol, or inadequate acoustic window.

In all patients MCE was performed 1 month after the index infarction. During the same examination, a low dose DE was performed in 42 patients who showed regional wall-motion abnormalities in more than two segments according to the American Society of Echocardiography.[10] ^{99m}Tc-Tetrofosmin SPECT was obtained in every patient within 1 week of the MCE examination. The protocol was approved by the local ethics committee and informed consent was obtained from all patients.

MCE

Levovist was the ultrasound contrast agent used in every patient. This commercially available first-generation agent is composed of semifree air-filled microbubbles stabilized by palmitic acid in a galactose water solution. These microbubbles are highly echogenic and sufficiently stable for transit through the pulmonary circulation. The estimated median bubble diameter is approximately 3–4 μm. Levovist (4 g) was reconstituted by adding 8 ml of sterile water to gain a concentration of 400 mg microparticles/ml. It was intravenously administered as a slow bolus (first 2 ml over a period of 4 sec), followed by a slow infusion (6 ml over a period of 2 min) and, subsequently, by a 5 ml saline flush. The safety of Levovist and its lack of adverse effects on hemodynamics, left ventricular (LV) function, and pulmonary gas exchange have been previously demonstrated.[11]

Ultrasound images were obtained by a commercially available scanner (Sonos 5500, Agilent Technologies, Andover, MA, USA). HPD imaging was performed with a transducer transmitting and receiving at a mean frequency of 1.8 and 3.6 MHZ, respectively. A dynamic range of 40 dB and a mechanical index of 1.0 were used. Time, lateral gain compensation, and focus were optimized at the beginning of the study and held constant throughout. HPD image acquisition in the apical 2- and 4-chamber views was started just before contrast injection and was continued until the contrast effect in the myocardium had dissipated. As soon as the contrast agent was injected, imaging was switched from continuous to intermittent. In this mode, images were acquired by gating to the peak of the T wave on an electrocardiogram (ECG) once every fourth cardiac cycle. End-systolic triggering was used, in line with previous studies,[9] because the myocardial wall segments are thicker and the LV cavity size smaller, thus resulting in the least contrast attenuation. All images were stored digitally on a magneto-optical disk and on super VHS videotape.

Low Dose DE

Shortly after the MCE examination, 42 patients underwent a low dose DE according to a standard protocol.[12] In brief, the infusion was started at a dose of 2.5 μg/Kg per minute and increased at 5-minute intervals to 5–10 μg/Kg per minute. The dobutamine dose was further increased to 20 μg/Kg per minute for another 5 minutes if no response in wall motion was noted with the 1-μg/Kg per minute dose. Continuous echocardiographic and ECG monitoring was performed during dobutamine infusion; blood pressure and 12-lead ECG were recorded at the end of each stage. Images at baseline and peak dobutamine doses were digitized on line in a quad-screen format.[13]

SPECT

All patients underwent a myocardial perfusion SPECT study within 1 week of the MCE examination and in the absence of a new significant clinical event. About 1 hour after the intravenous (IV) administration of 740 MBq of ^{99}Tc-tetrofosmin under resting condition, SPECT images were acquired using a dual detector gamma camera (Optima NT ELGEMS) equipped with LEHR collimators. Thirty-two views of 60 seconds each, over an orbit of 180 degrees, were acquired from the 45-degree RAO to the 45-degree left posterior oblique (LPO) projection on a matrix of 64 × 64 pixels (6-mm pixel size). The energy window used was 20% centered on the 140 KeV photopeak of ^{99}Tc. Tomographic reconstruction was performed with filtered back projection using a low pass Butterworth filter with a cutoff frequency of 0.4 cycles/cm and order 10. No attenuation or scatter correction was used. Transaxial slices (1-pixel thick) were then reoriented along the vertical and horizontal long axes and the short axis of the LV. For semiquantitative analysis, short-axis slices from the first apical to the last basal slice were used for generating a two-dimensional volume-weighted polar map.

