Myocardial Contrast Echocardiography for Distinguishing Ischemic From Nonischemic First-Onset Acute Heart Failure

Insights Into the Mechanism of Acute Heart Failure

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Background—Distinguishing ischemic from nonischemic origin in patients presenting with acute heart failure (AHF) not resulting from acute myocardial infarction has both therapeutic and prognostic implications. The aim of the study was to assess whether myocardial contrast echocardiography (MCE) can identify underlying coronary artery disease (CAD) as the cause of AHF.

Methods and Results—Fifty-two consecutive patients with AHF with no prior clinical history of CAD and no clinical evidence of acute myocardial infarction underwent resting echocardiography and MCE both at rest and after dipyridamole stress at a mean of 9 ± 2 days after admission. All patients underwent coronary arteriography before discharge. Of the 52 patients, 22 demonstrated flow-limiting CAD (>50% luminal diameter narrowing). Sensitivity, specificity, and positive and negative predictive values of MCE for the detection of CAD were 82%, 97%, 95%, and 88%, respectively. Among clinical, ECG, biochemical, resting echocardiographic, and MCE markers of CAD, MCE was the only independent predictor of CAD (P<0.0001). Quantitative MCE demonstrated significantly (P<0.0001) lower myocardial blood flow velocity reserve in vascular territories subtended by >50% CAD (0.59 ± 0.46) compared with patients with normal coronary arteries (1.99 ± 1.00). However, myocardial blood flow velocity reserve in patients with no significant CAD was significantly (P=0.03) lower compared with control (2.91 ± 0.41). Myocardial blood flow velocity reserve correlated significantly (P<0.0001) with increasing severity of CAD.

Conclusions—MCE, which is a bedside technique, may be used to detect CAD in patients presenting with AHF without a prior history of CAD or evidence of acute myocardial infarction. Quantitative MCE may further risk-stratify patients with AHF but no CAD.

Key Words: coronary disease • diagnosis • echocardiography • heart failure
Therefore, we sought to assess the feasibility and accuracy of vasodilator MCE for the detection of flow-limiting CAD in patients presenting with first onset of AHF not caused by AMI and with no prior history of CAD.

**Methods**

**Patients**

Consecutive patients presenting to the hospital with new-onset significant shortness of breath and a clinical diagnosis of heart failure based on Framingham criteria were included in the study. Patients excluded from the study were those with typical ST elevation or ST depression on ECG with creatine kinase rise of more than twice the normal values, past history of documented AMI, history of myocardial revascularization, significant valvular heart disease, or acute coronary syndromes. All patients signed a written consent form before being enrolled in the study. The study was approved by the local research ethics committee.

**Study Design**

A standard 12-lead ECG at the time of admission was recorded. All patients underwent transthoracic echocardiography within 48 to 72 hours of admission. MCE was performed at a mean of 9 ± 2 days, once the patients were medically stabilized. All patients underwent coronary arteriography, which is routine practice in our institution, before discharge from the hospital. Patients admitted with chest pain with nondiagnostic ECG changes, no cardiac enzyme rise, and normal regional and global LV function both at rest and during stress echocardiography acted as controls for quantitative MCE assessment.

**2D Echocardiography**

We performed 2D echocardiography in patients in standard apical and parasternal views using tissue harmonic imaging (SONOS 5500 and HD1 CV 5000, Philips Medical Systems) to assess regional wall thickening abnormalities and global LV ejection fraction (LVEF). We scored systolic wall thickening (1 = normal, 2 = reduced, 3 = absent, 4 = systolic wall thinning) using the American Society of Echocardiography 16-segment LV model.

