Detection of Left Ventricular Thrombus by Two-dimensional Echocardiography: Sensitivity, Specificity, and Causes of Uncertainty

JOHN R. STRATTON, M.D., GEORGE W. LIGHTY, JR., M.D., PH.D., ALAN S. PEARLMAN, M.D., AND JAMES L. RITCHIE, M.D.

SUMMARY To define the sensitivity, specificity and predictive accuracy of two-dimensional echocardiographic detection of left ventricular thrombus, the echocardiograms of 78 patients who had independent proof of the presence or absence of a left ventricular thrombus were interpreted without knowledge of any clinical data. The presence of thrombus was established by autopsy in four patients, by aneurysmectomy in three, and by indium-111 platelet imaging in 15; the absence of thrombus was proved by autopsy in 55 patients and by aneurysmectomy in one patient. The characteristics of true-positive and false-positive echocardiograms, interobserver variability, and clinical features associated with proved thrombus were also defined.

The echocardiogram was positive for thrombus in 22 patients, equivocal in seven and negative in 49. For detection of thrombus, a positive or equivocal echocardiogram had a sensitivity of 95% (21 of 22), a specificity of 86% (48 of 56), and a predictive value of 72% (21 of 29); the predictive value of a negative study was 98% (48 of 49). Considering positive and equivocal studies separately, the predictive value of a positive study was 86% (19 of 22), while that of an equivocal study was only 29% (two of seven).

Compared with patients who had no thrombus, patients with proved thrombus had a higher prevalence of electrocardiographic transmural anterior infarction (86% vs 13%), left ventricular aneurysm (73% vs 5%), and clinical systemic emboli (36% vs 7%) (all \(p < 0.05\)). These clinical features help to identify a subset of patients most likely to have left ventricular thrombi who may benefit from echocardiography.

Two-dimensional echocardiography is highly sensitive in detecting left ventricular thrombus, but false-positive studies are relatively common. Several echocardiographic criteria derived from analysis of the true and false positives in this study may help minimize diagnostic errors.

THE DEMONSTRATION of a left ventricular thrombus influences important clinical decisions regarding anticoagulation. Although several reports have described the two-dimensional echocardiographic appearance of left ventricular thrombus,\(^1\)\(^-\)\(^7\) no large series has been reported in which the presence or absence of thrombus has been independently verified. Therefore, the accuracy of two-dimensional echocardiographic detection of left ventricular thrombus remains uncertain.

In the two largest published studies, surgical or autopsy verification of the echocardiographic findings was available in 14 of 60 patients\(^6\) and seven of 25 patients.\(^6\) Ports et al.\(^1\) reported a sensitivity of 50% (four of eight). More recently, Al-Nouri et al.\(^5\) report- ed a sensitivity of 72% (13 of 18) and a specificity of 90% (27 of 30). Thus, the typical echocardiographic features of left ventricular thrombus have usually been described in patients in whom the presence of thrombus has not been confirmed by other techniques.\(^1\)\(^-\)\(^7\)

Also, because the proportion of false-positive echocardiographic diagnoses has been as high as 21% (three of 14) of all positive studies,\(^6\) additional information about the causes of false-positive studies is needed.

The purposes of this study were (1) to determine the sensitivity, specificity, and predictive value with which two-dimensional echocardiography can detect left ventricular thrombus; (2) to assess the echocardiographic features of proved thrombus; (3) to define interobserver variability; (4) to determine sources of false-positive echocardiographic diagnoses; and (5) to further define clinical features associated with proved ventricular thrombus and identify patients who are most likely to benefit from an echocardiogram performed to detect left ventricular thrombus.