Image Interpretation

The low dose DE and MCE images were interpreted by pairs of physicians experienced in echocardiography and blinded to all other information. Differences in opinion were resolved by consensus. SPECT data were evaluated by experienced nuclear cardiologists blinded to clinical and echocardiographic data.

Myocardial enhancement by HPD and regional wall motion by DE were evaluated according to a 16-segment model.[10] Volume-weighted polar maps generated by the SPECT study were also divided into 16 segments to be as close as possible to the echocardiographic segmentation. However, only ten segments for each patient were eligible for data analysis, because only two apical views were performed during contrast injection; moreover, basal lateral and basal anterior wall segments were excluded from the analysis because of the high incidence of attenuation artefacts in these regions.[14]

Myocardial enhancement by HPD was scored as normal (intense contrast effect), moderately reduced (low contrast enhancement in comparison to adjacent segments or contrast enhancement limited to the outer myocardial layers), or severely reduced (no contrast effect).[15] Contractile reserve was defined as an improvement in regional wall motion of dysfunctional segments by at least one grade according to the American Society of Echocardiography after dobutamine administration. In SPECT images, the segment with the highest mean tracer uptake in the volume-weighted polar map was normalized to 100% and the activity within the other segments was expressed as a percentage; myocardial infusion by SPECT was defined as normal (activity $>70\%$ of the peak tracer activity in the study), moderately reduced (activity $<70\%$ and $>50\%$ of the peak tracer activity in the study) or severely reduced (activity $<50\%$ of the peak tracer activity in the study).

In a further analysis, myocardial enhancement by HPD demonstrating the presence or absence of perfusion was assessed as adequate (normal perfusion) and as poor enhancement or no enhancement (perfusion defect). Similarly, SPECT perfusion was scored as $\geq 60\%$ or $<60\%$ of the peak tracer activity in study according to previous studies.[16]

Segments analyzed for myocardial perfusion were a priori assigned to one of the three coronary artery territories as previously described.[2]

Statistical Analysis

Continous variables are expressed as mean ± SD. Concordance between HPD and SPECT was evaluated by Kappa statistics. K values >0.2, >0.4, >0.6, and >0.8 indicated fair, moderate, good, and excellent agreement, respectively. The sensitivity, specificity, and accuracy of HPD detection of SPECT regional perfusion abnormalities were obtained according to corresponding equations. Values of $P < 0.05$ were considered statistically significant.

Results

Safety and Feasibility

The study was completed in all 57 enrolled patients. All the patients tolerated the contrast study well, and only one reported a mild burning sensation at the site of contrast administration. Monitoring of the ECG lead of the scanner showed no premature ventricular contractions in any of the patients after contrast administration, but did in two during low dose dobutamine echocardiography. No repetitive ventricular arrhythmias or conduction disturbances occurred during the tests.

After contrast, all patients had an apparent LV cavity signal enhancement and 55 (96%) had a visible myocardial contrast effect. In the remaining two patients, myocardial contrast enhancement was considered not interpretable and they were excluded from the analysis. In the 55 analyzed patients, an adequate myocardial enhancement was obtained in all 550 ventricular segments. As previously stated, DE was performed in 42 patients, as 13 patients did not show at least two ventricular segments with wall-motion abnormalities at baseline. The delineation of endocardial borders was interpretable in all these 42 patients at baseline and during dobutamine.

Comparison Between MCE and SPECT

Of 550 interpretable ventricular segments at MCE, myocardial enhancement was scored as normal in 436 (79%) segments, as moderate perfusion defect in 35 (6%), and as severe defect in 79 (15%) segments. The analysis of SPECT images showed normal perfusion in 321 (58%) segments, a moderate perfusion defect in 149 (27%), and a severe defect in 80 (15%) segments. Thus, SPECT identified more segments with perfusion abnormalities than contrast echocardiography.

