Characterization of Left Ventricular Opacification Using Sonicated Serum Albumin in Patients With Dilated Cardiomyopathy and Myocardial Infarction

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To elucidate whether the mode of left ventricular opacification using sonicated serum albumin (SSA) is dependent upon the severity of left ventricular dysfunction, SSA was administered intravenously to 26 patients with dilated cardiomyopathy, 24 patients with anteroseptal myocardial infarction, and 9 normal control subjects. The left ventricular inflow pattern in echocardiograms on the apical 4-chamber view was classified into 2 types: straight or whirling. The ratio of left ventricular opacified area to left ventricular end-diastolic area, called the percent left ventricular effective fraction (%LVEF), was also calculated. The inflow pattern was straight in all normal control subjects and 9 myocardial infarction patients, whereas 15 myocardial infarction and all dilated cardiomyopathy patients showed the whirling pattern. Percent LVEF was significantly smaller in patients with dilated cardiomyopathy (45±22%, p<0.0001) and myocardial infarction (65±14%, p<0.001) than in normal control subjects (84±7%). The area that was not opacified was observed only in the infarcted area in cases of myocardial infarction, and over wide regions in cases of dilated cardiomyopathy. In addition, there were significant correlations between %LVEF and ejection fraction or peak filling rate. These findings indicate that contrast echocardiography using SSA can reflect sensitively the severity of left ventricular dysfunctions and detect the regions involved in patients with dilated cardiomyopathy and myocardial infarction. (Jpn Circ J 1998; 62: 91–96)

Key Words: Contrast echocardiography; Sonicated serum albumin; Left ventricular function; Dilated cardiomyopathy; Myocardial infarction

Contrast echocardiography has evolved as a diagnostic technique since the early report of Gramiak and Shah. Contrast agents in early studies were removed by the lung after intravenous injection, and for that reason the direct evaluation of left ventricular function was impossible. Recently, several new contrast agents that are capable of pulmonary transmission have been developed. Sonicated serum albumin (SSA) is representative of these contrast agents. Several reports have shown the safety and efficacy of this contrast agent not only in experimental studies but also in clinical studies. However, there have been only a few clinical applications using this agent.

Recently, Mizushige et al reported that clearance of SSA from the left ventricular cavity was prolonged in patients with left ventricular dysfunction, and that the delayed washout of this contrast agent was correlated with the size of the left ventricle. In addition, Beppu et al reported in an experimental study in dogs that the inflow pattern from the atrium to the left ventricle was influenced markedly by the severity of left ventricular dysfunction associated with acute myocardial infarction. To our knowledge, no one has estimated the characteristics of the mode of left ventricular opacification and inflow pattern using SSA in patients with dilated cardiomyopathy and myocardial infarction.

Thus, the aim of the present study was firstly to elucidate the relation between left ventricular inflow pattern and severity of left ventricular dysfunction and, secondly, to elucidate whether there was a difference in the pattern of left ventricular opacification using SSA between patients with dilated cardiomyopathy and myocardial infarction.

Methods

Patients

Table 1 shows clinical profiles of the subjects. The study population consisted of 59 patients who underwent cardiac catheterization for the determination of diagnosis. Twenty-six patients had dilated cardiomyopathy, 24 myocardial infarction. Nine patients with chest pain syndrome but normal coronary arteries and a negative response to intracoronary acetylcholine administration served as control subjects.

Dilated cardiomyopathy was diagnosed based on the report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. Eight of 26 patients with dilated cardiomyopathy had severe symptoms (New York Heart Association functional class III or IV) and 18 had mild symptoms (class I or II). Two of 26 patients with dilated cardiomyopathy were in atrial fibrillation. Ejection fraction determined by radionuclide ventriculography in this group ranged between 9% and 37%.

In order to identify the affected region associated with myocardial infarction using an apical 4-chamber echocardiographic view, patients with myocardial infarction in
Table 1 Patients Profiles in 3 Groups

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age (years)</th>
<th>Male/Female</th>
<th>Heart rate (beats/min)</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control subjects</td>
<td>9</td>
<td>54±13</td>
<td>8/1</td>
<td>63±7</td>
<td>127±20</td>
<td>75±14</td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>24</td>
<td>61±11</td>
<td>2/21</td>
<td>71±10</td>
<td>119±17</td>
<td>69±14</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>26</td>
<td>54±14</td>
<td>2/15</td>
<td>75±14</td>
<td>111±13</td>
<td>69±10</td>
</tr>
</tbody>
</table>

Values are means ± SD.

