Characterization of Acute Experimental Left Ventricular Thrombi With Quantitative Backscatter Imaging

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Two-dimensional echocardiography is an excellent technique for detecting left ventricular thrombi, however, acute clot is sometimes difficult to differentiate from adjacent myocardium and intracavitary signals. We hypothesized that quantitative assessment of the acoustic properties of acute left ventricular thrombi using a quantitative backscatter imaging system would permit the differentiation of thrombus from adjacent myocardium and intracavitary echoes. Acute, experimental left ventricular thrombi in seven dogs were evaluated with a quantitative backscatter imaging system that allowed the measurement of relative integrated backscatter and cyclic (i.e., diastolic minus systolic) variation in integrated backscatter. Coronary ligation abolished the cyclic variation in relative backscatter that occurred in normal myocardium. The end-diastolic relative backscatter in the thrombus (16.9±1.3 dB) was significantly higher than in apical myocardium (13.2±0.6 dB, p<0.05). There was no significant difference in the cyclic variation in relative backscatter among thrombus, ischemic myocardium, or intracavitary blood. Thus, the quantitative assessment of the acoustic properties of left ventricular thrombi can be useful in their detection and in the differentiation from myocardium and intracavitary signals. (Circulation 1990;81:1017–1023)

Left ventricular thrombi are identified in 32–56% of patients with acute anterior myocardial infarctions using two-dimensional echocardiography.1 A thrombus appears as an echo-dense mass, adjacent to endocardium, commonly found in the apical region and associated with a wall motion abnormality. The reported sensitivity of two-dimensional echocardiography for the detection of left ventricular thrombi varies in the range of 77–95% with a specificity of 86–93%.1–4 False-positive studies can be related to artifacts caused by reverberations from the chest wall, from apical scar tissue, or from the plastic transducer casing. False-negative studies can result from the inability to differentiate thin, layered mural thrombi from adjacent myocardial wall. In an effort to improve the diagnostic accuracy of echocardiography in the detection of left ventricular thrombi, the usefulness of ultrasound tissue-characterization techniques has been studied.5,6 Using statistical analysis of image gray levels from echocardiograms, we previously showed that thrombi were distinguishable from myocardium and intracavitary signals (blood); however, computer analysis of digitized echocardiographic data in an off-line manner, using a separate image-analysis system, was required.5 In an effort to obtain on-line ultrasound characterization of left ventricular thrombi and, therefore, immediate analysis of tissue characterization data, our purpose was to study a quantitative two-dimensional integrated backscatter imaging system7,8 in an experimental model of acute ventricular thrombi.

Methods

Animal Preparation

We used a model of acute ventricular thrombi previously described.5,9 Seven adult mongrel dogs were studied (weight, 18–22 kg). Each dog was anesthetized with intravenously administered sodium pentobarbital (20–30 mg/kg), intubated with a cuffed
in intratracheal tube, and ventilated artificially with a mechanical respirator. Femoral arterial and venous catheters were inserted for hemodynamic monitoring and vascular access. The thorax and pericardium were opened by means of a left thoracotomy. Intravenous lidocaine (2 mg/kg) was administered, and then, all coronary arteries supplying the cardiac apex were ligated. Thrombin (1,000 IU) was injected at the endocardium-blood interface of the ischemic apical region to create a left ventricular mural thrombus. After completion of the study, and after euthanasia with 30 ml intravenously administered potassium chloride (while the dog was deeply anesthetized), the heart was removed and sectioned for examination.

**Echocardiography**

Each dog was placed in the right lateral decubitus position on a table with a cut-out to allow the echocardiographic transducer to be applied from below to the right parasternal area near the point of maximal impulse.

The quantitative two-dimensional echocardiographic integrated backscatter system used in this study was modified from a conventional two-dimensional echocardiographic system, altered to generate real-time backscatter images and to permit analysis of freeze-frame data during the echocardiographic examination. Displayed gray levels in this system bear a direct relation to relative integrated backscatter.