On the basis of a three-point scale (i.e., perfusion normal, moderately or severely reduced), the two methods were in agreement in 71% of segments (k = 0.414, weighted k = 0.505) (Fig. 1). An example of concordance between MCE and SPECT is shown in Figure 2, and an example of discordance in Figure 3. Discordance was mainly due to ventricular segments with normal perfusion by MCE and moderate perfusion abnormalities by SPECT (109 segments). Of these 109 segments, 78 (72%)

	MCE		
SPECT	Normal perfusion	Moderate perfusion defect	Severe perfusion defect
Normal perfusion	308	3	10
Moderate perfusion defect	109	26	14
Severe perfusion defect	19	6	55

Figure 1. *Contingency table comparing ^{99m}Tc tetrofosmin SPECT with myocardial contrast echocardiography (MCE) in the study of myocardial perfusion. SPECT = single photon emission computed tomography.*

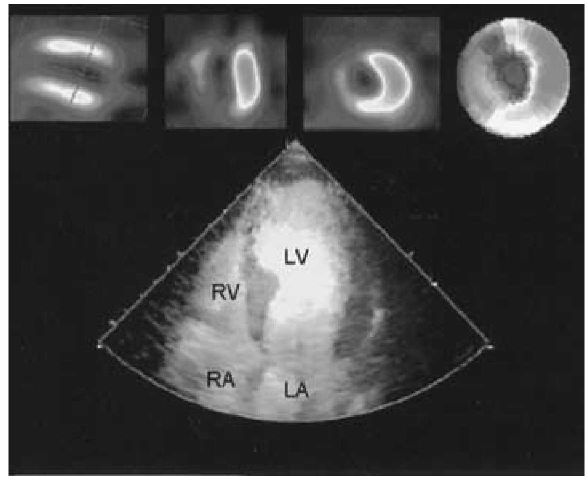

Figure 2. *Patient with an anterior infarction with markedly reduced apical ^{99m}Tc tetrofosmin uptake on SPECT (top) and similarly reduced myocardial enhancement on harmonic power Doppler imaging (bottom). SPECT images also reveal a moderate perfusion defect in the septum, while MCE shows normal perfusion in the same territory. LA = left atrium; LV = left ventricle; MCE = myocardial contrast echocardiography; RA = right atrium; RV = right ventricle; SPECT = single photon emission computed tomography.*

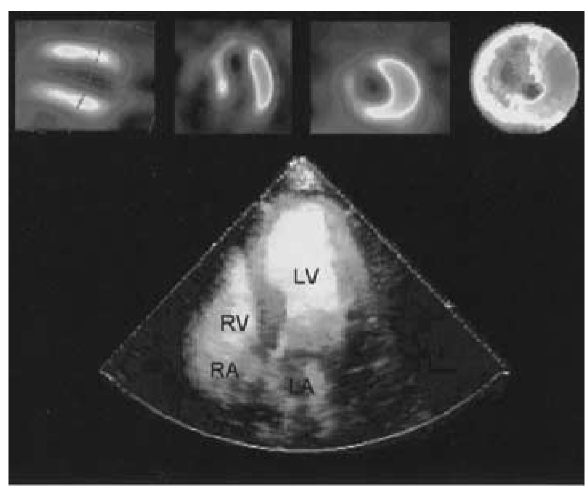

Figure 3. *Patient with an anterior infarction with a perfusion defect at the apical level on SPECT images (top) and a normal apical enhancement on harmonic power Doppler image (bottom). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; SPECT = single photon emission computed tomography.*