**MCE Study**

MCE was performed in the 3 apical views (ie, apical 4-, 2-, and 3-chamber views) using low-power-continuous, power-modulation MCE at a mechanical index of 0.1. Background gains were set so that minimal tissue signal was seen. The color gains were then adjusted so that no Doppler signal was seen except at the mitral valve and proximal to the apex. For the first 21 patients, Optison (Amersham Health) was administered as a slow bolus injection of 0.3 to 0.7 mL, followed by saline flush over 20 seconds. The remaining 31 patients underwent infusion of SonoVue (Bracco Research SA) at 50 to 70 mL/h with Vueject (BR-INF 100, Bracco Research SA), an infusion syringe-pump that rotates gently throughout the infusion to maintain the microbubbles in suspension. The infusion rate was adjusted to obtain the best possible myocardial opacification with minimal attenuation. Once optimized, the machine settings were kept constant throughout the study. The focus was set at the mitral valve level but moved toward the apex if there was concern about a near-field artifact. Nonstandard apical views (eg, bringing lateral wall into sector field) were used if required, to attempt to overcome basal attenuation artifacts. In large hearts, each myocardial wall (ie, inferior and anterior walls) was imaged separately when artifacts were observed in the peripheral fields. Flash echocardiography at a high mechanical index (1.7) was performed to destroy microbubbles in the myocardium and to observe replenishment. End-systolic frames up to 15 cardiac cycles after microbubble destruction were digitally captured in each view (3 sequences in each). Dipyridamole, a coronary vasodilator, was administered at 0.56 mg/kg over 4 minutes under continuous 12-lead ECG and blood pressure monitoring. Optison as slow bolus or SonoVue infusion was begun again at the same rate as rest imaging 1 minute after the end of dipyridamole infusion. MCE images were acquired in the same sequence as rest images at 1 minute after the contrast infusion was begun.

**Qualitative MCE**

A semiquantitative scoring system previously validated by our group was used to assess contrast intensity at 15 cardiac cycles after a destructive pulse: 2—homogenous opacification, 1—reduced or heterogeneous opacification, and 0—minimal or absent contrast opacification.1 The same 16-segment LV model was used. Nine segments were assigned to left anterior descending artery (LAD; anterior) and 7 to right coronary artery/left circumflex artery (RCA/LCx; infero-posterior) arterial distributions according to the vascular distribution of segments. Vascular territories were considered nonanalyzable if ≥2 contiguous segments could not be analyzed. A patient was considered to have normal myocardial perfusion at rest when both anterior and infero-posterior vascular territories showed homogenous contrast opacification. Reversible perfusion defect was considered present when contrast defect was observed 1 second after destructive imaging after vasodilator stress with the presence of a subendocardial perfusion defect or the presence of a transmural defect filling from subepicardium to subendocardium during subsequent cardiac cycles in ≥1 contiguous segments.9,14 Multivessel disease was considered present when a reversible perfusion defect was noted in >1 vascular territory.

**Quantification of MCE**

The QLab software (Philips Medical Systems) was used to quantify MCE. Regions of interest were placed in the myocardium at rest and the corresponding segments after stress. The region of interest was placed across the entire thickness of the myocardium, excluding the high-intensity endocardial and epicardial borders in the 4 apical segments, midanterior septum, and midanterior segment pertaining to the anterior coronary circulation and in the midinferior, midposterior, and midlateral segments pertaining to the posterior circulation at rest and stress.10 A single value was obtained for each circulation by averaging the results obtained. For each patient, the averages of anterior and posterior circulation values were calculated. Segments with artifacts or attenuation were excluded. QLab software (Philips Medical Systems) automatically constructed background-subtracted plots of peak myocardial contrast intensity, representing capillary blood volume versus pulsing intervals, from which the slope of the replenishment curve depicting mean microbubble velocity (β) was derived. Frames showing wide variation in contrast intensity were discarded to minimize errors in the analysis. It has been shown previously that, among the quantitative parameters, myocardial blood flow velocity (β) and β reserve (ie, stress β/rest β) most accurately reflected myocardial blood flow (MBF) and MBF reserve, respectively.9,10,15,16 Thus, in this study, only β parameter was used to assess MBF.