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this study were restricted to those with anteroseptal myocardial infarction. All patients with anteroseptal myocardial infarction were in New York Heart Association functional class I or II. Ejection fraction in this group ranged between 12% and 62%, and left ventricular aneurysm was observed in 7 patients.

Subjects with the complications of moderate to severe valvular regurgitation and pulmonary disease were excluded from this study.

All subjects participated in this study after giving informed consent.

Contrast Agent

The contrast material for echocardiographic study consisted of a preparation of air-filled microspheres created by sonication of 5% human SSA (Albunex; Molecular Biosystems, San Diego, CA, USA). Microspheres in this preparation ranged in size from 1 to 10 μm (mean particle size 4 μm), and the sonicated solution contained 400,000 microspheres/ml.

Protocol for Contrast Echocardiography

Echocardiographic examination was performed with an Aloka SSD 9000 imaging system (Tokyo, Japan) using an ultrasound transducer with a center frequency of 3.5 MHz. Images were obtained in the apical 4-chamber view. Recording of the 4-chamber view on videotape was begun before a bolus injection of 0.15–0.22 ml/kg SSA into a left brachial vein and was continued until contrast signals disappeared completely. The data gained from contrast echocardiography were analyzed using an off-line computer analyzing system (Cardio 500; Kontron Instruments, Munich, Germany).

The dose of SSA to be administered was determined as follows. Initially, 0.15 ml/kg SSA was administered at a rate of 1 ml/sec. When the initial administration of SSA failed to manifest a good opacification of the left ventricle, 0.22 ml/kg was administered again, 5 min after the initial administration, as reported by Crouse et al. A good opacification with a dose of 0.15 ml/kg SSA was obtained in 31 (52.5%) of 59 patients; 9 control subjects, 15 patients with myocardial infarction, and 7 with dilated cardiomyopathy; and with a dose of 0.22 ml/kg SSA in 28 patients (47.5%), 9 with myocardial infarction and 19 with dilated cardiomyopathy.

Estimation of Contrast Echocardiography

The pattern and the degree of left ventricular chamber opacification were evaluated as follows. Firstly, the inflow pattern of contrast agent from the left atrium into the left ventricle was examined. As reported by Beppu et al, 2 types of inflow pattern were classified in our study: a straight flow pattern and a whirling flow pattern. Fig 1 shows these representative patterns. In the straight inflow pattern, contrast echoes from the left atrium spread over the left ventricular cavity with 1 rash (top). In the whirling inflow pattern, contrast echoes do not reach the apex within 1 diastolic period, and the inflow pattern is not straight but whirling (bottom). Second, in the preliminary study, we found that full opacification of the left ventricle with contrast agent was not observed in patients with left ventricular dysfunction as shown in Fig 2 (top).
Table 2: Contrast Echocardiographic Data in 3 Groups

<table>
<thead>
<tr>
<th>Inflow pattern (WIS)</th>
<th>LV area (cm²)</th>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LV end-diastolic area</td>
<td>LV opacified area</td>
</tr>
<tr>
<td>Normal control subjects</td>
<td>09</td>
<td>30.3±8.0</td>
</tr>
<tr>
<td>Patients with old myocardial infarction</td>
<td>159*</td>
<td>36.8±8.8</td>
</tr>
<tr>
<td>Patients with dilated cardiomyopathy</td>
<td>2601*</td>
<td>44.3±11.910</td>
</tr>
</tbody>
</table>

Values are means±SD. *p<0.01, †p<0.001, ‡p<0.0001 compared with normal control subjects; *p<0.02, †p<0.001 compared with patients with old myocardial infarction; ‡p<0.005 compared with Interventricular septum. LV, left ventricular; LVEF, left ventricular effective fraction.

Fig. 2. Method for the determination of percent left ventricular effective fraction (%LVEF) using the apical 4-chamber view. Top (A) and bottom (B) show the method of determining total %LVEF, and IVS and FW %LVEF, respectively. S₀ and S₁ represent the end-diastolic ventricular area and the left ventricular opacified area. RV, right ventricle; LV, left ventricle; LA, left atrium; IVS, interventricular septum; FW, left ventricular free wall.

