Contrast Echocardiography for Evaluation of Left Ventricular Flow Dynamics Using Densitometric Analysis

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Background. Few data exist regarding intraventricular flow patterns in the presence of left ventricular dysfunction. Therefore, we examined the relation between intracavitary left ventricular flow dynamics and the presence of ventricular contractile abnormalities using videodensitometric analysis of transpulmonary contrast echocardiography.

Methods and Results. Two-dimensional echocardiography was performed before, during, and after intravenous injection of sonicated albumin in 8 normal subjects, 22 patients with infarction, and 6 patients with dilated cardiomyopathy. Time-intensity curves were recorded, and disappearance half-times (in cardiac cycles) were measured for regions of interest at the mitral orifice (Ta) and mid–left ventricular cavity (Tb). We observed contrast enhancement of the left ventricular cavity in 28 of 36 patients. Ta and Tb were identical (19 beats) in all normal patients, but Tb was greater than Ta (19 versus 22 beats, P < .001) in patients with dyssynergy. Patients with dyssynergy were divided in three groups: group A, in whom Tb-Ta ≤ 3; group B, in whom Tb-Ta ≥ 4; and group C, which was composed of patients without contrast enhancement. Left ventricular end-diastolic dimension was similar in normal patients (46.1 mm) and group A patients (50.3 mm) but was less in each cohort than in groups B (58.7 mm) and C (64.1 mm) (all P < .01). Significant correlation was observed between Tb-Ta and both ejection fraction (r = -.67, P < .001) and wall motion index (r = -.62, P < .001).

Conclusions. Clearance of contrast from the mid–left ventricular cavity is prolonged in patients with left ventricular dysfunction. This prolongation may be related to increased left ventricular diastolic volume, impaired intracavitary mixing, or paradoxical systolic flow. Delayed left ventricular contrast washout may have implications regarding the formation of left ventricular thrombi. (Circulation 1993;88:588-595)

Key Words • echocardiography • videodensitometry • flow • function, cardiac

Although cardiac hemodynamics have been the subject of intense study for many years, relatively little is known about the intracavitary flow dynamics of the left ventricle. The paucity of data regarding intraventricular flow patterns undoubtedly has been related to the limited technology available with which to study these phenomena. The development of Doppler color flow imaging has provided a modality with which to visualize intraventricular flow patterns and has been used to study paradoxical systolic flow toward the dyssynergetic segment in the setting of left ventricular dyskinesia. However, color Doppler mapping provides information regarding only the velocity and direction of flow and yields signals that represent the events for a single cardiac cycle.

Contrast echocardiography provides an alternate method with which to image the flow patterns within the cardiac chambers. Until recently, however, opacification of the left atrium and ventricle by contrast echocardiography required direct injection of the agent. Direct left atrial contrast injection was used by Beppu and colleagues in experimental animals to assess intracavitary left ventricular flow dynamics, and incomplete ventricular mixing was demonstrated in the setting of left ventricular dyskinesia.

Recently, several new classes of contrast agents have been developed that are capable of pulmonary transmission. Thus, sonicated iodinated radiographic contrast agents, sonicated human serum albumin, and a saccharide suspension have been demonstrated to produce left heart opacification following peripheral venous administration. The present study was conducted to examine intracavitary left ventricular flow dynamics in humans by using contrast echocardiography and to correlate these findings with measures of left ventricular function.

Methods

Subjects
The study population consisted of 36 subjects: 8 subjects (group 1) had no evidence of cardiovascular...
disease (4 men and 4 women; mean age, 49±12 years), 22 patients (group 2) had old (more than 6 months) myocardial infarction (16 anteroseptal myocardial infarctions and 6 inferior myocardial infarctions; 19 men and 3 women; mean age, 61±12 years), and 6 patients (group 3) had dilated cardiomyopathy (5 men and 1 woman; mean age, 57±13 years). We excluded patients with severely impaired cardiac function (New York Heart Association functional class IV), with moderate or severe valvular regurgitation, and with pulmonary disease. Informed consent was obtained from all subjects enrolled in the protocol.

**Sonicated Albumin**

With an ultrasound sonicator system (Sonifer II; Branson Ultrasonics Corp), we agitated a solution of 5% human serum albumin for 30 seconds with 20-W output power and 20-kHz ultrasound. This method has been shown to produce sonicated albumin containing 400 000 microbubbles per milliliter that range in diameter from 3 to 6 μm.¹

**Protocol**

A commercially available Doppler echocardiograph (SSH-160A; Toshiba Co Ltd) with an ultrasound transducer with a center frequency of 3.75 MHz was used in these studies. All subjects were examined while in the left lateral decubitus position. Images were obtained in the apical four-chamber view and were adjusted to provide optimal visualization of the mitral anulus and left ventricular cavity. The probe then was fixed manually at this position. Recording of this four-chamber view on ½-in. videotape was begun before a bolus injection of 0.1 mL/kg sonicated albumin into a forearm subcutaneous vein and was continued until contrast signals disappeared completely. All injections were performed immediately after sonication of the albumin.