**Coronary Arteriography**

Significant CAD was defined as the presence of >50% luminal diameter narrowing of ≥1 major epicardial arteries or major branches. Multivessel CAD was defined as CAD involving both anterior and infero-posterior circulations.

**Image Analysis**

Systolic wall thickening and MCE images were analyzed separately by independent observers who were blinded to clinical, angiographic, and other respective imaging data. Qualitative and quantitative MCE data were also analyzed separately by different observers.

**Statistical Analysis**

All categorical variables were expressed as percentages; continuous variables, as mean ± SD. The paired t test was used to compare continuous variables between rest and stress. One-way ANOVA was used to compare the MCE variables among various grades of stenosis. Receiver-operator characteristic (ROC) curves were plotted to determine the best cutoffs for predicting significant CAD. Sensitivity,
TABLE 1. Patient Demographic Data, Coronary Arteriographic Data, LVEF, Heart Rate, and Drug Therapy in Patients Without and With Significant CAD (>50% Diameter Stenosis)

<table>
<thead>
<tr>
<th></th>
<th>No CAD</th>
<th>CAD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient demographics, n (%)</td>
<td>30 (58)</td>
<td>22 (42)</td>
<td>0.19</td>
</tr>
<tr>
<td>Age, y</td>
<td>60±11</td>
<td>66±12</td>
<td>0.05</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>18 (60)</td>
<td>17 (77)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>15 (50)</td>
<td>10 (46)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>7 (23)</td>
<td>11 (50)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>6 (20)</td>
<td>7 (32)</td>
<td>0.33</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>3 (10)</td>
<td>3 (14)</td>
<td>0.69</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>2 (7)</td>
<td>3 (14)</td>
<td>0.40</td>
</tr>
<tr>
<td>Alcohol intake, n (%)</td>
<td>4 (13)</td>
<td>2 (5)</td>
<td>0.63</td>
</tr>
<tr>
<td>Coronary arteriography, n (%)</td>
<td>...</td>
<td>4 (18)</td>
<td>...</td>
</tr>
<tr>
<td>1-Vessel disease</td>
<td>...</td>
<td>7 (32)</td>
<td>...</td>
</tr>
<tr>
<td>2-Vessel disease</td>
<td>...</td>
<td>11 (50)</td>
<td>...</td>
</tr>
<tr>
<td>LAD disease</td>
<td>...</td>
<td>19 (86)</td>
<td>...</td>
</tr>
<tr>
<td>RCA/LCx disease</td>
<td>...</td>
<td>8 (31)</td>
<td>...</td>
</tr>
<tr>
<td>Multivessel disease (LAD+RCA/LCx)</td>
<td>...</td>
<td>16 (72)</td>
<td>...</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35±13</td>
<td>35±12</td>
<td>0.11</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>77±6</td>
<td>78±5</td>
<td>0.22</td>
</tr>
<tr>
<td>Drug therapy, n (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>β-blocker</td>
<td>12 (40)</td>
<td>9 (41)</td>
<td>0.95</td>
</tr>
<tr>
<td>Diuretics</td>
<td>26 (87)</td>
<td>19 (86)</td>
<td>0.98</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>21 (70)</td>
<td>16 (84)</td>
<td>0.83</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7 (23)</td>
<td>5 (23)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Categorical variables are presented as percentages; continuous variables, as mean±SD. n=52.

Results

Patient Demography
Table 1 describes the study population. The patients were predominantly male (67%) with a mean±SD age of 63±12 years, similar to the control group (n=17 patients), which also was predominantly male (65%) with a mean±SD age of 58±9 years (P=0.08). Two or more risk factors for CAD (age >45 years and male, age >65 years and female, diabetes mellitus, hypertension, hyperlipidemia, history of smoking, and family history of premature CAD) were present in 40 of the 52 patients with AHF (77%). There were no significant differences in patient demography, coronary risk factors, LVEF, and drug therapy in patients with and without CAD. The mean±SD LVEF was 35±13% (95% CI, 32.3 to 38.5). Most patients, ie, 42 of 52 (83%), demonstrated LVEF <45%; only 7 (13%) showed normal LVEF (>50%). Almost all patients (94%) had troponin values of <0.3 IU/L; the rest, ie, 3 patients, had a minimal rise in troponin.