**Methods**

**Patients**

The study population consisted of all patients who underwent two-dimensional echocardiography between January 1, 1979, and December 31, 1980, in whom independent confirmation of the presence or absence of left ventricular thrombus was also available. During this period, 2459 patients underwent two-dimensional echocardiography at one of the two participating hospitals. Eighty-eight of these patients also underwent other studies that established with certainty the presence (23 patients) or absence (65 patients) of left ventricular thrombus. Ten of these patients (one with and nine without thrombus) had technically inadequate echocardiograms and were excluded from further analysis. Thus, echocardiographic and clinical data were reviewed in 78 patients, 22 with and 56 without thrombus. The presence of thrombus was proved by autopsy in four patients, by aneurysmectomy in three and by unequivocally positive indium-111 platelet imaging in 15. The criteria for a positive platelet scan are described below. A positive platelet...
scan has never been reported in a patient without thrombus.\textsuperscript{5, 9, 10} Thrombus was proved absent by autopsy in 55 patients and by aneurysmectomy in one patient. A platelet scan that failed to demonstrate thrombus was not accepted as proof of the absence of thrombus, because some thrombi are not demonstrated by this technique.\textsuperscript{5, 9, 10} The mean age of patients with thrombus was 59.2 ± 13.1 years (± sd), compared with 56.1 ± 18.6 years in patients without thrombus (NS). All 22 patients with thrombus were male; 19 of the 56 patients without thrombus were female. Clinical embolic events were determined by detailed review of each patient’s chart. In all cases of cerebral embolism, the diagnosis was made by a neurologist. The echocardiographic findings in 12 patients (nine with and three without thrombus) have been reported.\textsuperscript{5, 11}

Autopsies were performed by standard methods.\textsuperscript{12} After the heart was removed, a series of parallel horizontal cuts 1 cm apart were made beginning at the apex of the heart and continuing to the base of the papillary muscles. Thus, the entire endocardial surface was well exposed. The presence or absence of left ventricular thrombus was determined by review of the detailed autopsy reports. When available, myocardial sections containing thrombus were reviewed for thrombus size.

Two-dimensional Echocardiography

Two-dimensional echocardiography was performed using either a wide-angle, phased-array sector scanner (Toshiba, 45 patients) or a wide-angle, mechanical sector scanner (A.T.L. Laboratories, 33 patients). Parasternal long- and short-axis and apical two- and four-chamber views were obtained using standard transducer positions. In most studies, nonstandard views were also obtained using apical and low parasternal echocardiographic windows to examine the apex more thoroughly. The mean interval between echocardiography and the definitive demonstration of the presence or absence of thrombus was 1.8 ± 5.2 weeks (range 0 days to 24 weeks) in patients with proved thrombus and 5.5 ± 8.8 weeks (range 0 days to 52 weeks) in those without (NS). This time interval was less than 1 month in 58 of the 78 patients.

Echocardiograms were interpreted independently by three observers who were unaware of any patient information. Echocardiograms were interpreted for the presence or absence of left ventricular thrombus, ventricular aneurysm, and other wall motion abnormalities. In 69 echocardiograms, all observers agreed as to the presence or absence of thrombus; in nine cases there was observer disagreement and a consensus was reached.

Thrombus by echocardiography was defined as a distinct mass of echoes in the left ventricular cavity that was seen clearly throughout the cardiac cycle in at least two different echocardiographic views. Additionally, we required this mass to be contiguous with the endocardium in an area of abnormal wall motion. Equivocal echocardiograms were those that met some, but not all, of these criteria. Left ventricular aneurysm was defined as a discrete akinetic or dyskinetic bulge interrupting the normal ventricular contour during diastole and systole. When more than one two-dimensional echocardiogram had been performed, only the study closest in time to surgery, autopsy or platelet imaging was analyzed to determine sensitivity and specificity.

After the initial blinded reading had been analyzed, all false-positive, false-negative, and true-positive studies were reviewed to define the echocardiographic features of true-positive studies and the sources of misinterpretation of the false-negative and false-positive studies.

Indium-111 Platelet Imaging

Platelet labeling was performed as previously described\textsuperscript{5} using a closed bag modification of the technique of Thakur et al.\textsuperscript{13} Anterior, 45\textdegree left anterior oblique, and left lateral images were taken typically 24, 48 and 72 hours after platelet injection. A total of 300,000 counts per view were recorded using a Sigma 410 Ohio Nuclear large field-of-view camera with a medium-energy, parallel-hole collimator. Platelet images were interpreted by two observers, who were unaware of the echocardiographic and clinical data, as positive for thrombus if a discrete area of intracardiac activity clearly greater than background blood pool was present (fig. 1). Studies\textsuperscript{5, 9, 10} have shown that platelet imaging is 100% specific for detection of thrombus in patients with surgical or autopsy verification.