In 21 subjects, this procedure was repeated 10 minutes after the disappearance of left ventricular cavity opacification to assess the reproducibility of measurements derived from contrast echocardiography. The intensity and duration of contrast visualization for the first injection were compared with that for the second injection for regions of interest at the mitral orifice and the middle of the left ventricle.

Several indexes of left ventricular function were obtained by Doppler echocardiography after completion of the contrast echocardiographic studies. We measured the left ventricular outflow tract dimension at a site just below the aortic valve from the parasternal long-axis image and recorded flow velocity at the same site from the apical long-axis view. Left ventricular end-diastolic dimension (LVEDD) was measured in the standard manner from a two-dimensional guided M-mode echocardiogram of the left ventricle. Stroke volume (SV) and ejection fraction (EF) were then calculated by the following formulas:¹⁵,¹⁶:

\[
SV = \pi(D/2)^2 \times f/vdt
\]

where D is dimension of left ventricular outflow tract and v is peak velocity of ejection.

\[
LV\text{ end-diastolic volume} = LVEDD^3
\]

\[
EF = SV/LVEDD^3
\]

**Fig 1.** Schematic of the left ventricular wall segmentation and the wall motion scoring using two-dimensional echocardiography. The left ventricular wall was divided into nine segments, and the degree of wall motion abnormality was scored for each segment from 0 (normal) to 4 (dyskinesis). The wall motion index was obtained as the summation of these scores.

A wall motion index indicative of the severity of left ventricular contractile abnormality was derived by visual analysis of two-dimensional echocardiography. We divided the left ventricular wall into nine segments (Fig 1, left) and scored the degree of wall motion abnormality for each segment from 0 (normal) to 4 (dyskinesis). The wall motion index was the summation of these scores (Fig 1).

**Videodensitometric Analysis**

With an off-line computer analyzing system (CARDIO 500; Kontron Co Ltd), echocardiographic images were digitized into a 768×480-pixel matrix with 32 bits corresponding to 256 gray levels of intensity per pixel. A 10×10-pixel region of interest was positioned within the left ventricle, and the resultant gray levels were used to derive a time-intensity curve that was displayed after undergoing a smoothing algorithm.

Using the end-diastolic echocardiographic images of consecutive cardiac cycles, we placed a videodensitometric region of interest in two sites: at the mitral valve orifice (ROIa) and at the middle of the left ventricle (ROIb). From the time-intensity curve of left ventricular contrast echocardiography derived at each site, we measured the number of cardiac cycles between the time of initial detection and the half-disappearance point of contrast agent, designated as Ta for ROIa and Tb for ROIb, respectively (Fig 2). The horizontal axis of the time-intensity curves was originally outputted by the computer as time in seconds. However, we transformed the horizontal axis to beats by dividing the time by the RR interval because this curve was constructed using only end-diastolic images. It is possible that the absolute values of Ta and Tb in seconds may not have been precisely reflected by expressing duration in beats because heart rate is an additional variable in this formulation. However, the primary entity analyzed in this study was the difference between Ta and Tb in an individual patient, and this relation will be identical whether expressed in seconds or cardiac cycles.

**Statistical Analysis**

All values are expressed as mean±SD. Statistic analysis was performed using unpaired Student's t test.
FIG 2. Measurement of half-disappearance beats on the time-intensity curve. The videodensitometric time-intensity curve was obtained at the sites of mitral orifice (ROIa) and mid-left ventricle (ROIb), and on each curve, the half-disappearance beats (Ta and Tb) were measured as the beats from the time of initial detection of contrast agent to the half-disappearance point of contrast agent.

P<.05 was considered significant. Linear regression analysis was also performed to compare measures of left ventricular size and function with the difference in half-disappearance times at the mitral and midventricular levels.

Results

Left Ventricular Cavity Enhancement

We observed opacification of the left ventricular cavity by the contrast agent in all 8 normal subjects and in 20 of 28 patients with wall motion abnormality (17 in group 2 and 3 in group 3). Cavity opacification was classified as mild, moderate, or complete based on the area of enhancement in the left ventricle as follows: mild, contrast from mitral orifice to the mid portion of the left ventricle; complete, contrast to apex of the left ventricle; and moderate, intermediate distribution of contrast. Classification of the grade of enhancement was performed by two observers. The various grades of image enhancement are shown in Fig 3. Mildly enhanced images were obtained in 4 subjects, moderately enhanced images were obtained in 12 subjects, and complete image enhancement was obtained in 12 subjects.