Echocardiography
Regional systolic wall thickening abnormality suggestive of CAD was present in 16 patients (31%). Figure 1 summarizes the relationship between CAD detected by resting echocardiography based on the presence or absence of regional systolic wall thickening abnormality and coronary arteriographic diagnosis of significant CAD. The sensitivity, specificity, and positive and negative predictive values were 59%, 90%, 81%, and 75% for detection of CAD.

MCE Study
Qualitative
During MCE, the most common artifacts observed were basal in all 3 apical views, but in each patient, contiguous segments were always visualized using the imaging technique described previously. According to the criteria used, all patients had analyzable images. Of the 52 patients, resting MCE defects were seen in 4 patients. Of these, 3 patients had significant CAD. Of the 4 patients with resting defects, 3 patients demonstrated worsening of these defects during stress (reversible), and 15 patients developed additional defects during stress. Thus, a total of 19 patients had perfusion defects (1 fixed, 18 reversible).

The relationship between presence of perfusion defects (rest and stress) and coronary arteriographic findings is shown in Figure 2. The sensitivity, specificity, and positive and negative predictive values of MCE for detecting significant CAD were 82%, 97%, 95%, and 88%. No significant differences were observed in either the sensitivity between...
the LAD (79%) and RCA/LCx (89%) or the specificity (97% and 100%, respectively) between these vascular territories for the detection of CAD. Of the 33 vascular territories with $\geq 50\%$ CAD, MCE detected perfusion defects in 28 (85%); of those with $\geq 70\%$ CAD, MCE detected 27 of 31 (87%); and of those with $\geq 90\%$ CAD, MCE detected defects in 17 of 19 (90%) vascular territories. MCE detected 15 of 16 patients (94%) with multivessel disease. It detected all 11 patients with 3-vessel disease. Furthermore, MCE correctly predicted multivessel disease in 14 of 16 patients (88%).

**Quantitative**

Quantitative MCE was performed in 49 coronary territories (28 patients with AHF who had undergone SonoVue infusion) in which adequate digital images were obtained. Quantitative MCE was also performed in age- and sex-matched controls (n=17 patients), as described previously. In AHF patients with angiographically normal coronary arteries ($<50\%$ coronary stenosis; n=28), $\beta$ reserve was significantly lower ($P=0.03$) than in the control group but was significantly higher ($P<0.0001$) compared with coronary artery territories with $>50\%$ coronary stenosis (n=21) (Table 2).

Furthermore, $\beta$ reserve demonstrated significant reductions in values with increasing grades of coronary stenosis (Figure 3). Figure 4 shows the ROC curve analysis. Area under the curve for $\beta$ reserve was 0.93. A $\beta$ reserve of 1.00 detected $>50\%$ CAD with a sensitivity of 91% and a specificity of 89%.

No significant difference in resting $\beta$ was noted among patients with AHF with and without CAD and in patients in the control group (Table 2). The $\beta$ reserve was higher in the group with AHF and no CAD but with $<2$ risk factors (1.99±0.65) compared with patients with $\geq2$ risk factors (1.67±0.87) but did not reach statistical significance ($P=0.40$). In the group with AHF and no CAD, the mean LV wall thickness was 0.92±0.15 cm. No significant correlation was observed between LV wall thickness and $\beta$ reserve. However, $\beta$ reserve showed a significant trend ($P<0.001$) of stepwise decrement with increasing systolic wall thickening abnormality (normal systolic wall thickening, 2.6±0.37; mildly reduced, 1.7±0.37; severely reduced, 1.5±0.27; absent, 1.20±0.22) in patients with AHF and no CAD. Although there was also a trend showing lower $\beta$ reserve with lower LVEF ($r=0.44$), it was not statistically significant.