In the backscatter imaging system, relative integrated backscatter refers to the ratio of energy (E) from a region of interest (ROI) to the energy from an internal reference (Ref) standard (10 log(E_{ROI}/E_{Ref})). This differs from previous work in which integrated backscatter is the ratio of energy from a region of interest to the energy from a perfect (steel) reflector. Thus, measurements were obtained in thrombus, myocardium, and blood, and these measurements were related to an internal reference standard rather than to sources of maximum intensity, such as posterior pericardium. The integrated backscatter processor converts the analog signal to a digitized format. Backscatter (in dB) is measured within an operator-defined ROI from the digitized data and is proportional to 10 log (data in ROI + Ref), where the internal reference is the least significant level of the digital signal as defined by the analog-to-digital converter. The internal reference does not compensate for time-gain settings. Thus, the individual measurements of backscatter will vary with the time-gain setting but the cyclic variation will not vary.

Digitized image (backscatter) data are stored within the imaging system, and these data can be quantitatively evaluated by a trackball-controlled interactive program in the imaging system. Analysis of relative integrated backscatter is obtained from square or arbitrarily shaped ROIs on freeze-frame images. The system displays end-diastolic and end-systolic frames in a split-screen format. The displayed dynamic range is 31.5 dB; in this study, the system was used with a standard commercial 3.5 MHz transducer with a nominal fractional bandwidth of 40%. The integration length was set for 3 μsec. Transmit power and time-gain compensation were adjusted to minimize intracavitary backscatter and to demonstrate cyclic variation of backscatter in normal myocardium. The time-gain compensation was then maintained constant during each study. No attempts were made to standardize overall image brightness across dog subjects. ROIs were drawn on freeze-frame images obtained at end diastole (onset of the QRS complex) and end systole (frame corresponding to initial closure of the aortic valves).

Single measurements of relative integrated backscatter were obtained within two regions of the myocardium (anterobasal and apical segments), the cavity, and the acute thrombus (Figure 1). Regions of interest in the myocardium were transmural but excluded specular reflections from the endocardium and epicardium. ROIs in the thrombus excluded the specular reflectors from the intracavitary blood-thrombus interface. Average relative integrated backscatter values within the regions were displayed on the video screen. Cyclic variation in relative integrated backscatter was the difference between end-diastolic and end-systolic values of relative integrated backscatter. Because the measurements were obtained at the time of study, they were performed "unblinded," with observers aware of experimental conditions. The purpose of the study, however, was to evaluate the tissue characteristics of left ventricular thrombi rather than to test the sensitivity or specificity of this technique in their detection.

**Protocol**

Baseline two-dimensional conventional and quantitative backscatter echocardiograms were performed through the chest wall from the right side of the dogs. After ligating the coronary arteries supplying the apex and permitting the dog to stabilize for at least 15 minutes, conventional and quantitative backscatter two-dimensional echocardiograms were repeated to document apical dyskinesis. After injecting thrombin...
and inducing a left ventricular thrombus, the conventional (Figure 2) and quantitative backscatter (Figure 3) two-dimensional echocardiograms were repeated. After the injection of thrombin, thrombi were often identified immediately with standard echocardiography. There were cases, however, where thrombi were not evident and, therefore, repeat injections of thrombin were necessary to obtain visually apparent thrombi.

Figure 2. Standard two-dimensional echocardiogram of left ventricle in modified long axis, with an apical thrombus (arrows).

Figure 3. Quantitative integrated backscatter echocardiogram of experimental acute left ventricular thrombus. Parasternal long axis views in end diastole (left) and in end systole (right) are displayed in freeze-frame format. Region of interest (arrows) is drawn directly on image and integrated backscatter is displayed.
TABLE 1. Cyclic Variation of Backscatter (dB) in Individual Dogs

<table>
<thead>
<tr>
<th>Dog</th>
<th>Anterobasal myocardium</th>
<th>Apical myocardium</th>
<th>Intracavitary blood (base)</th>
<th>Intracavitary blood (apex)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Occlude LAD</td>
<td>Induce clot</td>
<td>Baseline</td>
</tr>
<tr>
<td>1</td>
<td>14.8</td>
<td>14.2</td>
<td>11.8</td>
<td>15.0</td>
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<td>13.0</td>
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<tr>
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<td>13.5</td>
<td>13.0</td>
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<tr>
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<td>13.5</td>
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<td>11.8</td>
<td>12.0</td>
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<tr>
<td>7</td>
<td>14.0</td>
<td>14.2</td>
<td>14.0</td>
<td>10.5</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery.