The finding shows that the anatomical left ventricular end-diastolic area (S₀) does not reflect the functional end-diastolic volume. It is highly conceivable that the left ventricular opacified area (S₁) reflects the functional ventricular size. Thus, we measured 2 areas, S₀ and S₁, and compared each area among the 3 groups. In addition, a ratio of S₁ to S₀ (%), called the left ventricular effective fraction (LVEF), was calculated as the index of effective utilization of the left ventricle. Thirdly, to elucidate whether or not this contrast echocardiography with SSA can detect left ventricular regional dysfunction, the mode of opacification in patients with anteroseptal infarction was examined. As shown in Fig 2 (bottom), the left ventricle was divided into 2 by the line connecting the apex and the mid-point of mitral orifice, that is into an interventricular septum (IVS) and a free wall (FW); the %LVEF at each side was calculated from the same formula [%LVEF (IVS), %LVEF (FW)].

Estimation of Left Ventricular Regional Dysfunction

The percentage of abnormally contracting segments as determined by left ventriculography has been used to estimate left ventricular regional dysfunction. Thus, in this study percentage of abnormally contracting segments was determined by left ventriculography performed during cardiac catheterization in patients with myocardial infarction.

Hemodynamic Parameters

Both radionuclide ventriculography and contrast echocardiography were performed within 1 week. From the left ventricular time-activity curve obtained by radionuclide ventriculography, left ventricular ejection fraction, end-diastolic volume, peak filling rate, and 1/3 filling rate were calculated.

Statistical Analysis

All values are expressed as means±SD. Statistical analysis was performed by 1-way ANOVA with subsequent Scheffe’s multiple range test. Linear regression analysis was also performed to compare parameters of left ventricular function and %LVEF. Results were considered significant at the probability (p)<0.05 level.

Results

Clinical Profiles of the Study Subjects

Table 1 shows the clinical profiles of each group. There were no differences in age, proportion of male and female patients, or systolic and diastolic blood pressures among the 3 groups.

Contrast Echocardiographic Study

Table 2 shows the results of contrast echocardiographic
Table 3  Hemodynamic Parameters in 3 Groups

<table>
<thead>
<tr>
<th></th>
<th>End-diastolic volume (ml)</th>
<th>Ejection fraction (%)</th>
<th>Peak filling rate (EDV/sec)</th>
<th>1/3 filling rate (EDV/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control subjects</td>
<td>123 ± 32</td>
<td>58.6 ± 12.9</td>
<td>2.52 ± 0.76</td>
<td>2.32 ± 0.63</td>
</tr>
<tr>
<td>Patients with old myocardial infarction</td>
<td>169 ± 48*</td>
<td>35.3 ± 12.7*</td>
<td>1.29 ± 0.56*</td>
<td>1.20 ± 0.61*</td>
</tr>
<tr>
<td>Patients with dilated cardiomyopathy</td>
<td>235 ± 72†</td>
<td>25.2 ± 8.6†</td>
<td>0.88 ± 0.49†</td>
<td>0.78 ± 0.61†</td>
</tr>
</tbody>
</table>

Values are means ± SD. *p < 0.001, †p < 0.0001 compared with normal control subjects, ‡p < 0.001 compared with patients with old myocardial infarction.

Fig. 4. Relations between %LVEF and ejection fraction (left) and peak filling rate (right).

Fig. 5. Relation between %LVEF and percent abnormally contracting segments in patients with myocardial infarction.

A straight inflow pattern was observed in all normal control subjects and 9 patients with myocardial infarction. On the other hand, a whirling inflow pattern was observed in 15 patients with myocardial infarction and all patients with dilated cardiomyopathy. As shown in Table 2, the left ventricular end-diastolic area was greater in patients with dilated cardiomyopathy than in normal control subjects and patients with myocardial infarction. However, there was no significant difference in left ventricular opacified area among the 3 groups.

Fig 3 shows %LVEF in each patient, and Table 2 shows the mean value of each group. Percent LVEF in both patients with myocardial infarction and dilated cardiomyopathy was smaller than that in normal control subjects. Table 2 also shows the regional %LVEF in each group. In contrast to %LVEF in normal control subjects and patients with dilated cardiomyopathy, %LVEF in the IVS region, which represents the infarcted area, was significantly smaller than that in the FW region in patients with myocardial infarction.