FIGURE 1. Positive indium-111 platelet scan for ventricular thrombus in patient 20 (anterior view). Twenty-four hours after injection of labeled platelets, cardiac blood pool activity is well seen; an area of activity greater than the adjacent blood pool is present in the middle anterior wall (arrow), clearly denoting incorporation of labeled platelets into thrombus. By 96 hours, cardiac blood pool activity decreases and intense platelet deposition throughout a large apical thrombus is seen. In both images, the liver is at the lower left and the spleen at the lower right. Faint activity in the upper part of each image is an anatomic marker in the suprasternal notch.
tion. In each of the 15 patients included in this study solely on the basis of a positive platelet scan, the platelet scan was definitely positive for thrombus.

**Statistical Analysis**

Sensitivity was calculated as true positives divided by patients with proved thrombus. Specificity was calculated as true negatives divided by patients without thrombus. The predictive value of a positive test was defined as true positives/(true positives + false positives). The predictive value of a negative test was defined as true negatives/(true negatives + false negatives). Fisher’s exact probability test was used to test differences in the distribution of discrete variables between two groups. The t test was used to compare the differences between means of continuous variables between two groups. All data are expressed as the mean ± SD.

**Results**

**Sensitivity, Specificity and Predictive Value**

Among the 78 patients with independent proof of the presence (n = 22) or absence (n = 56) of thrombus, echocardiographic studies were considered positive for thrombus in 22 patients, equivocal in seven and negative in 49 (table 1). Data on all 22 patients with independently proved thrombus are summarized in table 2 and true-positive echocardiograms are shown in figures 2–4. When both positive and equivocal studies were considered to indicate the presence of thrombus, the sensitivity of two-dimensional echocardiography was 95% (21 of 22), the specificity 86% (48 of 56), the predictive value of a positive or equivocal echocardiogram 72% (21 of 29), and the predictive value of a negative echocardiogram 98% (48 of 49) (table 3). If the seven equivocal studies (two true-positive, five false-positive) were instead considered negative for thrombus, the sensitivity was 86%, the specificity 95%, the predictive value of a positive echocardiogram 86%, and the predictive value of a negative echocardiogram 95% (table 3).

Of the 22 studies interpreted as positive for thrombus, 19 were true positives and three were false positives (table 1). Of the seven studies considered equivocal for thrombus, two were true positives and five were false positives. Thus, considering both positive and equivocal studies together, there were 21 true-positive and eight false-positive echocardiograms. Equivocal echocardiograms were more likely to be falsely positive for thrombus (five of seven, 71%) than studies interpreted as positive (three of 21, 14%) (p = 0.01). The predictive value of a positive study for the presence of thrombus was 86% (19 of 22), while the predictive value of an equivocal study was only 29% (two of seven) (p < 0.001). The one false-negative study had been recorded 3 weeks before death in patient 22, who had hypercoagulability but no evidence of myocardial infarction, inflammation or coronary artery disease at autopsy. An organized white mural thrombus (3 cm³ by 0.8 cm thick) at least 1 week old was noted in an area that had been hypokinetic on the echocardiogram. In addition, recent premortem thrombi were found in the aorta and iliac artery. In six other patients, autopsy or operative estimation of thrombus size was approximately 6 cm³ by 0.5–1.0 cm thick (patient 4), 2 cm³ by 0.3 cm thick (patient 5), 8 cm³ by 0.1–0.2 cm thick (patient 2), 0.7 cm thick (patient 1), 0.9 cm thick (patient 3), and 1.2 cm in diameter (patient 8).

**Observer Agreement and Disagreement**

All three observers agreed regarding the interpretation of the echocardiogram as positive, equivocal or negative for the presence or absence of thrombus in 69 of the 78 patients (88%). In nine patients (12%), there was observer disagreement and a consensus was reached that was positive in two, equivocal in six and negative in one. The consensus reading and the individual observer sensitivities, specificities and predictive values varied only minimally (table 3).

Of the 21 true-positive readings, there was total observer agreement in 19 of the studies (90%). In contrast, there was total observer agreement in only two of the eight false-positive studies (25%) (p < 0.001). Thus, in the nine cases in which there was observer disagreement, the reading by consensus was usually equivocal or positive, and this reading usually proved to be falsely positive for thrombus (six of nine).