Figure 5 is an example of a patient with proximal LAD stenosis of 90% and occluded LCx. Reversible MCE defect was present in the apex, middle septum, and lateral wall even 3 seconds after a destructive impulse after dipyridamole.

**Logistic Regression Analysis for Prediction of CAD**

Among the clinical (age, gender, diabetes mellitus, hypertension, smoking history, family history of premature ischemic heart disease, alcohol intake, hyperlipidemia), ECG, biochemical, resting echocardiography (for regional wall thickening abnormalities) and vasodilator qualitative MCE mark-

![Figure 3. Relationship between MBF velocity ($\beta$) reserve and grades of CAD.](image)

**TABLE 2. Resting MBF Velocity and MBF Reserve**

<table>
<thead>
<tr>
<th>Resting MBF Velocity, dB/s</th>
<th>MBF Velocity Reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.70±0.35</td>
</tr>
<tr>
<td>No CAD</td>
<td>0.63±0.40</td>
</tr>
<tr>
<td>CAD</td>
<td>0.80±0.21</td>
</tr>
</tbody>
</table>

*P<0.03 vs control.
†P<0.0001 vs no CAD.
ers of CAD, univariate predictors of >50% CAD were diabetes mellitus \( (P=0.05) \), regional wall thickening abnormality on echocardiography \( (P=0.001) \), and qualitative vasodilator MCE \( (P<0.0001) \). The only independent predictor of CAD was qualitative vasodilator MCE \( (\text{odds ratio}, 131; \ 95\% \ CI, 13.5 \text{ to } 1261; \ P<0.00001) \). When both qualitative and quantitative MCE parameters were assessed in the logistic regression analysis, both qualitative MCE \( (P=0.03) \) and \( \beta \) reserve \( (P=0.03) \) were independent predictors of CAD. However, it is possible that, because of the lower power of this model, other parameters may not have reached significance.

Discussion

This is the first study demonstrating the value of vasodilator MCE in distinguishing ischemic from nonischemic origin in patients presenting with AHF without prior history of CAD or clinical features suggesting acute coronary syndrome. No clinical markers, including ECG, were useful in differentiating patients with and without underlying CAD. The accuracy of presence or absence of regional wall thickening abnormality during resting echocardiography was also less than desirable. MCE was the only independent predictor of CAD. The absence of regional perfusion defect virtually ruled out significant underlying CAD, whereas the presence of such defect confirmed the presence of CAD. The accuracy of MCE for predicting CAD was maintained regardless of the site of CAD. Furthermore, MCE diagnosed virtually all patients with multivessel disease, a group likely to benefit the most from revascularization. Quantitative MCE further supported the findings.

Mechanism of MCE Detection of Flow-Limiting CAD

MCE uses intravascular contrast agents, the signal intensity of which during a steady state such as an infusion denotes relative myocardial blood volume. Therefore, for quantitative assessment, only data obtained from patients who underwent infusion (SonoVue) was analyzed. MBF velocity may be assessed by observing the rate of replenishment of the myocardium by the contrast agent after a high-energy pulse. In patients with no coronary artery stenosis, vasodilator administration results in an increase in MBF velocity. This was also shown in our study in which \( \beta \) representing MBF velocity in the myocardium subtended by <50% CAD increased to twice the basal value. However, MBF velocity increase to \( \approx 3 \) to 5 times the resting value in the normal myocardium not subtended by any coronary stenosis. In our study, MBF velocity reserve was \( \approx 2 \) in the myocardium not subtended by significant CAD. In this study, MBF velocity reserve in patients without CAD was
significantly lower compared with that in patients admitted to the hospital without heart failure and no CAD. The probable reason is that even in absence of CAD, MBF velocity reserve in patients with LV dysfunction may be reduced as a result of both microcirculatory and mechanical factors.20,21 However, the presence of >50% coronary stenosis resulted in a significant decrease in MBF velocity reserve compared with vascular territories with <50% CAD. Thus, the presence of underlying significant CAD has a more profound effect on vasodilatory reserve than LV dysfunction alone, which explains in part the observation that patients with LV dysfunction and CAD have a worse outcome compared with those without LV dysfunction and CAD.1–4 Furthermore, this study also showed that increasing severity of coronary stenosis resulted in a stepwise reduction in MBF velocity reserve, which further confirms the profound effect of CAD on the vasodilatory reserve and its relationship to worse outcome with increasing severity of stenosis.