Time-Intensity Curves

Fig 4 demonstrates representative time-intensity curves for each sampling site. The average value of peak intensity in all 28 patients manifesting enhancement with contrast was 35.0 (range, 10 to 60) gray level per pixel at ROIa and 45.7 (range, 15 to 84) gray level per pixel at ROIb. The brightness induced by the contrast agent decayed gradually in both regions with superimposed fluctuation due to respiration. The left column of Fig 4 represents a normal subject with the same half-disappearance beats at sites ROIa and ROIb, and the right column represents a patient with cardiac disease and a prolonged half disappearance in ROIb. The

FIG 3. Shown is variation of left ventricular opacification with contrast echocardiography. Mildly enhanced images (A) were obtained in 4 subjects, moderately enhanced images (B) were obtained in 12 subjects, and complete image enhancement (C) was obtained in 12 subjects.
contrast decay time of the time-intensity curve in ROIb tended to be more prolonged than that in ROIs in patients with impaired cardiac function.

Reproducibility analysis of contrast echocardiographic enhancement yielded good results. In 8 of the 21 patients in whom we examined the reproducibility of enhancement, we did not observe opacification with either the first or second injection. In 13 of 21 patients, we obtained nearly the same opacification with two successive injections. The values for peak intensity were 40.5±19.4 (range, 11 to 66) gray level per pixel at ROIa and 49.5±21.4 (range, 15 to 84) gray level per pixel at ROIb for the first injection and 39.1±16.2 (range, 16 to 60) gray level per pixel at ROIa and 47.3±16.8 (range, 18 to 70) gray level per pixel at ROIb for the second injection, respectively. We observed significant correlation between the first and second injections (ROIa: y=0.7x+8.8, r=.90, P<.001; ROIb: y=0.7x+13.1, r=.88, P<.001). The duration of left ventricular opacification at ROIa was 21.4±5.6 (range, 13 to 30) seconds at the first trial and 21.8±4.4 (range, 12 to 31) seconds at the second trial; duration at ROIb was 22.5±4.8 (range, 15.5 to 31) seconds at the first trial and 22.1±6.1 (range, 13 to 34) seconds at the second trial. Significant correlation between the duration of individual injections was observed (ROIa: y=1.1x–1.2, r=.87, P<.001; ROIb: y=1.1x–1.6, r=.83, P<.001). Thus, we demonstrated good reproducibility of left ventricular cavity contrast echocardiographic enhancement.

In 8 normal subjects, the half-disappearance beats at ROIa (Ta) were 19±8 (range, 8 to 28) beats, and the half-disappearance beats at ROIb (Tb) were similar at 20±8 (range, 8 to 28) beats. In 20 patients with wall motion abnormality, Ta was 19±9 (range, 12 to 33) beats, but Tb was greater at 22±8 (range, 12 to 43) beats, which was significantly prolonged compared with both Tb in normal subjects (P<.001) and with Ta in patients with wall motion abnormality (P<.001).

Relation Between Microbubble Dynamics and Left Ventricular Wall Motion Abnormality

The patients with wall motion abnormality were divided into groups A, B, and C according to the following criteria: group A, enhancement observed and Tb–Ta≤3 beats; group B, enhancement observed and Tb–Ta≥4 beats; and group C, enhancement not observed. Values for cardiac dimension, stroke volume, ejection fraction, and wall motion index were compared for normal subjects and those in these three groups.

Group A consisted of 10 patients (9 from group 2 and 1 from group 3), group B consisted of 10 patients (8 from group 2 and 2 from group 3), and group C consisted of 8 patients (5 from group 2 and 3 from group 3). Because of the oscillation of the time-intensity curves coinciding with the respiratory cycle, we defined the patients with less than 3 beats difference between Tb and Ta as having values of Tb and Ta that were similar.
The mean values for LVEDD were 46.1±3.9 mm in normal subjects and were 50.3±6.2, 58.7±6.3, and 64.1±7.2 mm for groups A, B, and C, respectively. Thus, groups B and C showed significantly greater dilatation of the left ventricle than did normal subjects (group 1) and group A (group B versus group A and normal subjects, \( P < 0.01 \); group C versus group A and normal subjects, \( P < 0.01 \)) (Table 1). LVEDD and Tb–Ta showed significant correlation (\( r = 0.61, P < 0.001 \)) (Fig 5).