**Characteristics of True-positive Echocardiograms**

In addition to the presence of thrombus, we characterized its location, motion, border, reflectance and approximate size. By echocardiography, 19 of 21 true-positive studies revealed thrombus at the apex; two thrombi were located along the inferior wall in a true aneurysm (patient 19) or a pseudoaneurysm (patient 17). In all but one case, echocardiographic localization of thrombus was confirmed independently. In patient 5, the echocardiographic study done 5 weeks before death suggested a large thrombus in the distal part of an apical aneurysm. At autopsy, only a small thrombus was present at the mouth of the aneurysm. In the 5 weeks between echocardiography and death, the patient had had embolic events to both his brain and kidney, which might explain the apparent discrepancy.

Of the 21 true-positive studies, thrombus motion differing from that of the adjacent myocardial wall was noted in only three (patients 8, 13 and 21). In the remaining 18 patients, thrombus motion was similar to that of the adjacent wall, and the thrombus was attached along a broad base that was generally longer than the free edge of the thrombus (figs. 2 and 3).

In most of the true-positive echocardiograms, thrombi had bright, relatively smooth, well-delineated

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**Table 1. Echocardiographic Diagnosis of Positive, Equivocal or Negative Ventricular Thrombus vs True Diagnosis**

<table>
<thead>
<tr>
<th>Echocardiographic diagnosis*</th>
<th>Positive</th>
<th>Equivocal</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus present</td>
<td>19</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Thrombus absent</td>
<td>3</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>7</td>
<td>49</td>
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</table>

*Consensus reading of three observers.
TABLE 2. Data on Patients with Independently Proved Thrombus

<table>
<thead>
<tr>
<th>Pt</th>
<th>ECG infarct location</th>
<th>Interval between echo and proof of thrombus (weeks)</th>
<th>Diagnosis of thrombus</th>
<th>Platelet imaging</th>
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<tr>
<td>1</td>
<td>AMI</td>
<td>0.5</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>0.5</td>
<td>E</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>AMI</td>
<td>0.2</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>AMI</td>
<td>1.0</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>AMI</td>
<td>5.0</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>AMI, DMI</td>
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<td>ND</td>
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<tr>
<td>7</td>
<td>AMI, DMI</td>
<td>0</td>
<td>+</td>
<td>ND</td>
</tr>
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<td>9</td>
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<td>ND</td>
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<td>24</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>20</td>
<td>AMI</td>
<td>1.0</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>21</td>
<td>AMI, DMI</td>
<td>0</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>22</td>
<td>None</td>
<td>3.0</td>
<td>–</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: AMI = transmural anterior myocardial infarction; DMI = transmural inferior myocardial infarction; + = positive for thrombus; − = negative or not present; ND = not done; E = equivalently positive for thrombus.

Free margins (figs. 2–4). Portions of the borders of six thrombi appeared irregular, shaggy or invaginated, often at the junction of the thrombus with the ventricular wall (fig. 4). In most patients, the thrombus mass had a homogeneous, grainy echocardiographic appearance similar to that of normal myocardium (fig. 3). In a few patients, the thrombus appeared slightly more echodense than normal myocardium. In only two cases was a definite area of central lucency seen within the thrombus. In true-positive studies, thrombus size by echocardiography was graded as small (< 1.0 cm in largest dimension) in one patient, medium (1–2 cm) in 10 patients and large (> 2 cm) in 10 patients.

Characteristics of False-positive Echocardiograms

Data from all eight patients with false-positive studies are listed in table 4. No clinical feature helped to separate patients with true-positive from those with false-positive studies. Five of the eight false-positive studies (63%) were read as equivocal. In all false-positive studies, thrombus was thought to be present at the apex. In no case was motion independent of the myocardial wall. The border between the apparent thrombus and the ventricular cavity often did not appear as bright or discrete as in true positive studies (figs. 5 and 6). Thrombus size in false-positive studies was rated as small (< 1.0 cm in largest dimension) in four patients (fig. 5) and medium (1–2 cm) in four other patients (fig. 6). Thus, most of the echocardiograms (four of five) interpreted as showing small thrombi were falsely positive.