We used conventional imaging to document the presence of thrombi before analyzing relative backscatter with the quantitative backscatter imaging system.

Statistical Analysis

All data are expressed as mean±SEM. Paired t tests were used to assess the significance of differences between end diastole and end systole (i.e., cyclic variation in each region). Analysis of variance was used to assess the significance of differences in end diastolic relative integrated backscatter (dB) and cyclic variation (dB) measurements obtained in different regions at a particular stage of the study. A p value of less than 0.05 was considered to indicate statistical significance.

Results

On pathological examination, apical left ventricular thrombi were present in all dogs. All clots were organized and greater than 0.5 cm in diameter. At baseline, normal apical and anterobasal wall myocardium demonstrated cyclic variation of relative integrated backscatter (1.6±0.4 dB and 2.1±0.4 dB, respectively; p<0.05 for diastole vs. systole) (Table 1).

In the presence of apical dyskinesis after coronary ligation, there was no significant cyclic variation of the relative integrated backscatter in the apical myocardium (0.2±0.3 dB, p=0.59) but cyclic variation was present in the anterobasal wall (1.8±0.3 dB, p<0.05).

In the presence of thrombus and dyskinesis, the relative integrated backscatter at end diastole in the thrombus (16.9±1.3 dB) was significantly (p<0.05) higher than in the apical (13.2±0.6 dB) and anterobasal (13.4±0.5 dB) walls of the myocardium, as well as in intracavitary blood (0.8±0.1 dB) (Table 2 and Figure 4). Although there was cyclic variation in anterobasal myocardium (0.5±0.2 dB, p<0.05), it was not significantly different from apical myocardium (0.6±0.5 dB), thrombus (−0.6±0.7 dB), or intracavitary blood (−0.5±0.4 dB).

Discussion

The significant finding of this study was that the quantitative acoustic properties of acute left ventricular thrombi permitted their differentiation from adjacent myocardium. Specifically, the relative backscatter of intracavitary thrombi induced experimentally was higher than that of surrounding myocardium and intracavitary blood. This acoustic property might potentially be useful in the clinical differentiation of clot from surrounding blood, adjacent myo-

TABLE 2. Relative (End-Diastolic) Integrated Backscatter (dB) in Individual Dogs

<table>
<thead>
<tr>
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LAD, left anterior descending coronary artery.

*p<0.05 vs. apical myocardium and intracavitary (base) blood.

†p<0.05 vs. thrombus and intracavitary (base) blood.
cardium, and extraneous echoes. There was no significant cyclic variation in integrated backscatter in left ventricular thrombi, ischemic apical myocardium, and intracavitary blood. Normal myocardium, as shown previously,7,12 did exhibit significant cyclic backscatter variation.

In the presence of left ventricular thrombus developing after acute myocardial infarction, the incidence of embolization is in the range of 6–35%.13-15 Because these patients have a high risk of embolization,16 it is important to be able to reliably identify those with a left ventricular thrombus. Conventional two-dimensional echocardiography is a useful method for the detection of left ventricular thrombi but sensitivity for their detection in some studies is only 77%.1 False-negative studies can be related to the difficulty in detecting layered thrombi in an aneurysmal apex because normal wall thickness can be stimulated. Although limits in the resolution of conventional two-dimensional echocardiography can cause false-negative studies, Seibold et al9 demonstrated that experimental left ventricular thrombi as small as 0.08 ml in volume are detected by echocardiography. Additionally, false-negative studies can relate to the dynamic range compression of echo amplitudes, which can make distinction of thrombus from myocardium difficult. In conventional two-dimensional echocardiographic systems, however, dynamic range can be expanded to improve the visibility of the thrombus.