Qualitative assessment demonstrated high accuracy for the detection of CAD. Despite a reduction in MBF reserve in patients with normal coronary arteries but AHF, qualitative MCE provided high specificity. A possible explanation is that despite longer contrast myocardial replenishment in some patients, none demonstrated the typical regional subendocardial defect seen in patients with CAD. Although a relative reduction in subendocardial blood flow reserve compared with epicardial blood flow reserve has been described by other authors in this group of patients, it may have been too subtle to discern qualitatively.22

Possible Mechanism of AHF
This study also provides some insights into the heterogeneous mechanisms contributing to AHF. In patients with significant CAD, in our study, resting MBF velocity was similar to that in the control group. Resting MBF velocity may be normal despite the presence of coronary artery stenosis because of coronary arteriolar vasodilation or collateral MBF from non–flow-limiting coronary arteries.23,24 Thus, persistent LV dysfunction is unlikely to be due to ongoing myocardial ischemia or myocardial necrosis (there was no increase in cardiac enzymes). However, these patients had severely impaired MBF velocity reserve. Thus, despite adequate myocardial perfusion at rest, impaired MBF reserve results in failure to increase MBF during exercise, tachyarrhythmias, or acute surges of catecholamines. The mismatch between MBF and demand induces myocardial ischemia. Besides inducing acute myocardial dysfunction and transiently exacerbating ischemic mitral regurgitation,23 if myocardial ischemia is prolonged, persistent myocardial dysfunction ensues, despite the presence of normal resting MBF. Thus, the major mechanism of AHF in this group of patients is likely to be a combination of acute transient ischemia at the time of presentation, transient exacerbation of ischemic mitral regurgitation, and myocardial stunning.25–27 In our study, in patients without CAD, normal resting MBF was also observed. However, in these patients, MBF velocity reserve was only modestly reduced. Although acute transient ischemia and myocardial stunning can still partly explain the mechanism of AHF, myocardial dysfunction resulting from primary myocyte dysfunction may be an important contributory mechanism without concomitant involvement of the microvasculature. Microcirculatory disorder, however, may gradually ensue over a period of weeks or months. Both a reduction in resting MBF and severe impairment of MBF reserve have been observed in patients with chronic LV dysfunction without CAD.28,29

Clinical Implications
MCE is a bedside technique that can be used early in patients presenting with AHF to rapidly assess LV function (regional and global) and perfusion (rest and stress). Demonstration of normal resting myocardial perfusion in patients with AHF indicates viable myocardium. The presence of significant reversible myocardial perfusion defects in these patients establishes the diagnosis of flow-limiting CAD and should prompt the attending physician to plan for urgent coronary arteriography and revascularization. Coronary arteriography may not be warranted in patients with no demonstrable myocardial perfusion defects. However, even in the absence of obvious myocardial perfusion deficits, determination of MBF reserve may help to predict the outcome of patients with heart failure.30 These findings are likely to affect the routine practice of all AHF patients in our institution undergoing coronary arteriography.

Conclusions
MCE is accurate in distinguishing ischemic from nonischemic heart failure and can be used to further risk-stratify patients with AHF without a prior history of CAD or clinical features suggestive of an acute coronary syndrome. The ability of contrast echocardiography to provide a comprehensive assessment of cardiac structure, function, and perfusion at the bedside is likely to make it the technique of choice for this group of patients.

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