Hemodynamic Parameters (Table 3)

End-diastolic volume was largest in patients with dilated cardiomyopathy, then in patients with myocardial infarction, and smallest in normal control subjects. Ejection fraction was smaller in patients with myocardial infarction and dilated cardiomyopathy than in normal control subjects. Peak filling rate and 1/3 filling rate became smaller in the order of normal control subjects, patients with myocardial infarction, and patients with dilated cardiomyopathy.

Relation Between Contrast Echocardiographic Parameters and Hemodynamic Parameters

The ejection fraction in patients with myocardial infarction who showed the whirling inflow pattern was 31 ± 11%, and that in patients with the straight inflow pattern was 44 ± 11% (p < 0.05, vs patients with whirling flow pattern).

Fig 4 shows the relationships between %LVEF and ejection fraction (left) and peak filling rate (right) in all subjects. There were significant positive correlations between %LVEF and the 2 variables. In addition, there were negative correlations between %LVEF and left ventricular end-diastolic volume (r = −0.551, p < 0.0001), and positive correlations between %LVEF and 1/3 filling rate (r = 0.602, p < 0.0001) in all subjects.

Fig 5 shows the relation between %LVEF and percent abnormally contracting segments in patients with myocardial infarction. There was a good negative correlation between 2 variables (r = −0.869, p < 0.0001).

Comparison of the Mode of Left Ventricular Opacification Between Dilated Cardiomyopathy and Myocardial Infarction

Fig 2 shows the representative pattern of left ventricular opacification in a patient with dilated cardiomyopathy (top) and in a patient with anteroseptal myocardial infarction (bottom). Left ventricular opacification was characterized by a defect in contrast agent in both the septal and free wall regions in patients with dilated cardiomyopathy, and a triangular- or crescent-shaped
defect at the apical to septal regions in patients with anteroseptal myocardial infarction.

**Discussion**

The present study reveals, firstly, that the inflow pattern of contrast echoes is markedly influenced by left ventricular function. In patients whose left ventricular function remains normal or mildly suppressed, the inflow pattern is straight. In patients whose left ventricular function is markedly reduced, the inflow pattern is whirling. Secondly, the left ventricular cavity was not completely filled with contrast echoes, and the severity of contrast agent defect depends on the severity of left ventricular regional dysfunction. Thus, the mode of opacification of contrast agent in patients with anteroseptal myocardial infarction is characterized by a triangular- or crescent-shaped defect at the apical to septal regions, which are supplied by the left anterior descending artery.

**Clinical Application of SSA**

It has been reported that the degree of ventricular cavity opacification is correlated with dose or concentration. In fact, at doses less than 0.12 ml/kg, good opacification of the left ventricle was observed in 41–63% of cases. However, at the dose of 0.22 ml/kg, the frequency of good opacification increased up to 94% without adverse clinical, hemodynamic, or respiratory reactions. Thus, in this study we performed a contrast echocardiographic study with 0.15 or 0.22 ml/kg SSA.

Very recently, Gandhok et al. reported that reduced forward output states affect left ventricular opacification after intravenous administration of SSA. A significant reduction in left ventricular opacification is noted in patients with systolic dysfunction, mitral regurgitation, tricuspid regurgitation, or pulmonary hypertension, but atrial fibrillation alone appears to affect left ventricular opacification less significantly than the other conditions. Increasing transit time through the pulmonary circulation in patients with reduced states of forward flow could lead to increased time of exposure to ultrasound waves and hence increased bubble destruction and decreased opacification of the left ventricle with an intravenous contrast agent. Thus, in the clinical application of SSA, we must evaluate carefully the extent of left ventricular opacification in patients with various heart diseases.

**Inflow Pattern of Contrast Medium**

Using contrast echocardiography, Beppu et al. reported the formation of a whirling flow pattern during coronary occlusion of the left coronary artery in dogs. They speculated that this abnormal blood flow was closely related to apical wall motion abnormality and decreased blood flow velocity during early diastolic filling associated with myocardial infarction. In addition, a reduction in the effective filling period associated with the prolongation of isometric relaxation time was another reason for this abnormal inflow pattern. In our study, patients with old myocardial infarction whose ventricular size was near to normal showed the straight pattern. Therefore, the enlargement of the left ventricle was also closely related to this abnormal blood inflow pattern. Clinically, this whirling flow pattern seems to be an important sign of markedly suppressed cardiac function.