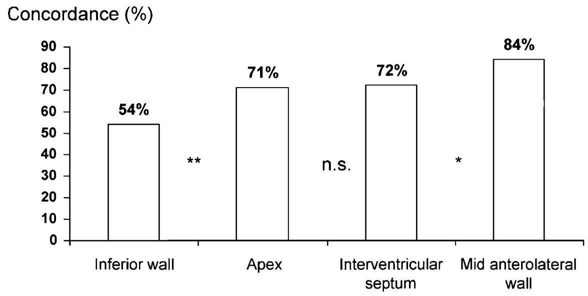

Figure 4. *Concordance between MCE and ^{99m}Tc tetrofosmin SPECT in detecting myocardial perfusion defect according to the involved wall. *P < 0.01; **P < 0.001. MCE = myocardial contrast echocardiography; SPECT = single photon emission computed tomography.*

showed normal contractile function at rest. Complete discordance (i.e., normal perfusion by one method and a severe perfusion defect by the other) was present in 29 (5%) segments. As shown in Figure 4, discordant segments were more frequently located in the inferior wall, while concordant segments more commonly corresponded to the mid-anterolateral wall, the interventricular septum, and LV apex. On the basis of a two-point score (i.e., perfusion present or absent), the agreement between the two methods improved to as much as 86% (k = 0.59, P < 0.001). Sensitivity and specificity of HPD for identifying SPECT perfusion defects were 63% and 93%, respectively; positive and negative predictive value were 73% and 89%, respectively. The agreement between MCE and SPECT was higher (85%, k = 0.627) in the patients with anterior infarction, and lower in those with inferior or inferolateral infarction (concordance 84%, k = 0.355) (Table I). Assuming that the TIMI III flow was preserved at the time of the MCE exam, the concordance of MCE and SPECT in respect to specific coronary territories was 76% (k = 0.52) for LAD territory in patients in which the IRA was the LAD artery, and 66% (k = 0.13) for LCx and RCA territory in patients in which the IRA was the LCx artery or the RCA. Table II shows the frequency distribution of segments with MCE and SPECT perfusion defect according to the IRA. The sensitivity and specificity of MCE according to the IRA were respectively 71% and 82% for LAD territory, and 34% and 76% for the LCx and RCA territory.

TABLE I

Concordance, Sensitivity and Specificity of MCE in Prediction of SPECT Perfusion Defect

	Concordance	Sensitivity	Specificity
All patients (n = 55)	86% (k = 0.59)	63%	93%
LAD infarct (n = 35)	85% (k = 0.62)	65%	94%
RCA-LCx infarct (n = 20)	84% (k = 0.35)	45%*	90%

*p < 0.0001. LAD = left anterior descending artery; LCx = left circumfley artery; MCE = myocardial contrast echocardiography; RCA = right coronary artery; SPECT = single photon emission computed tomography.

TABLE II

Frequency Distribution of Segments with MCE and SPECT Perfusion Defect According to the Infarct Related Artery

	Severe Perfusion Defect	Moderate Perfusion Defect	Normal Perfusion
Infarct Related Artery: LAD			
MCE	62	18	95
SPECT	65	57	53
Infarct Related Artery: LCx and RCA			
MCE	7	10	45
SPECT	6	26	30

See Table I for definitions.

Comparison Between MCE and DE

Thirteen patients recovered their contractile function at 4 weeks, thus a low dose DE was performed only in 42 patients. Of 420 analyzed ventricular segments, 168 showed regional wall-motion abnormalities at rest. Of 252 ventricular segments with normal contractile function at rest, myocardial perfusion at MCE was scored as normal in 245 (97%) segments, as moderate perfusion defect in 6 (2%), and as severe defect in 1 segment. Of 168 dysfunctional segments, 164 were located in the region subtended by the open infarct related coronary artery, while four akinetic segments of three patients with multivessel disease were not related to the infarct artery and were then excluded from the study. An improvement in regional contractile function after dobutamine was noted in 79 (48%) of 164 dysfunctional segments. In 71 of these segments, normal perfusion or a moderate perfusion defect was detected by contrast echocardiography (Fig. 5). In the 85 ventricular segments which did not show wall-motion changes after dobutamine, a severe perfusion defect was