Alternative methods for the detection of left ventricular thrombi have included indium 111–labeled platelet scintigraphy.3,9,17,18 The sensitivity of 71% is comparable with that of two-dimensional echocardiography.3 Three to 4 days after the initial labeled platelet injection, however, seems to be the optimal time for imaging chronic left ventricular thrombi.18

Quantitative acoustic characterization of thrombi has potential for the objective identification of ventricular thrombi. Green et al6 obtained amplitude histograms of digitized ultrasonic signals from 15 patients with two-dimensional echocardiograms suggestive of intracardiac masses. The evaluation of the probability-density function of echo amplitudes was useful in the differentiation of thrombus from artifact and tumor. Lloret et al19 analyzed echocardiographic and clinical variables in the prediction of embolic risk from left ventricular thrombi. Among variables useful in classifying thrombi as potentially embolic were measures of echocardiographic image texture. McPherson et al5 have studied the acoustic properties of experimental left ventricular thrombi in an attempt to differentiate thrombi from blood and myocardium. Thrombi were distinguished from myocardium by mean gray level and standard deviation. Mean gray level, standard deviation, and skewness all distinguished thrombus from intracavitary blood. In our study, left ventricular thrombi had increased relative integrated backscatter compared with myocardium and intracavitary blood, supporting the finding of McPherson et al.5 Additionally, in vitro studies of clotted blood have demonstrated that attenuation-compensated backscatter increases with thrombus formation.20

We reported the data in cyclic variation for the anterobasal region before coronary occlusion to confirm the normal cyclic variation that occurs in normal human myocardium.7,12 Animal studies have also demonstrated the cyclic variation of backscatter in normal myocardium. In open-chest dogs, Madaras et al23 obtained myocardial ultrasonic backscatter measurements throughout the cardiac cycle and demonstrated elevated values at end diastole and significantly lower values at end systole. In a similar canine study by Fitzgerald et al,24 backscatter power was highest during diastole and lowest during systole.

The blunting of the normal cyclic variation of relative integrated backscatter in the ischemic apical myocardium was presumably related to the impaired contractile performance.21,22 There was a decrease in cyclic variation in the anterobasal region with thrombus formation, and this was possibly related to the occlusion of left anterior descending artery collateral vessels perfusing the anterobasal region.

Limitations

Our study was performed in an acute experimental model of left ventricular thrombi. Thus, our findings might not apply to the evaluation of tissue characteristics of chronic thrombi. Embolization from left ventricular thrombi, however, tends to occur early after the occurrence of an acute myocardial infarction,13-15,25 and thus, a model of acute rather than long-term experimental left ventricular thrombus is of direct importance.

Acute left ventricular thrombi were equally well-detected qualitatively with both conventional and quantitative backscatter imaging modalities. The purpose of the study, however, was not to compare the imaging modalities but to determine the potential of quantitative backscatter two-dimensional imaging. A blinded comparison of the two imaging modalities would be of interest in future studies. Although the well-defined thrombi induced for the purpose of this study would not offer a diagnostic challenge to expe-
rienced echocardiographers, there might be an application of quantitative backscatter imaging in the presence of less well-defined thrombi (i.e., layered thrombi); however, this requires further study.

The use of only two measurements per cycle is a limitation of the current imaging system. Although previous studies have obtained multiple measurements throughout the cardiac cycle with off-line computer analysis,7,8 our study used an instrument capable of storing only two frames in memory for on-line analysis. We anticipate that future developments in computer software will allow multiple on-line measurements within a cardiac cycle. These two measurements at end diastole and end systole, therefore, might not necessarily reflect maximal cyclic variation of backscatter. This perhaps explains the relatively low magnitude of cyclic variation at baseline in most dogs.

The use of multiple rather than single measurements presumably would have reduced variability of the relative integrated backscatter measurements. Despite this limitation, the standard error of the means of all backscatter measurements was less than 1 dB.

Acute left ventricular thrombi can be distinguished from ischemic myocardium and intracavitary blood by relative integrated backscatter, using a quantitative backscatter imaging system. Although ischemic myocardium demonstrates a blunting of the normal cyclic variation in relative backscatter, the variation is not significantly different from thrombus. Thrombi exhibit increased backscatter, however, as compared with ischemic myocardium. Thus, the quantitative assessment of the acoustic properties of left ventricular thrombi can be useful in their detection and differentiation from myocardium and intracavitary signals.

Acknowledgment

We are grateful for the expert secretarial assistance of Marlene Blakley.

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**KEY WORDS** • echocardiography • myocardial ischemia • thrombus • tissue characterization
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