**Pattern of Left Ventricular Opacification and Its Relation to Left Ventricular Function**

The most surprising result in this study is that the whole left ventricle is not necessarily opacified by contrast agent. The area not opacified by contrast agent was a wide region of the left ventricle in patients with dilated cardiomyopathy and the apex to interventricular septal region in patients with anteroseptal infarction. Interestingly, the left ventricular opacified area showed no significant difference among the 3 groups, although the left ventricular end-diastolic area was different among the 3 groups. The former result may indicate that stroke volume is close to that of normal control subjects in patients with myocardial infarction and dilated cardiomyopathy. The latter may indicate that the effective utilization of the left ventricular cavity for cardiac performance is significantly suppressed in disturbed left ventricular function as shown in %LVEF of each group.

Percent LVEF may be related to left ventricular function. In fact, there are significant correlations between %LVEF and left ventricular systolic and diastolic functions. In contrast to the pattern in normal control subjects and patients with dilated cardiomyopathy, there was a difference in %LVEF between IVS and FW in patients with myocardial infarction. In addition, there was a good correlation between %LVEF and percent abnormally contracting segment in patients with myocardial infarction. In view of these findings, contrast echocardiography using SSA can detect sensitively the region with damaged myocardium in the left ventricle.

**Mechanisms for the Existence of Non-Opacified Area**

It is well recognized that relaxation rate, ventricular diastolic suction, and left atrial filling pressure are important determinants of ventricular filling. In view of the finding that contrast-echo defect is found only in the infarcted region in patients with myocardial infarction, the main factor influencing contrast-echo defect might be the decrease in active suction associated with myocardial necrosis. Left ventricular diastolic suction, reflected by negative left ventricular pressure, maintains adequate filling in normal heart. This diastolic suction reflected by the value of left ventricular minimal pressure is augmented by an increase in contractility and left ventricular minimal pressure correlates with left ventricular volume. High left ventricular minimal pressure may disturb early diastolic filling in patients with myocardial infarction and heart failure. Thus, it is conceivable that diastolic suction in the infarcted area is so weak that it results in a contrast-echo defect area.

The existence of a contrast-echo defect area, in which inflowing blood is distributed over an extremely small or blood stagnation develops, may promote clot formation. Thus, careful observation must be required to determine whether the contrast-echo defect area contains mural thrombi.

**Study Limitations**

In our study, 2 different doses of SSA, 0.15 ml/kg and 0.22 ml/kg, were used to visualize the left ventricle. Unfortunately, we did not compare left ventricular opacification obtained with 0.15 ml/kg with that obtained with 0.22 ml/kg. Difference in the dose used may affect the intensity or extent of left ventricular opacification. Recently, Ota et al. studied the conditions affecting the
intensity of left ventricular opacification. They reported that certain ultrasound machine settings, such as a higher acoustic power or lower transducer frequency, can affect the acoustic properties of SSA microspheres, resulting in a decrease in mean image intensity. In addition, higher concentrations of SSA were less affected by acoustic power and transducer frequency than were lower concentrations. However, an injection of higher concentrations causes a remarkable decrease in echo intensities because of strong attenuation. They concluded that the appropriate concentration range is 0.02–0.2 μL/mL human serum albumin. According to our calculation, 0.15 and 0.22 mL/kg of SSA correspond to 0.10 and 0.14 mL/mL human serum albumin, respectively. Thus, the dose used in our study falls within the appropriate range and our findings indicate that the intensity of left ventricular opacification varies with dose but that the extent does not.

In our study, the dose of 0.22 mL/kg was used in none of the control subjects, 37.5% of patients with myocardial infarction, and 73.1% of patients with dilated cardiomyopathy. Thus, in our study, a higher dose of SSA was used in patients with lower ejection fraction. In view of the finding that higher concentrations of SSA result in higher intensity and less decrease in intensity, it is conceivable that %FLV is in patients with myocardial infarction and dilated cardiomyopathy is overestimated, compared with control subjects.

Acknowledgment

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References