The values for stroke volume were normal subjects, 71.1±21.6 mL/beat; group A, 59.6±13.8 mL/beat; group B, 50.1±8.0 mL/beat; and group C, 46.5±8.1 mL/beat. Groups B and C had significantly lower stroke volume (group B versus normal subjects, \( P < 0.05 \); group C versus group A and normal subjects, \( P < 0.05 \)) (Table 1). Stroke volume and Tb–Ta showed significant but weak correlation (\( r = -0.35, P < 0.05 \)) (Fig 6).

The ejection fraction values gradually decreased in order of group: normal subjects, 64.6±9.8%; group A, 47.0±12.8%; group B, 25.6±6.4%; and group C, 18.9±5.4%. These differences were significant (normal subjects versus group A, \( P < 0.01 \); group A versus group B, \( P < 0.01 \); group B versus group C, \( P < 0.05 \), respectively) (Table 1). Ejection fraction and Tb–Ta showed significant correlation (\( r = -0.67, P < 0.001 \)) (Fig 6).

No wall motion abnormalities were observed in the normal subjects. Values for wall motion index were group A, 7.0±5.0; group B, 12.3±4.8; and group C, 18.1±2.8, respectively (Table 1). Wall motion index and Tb–Ta showed significant correlation (\( r = 0.62, P < 0.001 \)) (Fig 5).

**TABLE 1.** Wall Motion Index, Left Ventricular End-Diastolic Dimension, Stroke Volume, and Ejection Fraction in Each Group

<table>
<thead>
<tr>
<th>Group</th>
<th>WMI</th>
<th>LVEDD (mm)</th>
<th>SV (mL/beat)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>0</td>
<td>46.1±3.9</td>
<td>71.1±21.6</td>
<td>64.6±9.8</td>
</tr>
<tr>
<td>Group A</td>
<td>7.0±5.0</td>
<td>50.3±6.2</td>
<td>59.6±13.8</td>
<td>47.0±12.8</td>
</tr>
<tr>
<td>Group B</td>
<td>12.3±4.8</td>
<td>58.7±6.3</td>
<td>50.1±8.0</td>
<td>25.6±6.4</td>
</tr>
<tr>
<td>Group C</td>
<td>18.1±2.8</td>
<td>64.1±7.2</td>
<td>46.5±8.1</td>
<td>18.9±5.4</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*\( P < 0.05 \), \( tP < 0.01 \).

FIG 5. Scatterplots of correlation of Tb–Ta (disappearance half-times) to left ventricular end-diastolic dimension (LVEDD) (top) and wall motion index (WMI) (bottom). Significant correlations between left ventricular end-diastolic dimension and Tb–Ta and between wall motion index and Tb–Ta are shown.
Discussion

Assessment of left ventricular function has focused primarily on systolic emptying. Little data have been available regarding intracavitary left ventricular flow. In the present study, we used contrast echocardiography to assess the flow dynamics of the left ventricle under normal and abnormal conditions. Our data demonstrate that although the inflow of contrast into the left ventricle through the mitral orifice is not significantly altered in the presence of left ventricular dysfunction, clearance of contrast is significantly delayed in the setting of dilation and dyssnergy. This persistence of contrast within the left ventricle is indicative of stagnation of blood and may be a marker of the propensity for thrombus formation.

Good left heart contrast opacification has been achieved with a variety of agents, and the videodensitometric approach to contrast opacification has been well described and validated. Accordingly, we used a sonicated left heart contrast agent and videodensitometry to study intracavitary left ventricular flow dynamics in the present study. By placing a region of interest in both the mitral orifice and mid–left ventricle, we recorded indicator dilution type curves from which clearance times could be measured. In this manner, we were able to obtain data regarding left ventricular inflow and clearance dynamics and to document the delayed washout of contrast with left ventricular dysfunction.

It is likely that the persistence of contrast within the left ventricle was primarily related to the combined effects of increased left ventricular volume and decreased ejection fraction. In this regard, dilation of the left ventricle would have resulted in increased residual volume into which the contrast effect could be mixed. Moreover, the reduced ejection fraction would have rendered the number of cardiac cycles required to clear the contrast in the residual volume to be increased. Nevertheless, clearance of contrast from the mitral orifice before that of the mid–left ventricle documents the prolonged transit time through the left ventricle independent of reduced cardiac output and supports the concept of susceptibility to thrombus formation.