Echocardiographic artifacts probably accounted for

**FIGURE 2.** Apical four-chamber view in patient 10, showing an apical thrombus (arrows) whose border is discrete, bright and concave toward the left ventricular cavity. LV = left ventricle; MV = mitral valve; RV = right ventricle.
six of the eight false-positive studies. These artifacts apparently represented reverberations from the transducer itself, from the chest wall or from dense apical myocardial scar. These artifacts appeared as convincing apical intraventricular masses whose borders were often convex towards the ventricular cavity (fig. 6). In one false-positive study in a patient with a large apical aneurysm, the mass of artifact appeared large on the apical long-axis view but markedly smaller on the apical four-chamber view. Such inconsistency in thrombus size when the same area of the ventricle is imaged from different orientations may help detect artifact in some cases, and was not observed in true-positive studies.

In two studies, misinterpretation of the echocardiogram may have been due to alterations in ventricular anatomy. Patient 26 had had a prior aneurysmectomy with insertion of a prosthetic patch. An echocardiogram performed 2 weeks before death (fig. 5) was thought to show a small, bright, irregular apical thrombus. At autopsy, no thrombus was present, but the apex was scarred and irregular as a result of surgery. In patient 27, marked ventricular hypertrophy with marked trabeculation may have been the cause of the apical defect that was interpreted as thrombus.

Clinical Features Associated with Thrombus (table 5)

Myocardial Infarction and Anticoagulation

By electrocardiography, 19 of 22 patients (86%) with proved thrombus had transmural anterior infarctions; four of these patients also had transmural inferior infarctions. No patient with proved thrombus had an isolated inferior infarction by ECG. Two of the three patients with proved thrombus but no electrocardiographic evidence of myocardial infarction had enzymatic documentation of prior myocardial infarction (patients 2 and 12). Thus, all but one patient had ischemic heart disease associated with ventricular thrombus. In contrast, only seven of 56 patients (13%) without thrombus had an anterior infarction by ECG ($p < 0.001$), although 27 (48%) had regional wall motion abnormalities by echocardiography. That is, 19 of 26 patients (73%) with electrocardiographic evidence of transmural anterior infarction (with or without inferior infarction) had ventricular thrombus, compared with three of 52 patients (6%) without anterior infarction ($p < 0.001$). The mean interval from myocardial infarction to echocardiography was 31.3 ± 39.1 months (range 3 weeks to 120 months) in patients with thrombus.

Seven of the 22 patients with proved thrombus had been anticoagulated with heparin or warfarin before echocardiographic study, either transiently at the time of a myocardial infarction (patients 1, 3, 4 and 11) or chronically (patients 2, 3, 11, 15 and 18) for 1 month to 2 years. None of these patients underwent echocardiography before anticoagulation.

Left Ventricular Aneurysm

Sixteen of 22 patients (73%) with documented thrombus had left ventricular aneurysm by two-dimensional echocardiography, compared with only three of 56 patients (5%) without thrombus ($p < 0.001$). Stated differently, 16 of 19 patients (85%) with left ventricular aneurysm by echocardiography had documented thrombus, while only six of 59 patients (10%) without left ventricular aneurysm had thrombus ($p < 0.001$).

Ejection Fraction

Left ventricular ejection fraction was measured by
either radionuclide or contrast angiography in 15 patients with proved thrombus and 24 patients without thrombus. The mean ejection fraction was 0.30 ± 0.15 (range 0.11–0.61) in patients with thrombus and 0.38 ± 0.19 (range 0.09–0.64) in patients without thrombus (NS).

**Systemic Emboli**

Eight of 22 patients (36%) with proved thrombus had clinically diagnosed embolic events before echocardiography, with autopsy confirmation in two (patients 5 and 22) (table 6). In addition, two patients had autopsy evidence of embolization that was clinically silent. Thus, among 22 patients with proved thrombus, 10 (45%) had clinical or autopsy evidence of systemic emboli. One of the 10 patients with proved ventricular thrombus and embolic events had another potential embolic source (septicemia with possible endocarditis).

In contrast, only four of 56 patients (7%) without thrombus had probable clinical embolic events (p < 0.01 vs patients with thrombus), while four other patients without thrombus had emboli only at autopsy. Thus, among patients without thrombus, only eight of 56 (14%) had clinical or autopsy evidence of emboli (p < 0.01). Each of these patients had other potential sources of emboli (table 6).