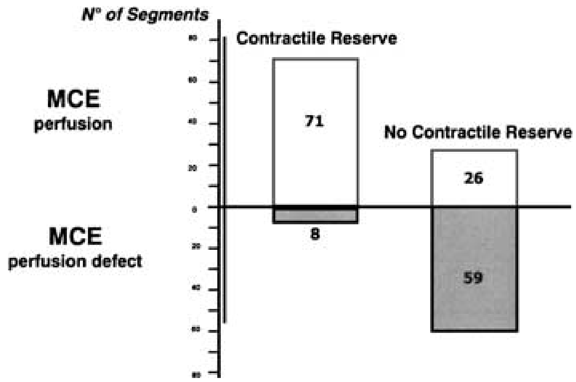

Figure 5. *Comparison between contractile reserve by dobutamine echocardiography and myocardial perfusion by contrast echocardiography. MCE = myocardial contrast echocardiography.*

detected by contrast echocardiography in 59 (69%) (Fig. 5), while normal perfusion or a moderate perfusion defect was detected by contrast echocardiography in 26 segments. Sensitivity and specificity by HPD in detecting segments with contractile reserve were 90% and 69%, respectively. Table III shows sensitivity and specificity of MCE for detection of segments with contractile reserve according to the IRA.

Discussion

This study demonstrates that intermittent HPD during intravenous Levovist administration allows the detection of perfusion abnormalities in patients with recent infarction. The concordance between MCE and SPECT was moderate, the two methods being in agreement in 71% of segments. However, the concordance varied according to the scoring system, and it improved significantly up to 86% using a two-point score for myocardial perfusion (i.e., present or absent). Moreover, MCE showed a limited sensitivity but a high specificity in detecting SPECT perfusion defects. Conversely, MCE showed good sensitivity and a limited specificity in detecting segments with contractile reserve elicited by dobutamine infusion.

TABLE III

Sensitivity and Specificity of MCE in Detection of Segments with Contractile Reserve According to the Infact Related Artery

	Sensitivity	Specificity
All patients (n = 42)	90%	69%
IRA: LAD (n = 29)	88%	73%
IRA: RCA or LCx (n = 13)	95%	40%

See Table I for definitions.

Comparison with Previous Studies

In a multicenter trial, Marwick et al.[3] intravenously injected the contrast agent NC100100 (Sonazoid, Nycomed-Amersham, Norway) in 203 patients with previous infarction. Using intermittent harmonic imaging and the highest contrast dose, the specificity of contrast echocardiography for detection of perfusion defects identified by SPECT was excellent (93%), as in the present study, while the sensitivity was poor (31%). As in this study, the fact that 70% of segments with severe defects on SPECT imaging had normal regional function by echocardiography raises the question of false-positive SPECT defects. Mild agreement between contrast echo and nuclear imaging was also obtained by Juquois et al.[4] and more recently by Heinle et al.[7] who compared HPD imaging of myocardial perfusion with Technetium-99 SPECT in 123 patients with known or suspected coronary artery disease. Overall concordance between HPD imaging and SPECT was 81% for normal versus abnormal perfusion. In all these studies, including the present investigation, MCE images were analyzed qualitatively. At variance, an optimal agreement between contrast imaging and SPECT was found in different studies,[1,2,6] where an excellent concordance between MCE and SPECT was obtained using postprocessing algorithms or quantitative videodensitometric analysis. Using a low mechanical index and accelerated intermittent imaging, a good agreement between MCE and both SPECT and wall-motion abnormalities was obtained by Shimoni et al.[17] in patients undergoing dobutamine or exercise stress. More recently, new contrast agents and imaging technologies have been developed that enable myocardial opacification to be achieved during real-time imaging. Experimental data demonstrate that microbubble replenishment rate and peak intensity after bubble destruction provide excellent parameters of regional microcirculatory volume and flow.[18,19]