Several additional mechanisms may have contributed to the prolonged period of contrast within the left ventricle. It is possible that incomplete intracavitary mixing was produced by the left ventricular dysfunction. Such incomplete mixing could result in persistence of the contrast effect within an individual region of the left ventricle. It was impossible for us to determine whether incomplete mixing was a factor in our patients, but the contrast that remained in the left ventricle appeared to be distributed throughout the chamber. More detailed measurements will be required to establish the potential

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**Figure 6.** Scatterplots of correlation of Tb-Ta (disappearance half-times) to stroke volume (SV) (top) and ejection fraction (EF) (bottom). SV and Tb-Ta show significant but weak correlation; EF and Tb-Ta show significant correlation.
role of abnormal mixing in the setting of left ventricular dysfunction.

The persistence of left ventricular contrast in the presence of dysfunction may also relate to abnormal intracavitary flow patterns. Previous studies in our laboratory have demonstrated the existence of paradoxical systolic flow toward dyskinetic segments in patients with regional contractile abnormalities. Left ventricular blood was observed to flow toward the apex and away from the base in patients with apical dyskinetic segments. Similar findings have been reported by Beppu and coworkers. Such abnormal intracavitary flow could readily impair the clearance of contrast from the left ventricle and, again, account for a prolonged transit time within this chamber. In this case, however, blood stasis might be reduced or even eliminated.

A number of technical factors may have influenced the results obtained in our studies. Several variables may affect the appearance and disappearance of ultrasonic contrast, including the size of the pulmonary capillary bed, the pressures within the central circulation, and the ability to achieve transmission of the ultrasonic signal through the thorax. We were unable to produce visible left ventricular opacification in 8 of the 36 patients (22.2%) we studied. Although the effects of the above variables on our data cannot be determined precisely, it is of importance that these effects should have been similar for both the mitral orifice and midventricular sites.

Several additional variables capable of influencing our data involved the quantitation of the contrast effect. In regard to contrast intensity, it would be anticipated that larger microbubbles would produce more intense signals than would smaller gas particles. It is not likely, however, that microbubble size would vary considerably in the two sites examined. Our videodensitometric measurements have assumed a linear relation between contrast concentration and the intensity (brightness) of the signal displayed by the echograph. Although linearity often is not present due to image-processing alterations within the instrument, both the intensity and time course of the signals obtained from the mitral orifice and mid–left ventricle should have been affected identically.

Study Limitations

The left ventricular end-diastolic volume was calculated as LVEDD in the present study. This method tends to overestimate volume in patients with myocardial infarction and dilated ventricle. Because Doppler stroke volume measures remain valid under these circumstances, the ejection fractions were probably underestimated. It is unlikely, however, that any underestimation or overestimation would negate the general relation between cardiac function and the rate of contrast washout in the left ventricle.

Patients with poor cardiac function often failed to manifest opacification of the left ventricle. Thus, patients in whom left ventricular contrast was absent exhibited higher diastolic dimension and wall motion index and lower stroke volume and ejection fraction than did normal subjects or patients with opacification (Table 1). The lack of left ventricular opacification in patients with cardiac dysfunction represents an important limitation of contrast echocardiography because this cohort presumably is at the highest risk of flow stasis and thrombus formation. The reasons for the failure of pulmonary transmission of contrast are unclear, but they may relate to damage to microbubbles by elevation of pressure within the pulmonary circulation. Because there was an overlap in values of LVEDD, wall motion index, stroke volume, and ejection fraction between group B, patients who manifested left ventricular contrast, and group C, patients who did not, it is unlikely that these variables alone account for the failure of left ventricular opacification. Further studies of the morphology and pathophysiology of the pulmonary circulation will be required to understand the mechanism of this phenomenon. Evaluation of intracavitary flow velocities by Doppler techniques such as have been performed by Delemarre and colleagues and Maze and colleagues may provide an alternative method with which to identify left ventricular stasis in patients in whom contrast visualization is not possible.

Clinical Implications

Our data have established the presence of contrast within the left ventricular body in the setting of left ventricular dysfunction. In addition, the degree of prolongation has been related to the magnitude of left ventricular enlargement and reduction of ejection fraction. Because the flow dynamics of contrast microbubbles have been demonstrated to be similar to those of red blood cells, these data indicate the presence of relative blood flow stasis in the presence of impaired left ventricular performance. Such relative stasis clearly predisposes to thrombus formation and thus to subsequent thromboembolic phenomena. It is possible that contrast echocardiography may enable identification of patients at risk to thrombus formation and provide a measure of the magnitude of risk. These data could well be the basis on which anticoagulant or antiplatelet therapy is used. At present, these data serve to emphasize the consequences of left ventricular dysfunction on intracavitary flow.

References

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