Disagreement Between Contrast Echocardiography and SPECT

Most of the segments showing disagreement between contrast enhancement and technetium uptake had a normal contrast effect by HPD and moderately abnormal perfusion by SPECT, suggesting a greater sensitivity of nuclear imaging in detecting perfusion abnormalities. This discrepancy could have been partly caused by an imperfect matching of planes between the two techniques, which represents an ordinary difficulty when comparing different approaches for tomographic imaging. However, the finding that >70% of these segments exhibited normal regional function at echocardiography raises the issue of possible SPECT artifacts or partial volume effect. It is well documented that, owing to overlying soft tissues, photon attenuation is able to generate false perfusion defects, especially in the inferior LV wall, where the concordance between the contrast enhancement and nuclear perfusion declines. A lack of consistency in exploring the inferior LV wall by contrast echocardiography was recently demonstrated in patients with acute myocardial infarction, where TIMI 0 flow was considered as the criterion standard for perfusion.[20,21] In the investigator's opinion, the ability of contrast echocardiography to explore the perfusion of the inferior wall is still an unsolved issue, which should be addressed before this technology is introduced into routine clinical use.

Comparison Between Contrast and DE

In patients with acute or previous myocardial infarction,[22–27] a preserved myocardial perfusion following intracoronary contrast administration appears to be a sensitive method for detecting irreversibly damaged myocardium, albeit characterized by a limited specificity. Few data are so far available on intravenous MCE in this clinical setting. In the present study intravenous MCE showed good sensitivity (90%) and a limited specificity (69%) in detecting segments with contractile reserve elicited by dobutamine infusion. Indeed, the majority of segments (90%) showing a contractile reserve by DE were found to be perfused at contrast echocardiography, as were also a significant proportion (31%) of segments that did not respond to dobutamine. Myocyte viability and contractile reserve are not synonymous; in fact a positive contractile response to dobutamine may require a higher number of viable, functional myocytes (at least 50%) than does preserved myocardial perfusion.[28] Thus, microvascular perfusion does not necessarily imply contractile reserve because small islands of viable myocytes may survive within predominantly infracted regions that will probably be unable to respond to dobutamine. Moreover, a positive inotropic response to dobutamine is dependent on the complex relation between the transmural extent of necrosis and the degree of perfusion within the infarct zone. If the endocardium is necrosed, wall thickening will be significantly decreased even if blood flow is restored to the outer ventricular wall. The clinical or prognostic impact of a preserved perfusion in the absence of contractile reserve is still undefined, even if preliminary data suggests that a remodeling parameter is a better predictor of LV viability than functional recovery.[29]

Study Limitations

Account should be taken of the fact that myocardial perfusion by intravenous contrast administration and HPD is affected by a variety of artifacts. The blooming effect, due to excessive agent dosage or gain setting or to improper contrast administration,[14] can produce false-negative results, as myocardial perfusion defects may go undetected during blooming. Shadowing artifacts, characterized by attenuation of the ultrasound beam and inability to visualize far-field structures, can produce false-negative results. Poor contrast enhancement of entire walls, like 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 (e.g., ribs or lungs). Wall-motion artifacts are also frequent, mainly when the pulse repetition frequency is too low, allowing detection of heart movements. Finally, heterogeneity of the ultrasound beam within the sector should be considered, since the mechanical is different in the lateral portions of the sector and in its center. These limitations might be overcame by real-time perfusion imaging.[30] Finally, recent studies have demonstrated that myocardial perfusion can be assessed using increasing pulsing intervals, to account for possible low myocardial blood flow despite patent artery, while a fixed trigger interval (1 : 4) was used in this study.[31]

Conclusions

Intermittent HPD during intravenous Levovist infusion allows myocardial perfusion abnormalities to be detected in patients with recent myocardial infarction. The closest correlation between MCE and SPECT was found using simplified image analysis. In the near future, the combined use of DE and MCE during the same study, performed with a second generation contrast agent and the real-time imaging modality, might provide additional useful information about myocardial perfusion and contractile reserve. Furthermore, the quantitative approach to the analysis of MCE images using adequate algorithms could help to obtain better definition of the microbubble kinetics through myocardial capillaries.

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