**Table 3. Sensitivity, Specificity, and Predictive Value of Two-dimensional Echocardiographic Detection of Left Ventricular Thrombi**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive value of a positive test</th>
<th>Predictive value of a negative test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus reading (equivocals counted as positive)</td>
<td>95% (21/22)</td>
<td>86% (48/56)</td>
<td>72% (21/29)</td>
<td>98% (48/49)</td>
</tr>
<tr>
<td>Consensus reading (equivocals counted as negative)</td>
<td>86% (19/22)</td>
<td>95% (53/56)</td>
<td>86% (19/22)</td>
<td>95% (53/56)</td>
</tr>
<tr>
<td>Observer A*</td>
<td>91% (20/22)</td>
<td>95% (53/56)</td>
<td>87% (20/23)</td>
<td>96% (53/55)</td>
</tr>
<tr>
<td>Observer B</td>
<td>95% (21/22)</td>
<td>84% (47/56)</td>
<td>70% (21/30)</td>
<td>98% (47/48)</td>
</tr>
<tr>
<td>Observer C</td>
<td>95% (21/22)</td>
<td>86% (48/56)</td>
<td>72% (21/29)</td>
<td>98% (48/49)</td>
</tr>
</tbody>
</table>

*The only statistically significant difference between observers was the higher specificity of observer A (95%) compared with observer B (84%) (p = 0.05).

**Discussion**

**Accuracy of Echocardiographic Detection of Left Ventricular Thrombus**

This study further establishes the value of two-dimensional echocardiography in detecting left ventricular thrombus. The overall sensitivity of 95% and specificity of 86% are similar to previously reported figures in smaller series.1–4,8 Using our predefined criteria to diagnose ventricular thrombus, we noted excellent observer agreement (88%) and only minor differences in interobserver sensitivity, specificity and predictive accuracy.

The sensitivity and specificity of echocardiography compare favorably with other invasive and noninvasive techniques for detecting left ventricular thrombus. Contrast angiography has a sensitivity of 20–50%;14,16 specificity was 75% (39 of 52 patients) in the largest series.16 We previously reported that noninvasive detection of ventricular thrombus by radionuclide angiography has a sensitivity of 77% (10 of 13 patients) and a specificity of 88% (23 of 26 patients).11 Echocardiography, with its intrinsically higher resolution, generally offers better visualization of ventricular thrombi than does radionuclide angiography. Although a filling defect on the anterior view of the radionuclide angiogram may be a useful clue to the

**Table 4. Data on Patients with False-positive Echocardiograms**

<table>
<thead>
<tr>
<th>clinical features</th>
<th>diagnosis of thrombus</th>
<th>platelet imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>pt</td>
<td>echo</td>
<td>autopsy</td>
</tr>
<tr>
<td>23</td>
<td>AMI</td>
<td>E</td>
</tr>
<tr>
<td>24</td>
<td>AMI, DMI</td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>LBBB</td>
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<td>30</td>
<td>None</td>
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</table>

Abbreviations: AMI = transmural anterior myocardial infarction; DMI = transmural inferior myocardial infarction; LBBB = left bundle branch block; E = equivocally positive for thrombus; + = positive for thrombus; – = negative or not present; ND = not done.
presence of thrombus, we prefer to use two-dimensional echocardiography to screen for thrombus.

We and others have reported the detection of ventricular thrombus by indium-111 platelet imaging. Although the sensitivity of platelet imaging may prove to be similar to that of echocardiography, platelet imaging is time-consuming, not widely available, and necessitates radiation exposure.

Limitations of the Echocardiographic Detection of Thrombus

Technically satisfactory echocardiograms were not always obtainable. In this study, 10 of 88 echocardiograms (11%) were excluded as technically inadequate, always because the apex was not well visualized. Our experience contrasts with that of Bansal et al., who obtained adequate apical views in 99% of 200 patients. Their data suggest that a more thorough examination of the apex may have been feasible and productive in some of the patients we excluded. Because most thrombi occur at the apex, a study that does not show the apex well does not exclude thrombus. Indeed, one of our patients with a technically inadequate study had thrombus at autopsy.

Another limitation of echocardiography is that, unlike platelet imaging, it may not define thrombus activity. Presumably, fresh and hematologically active thrombi are more likely to embolize than old organized thrombi. In a preliminary report, Mikell et al. noted that some recently formed left ventricular thrombi had dynamic mobile echoes of at least two types. These investigators also noted that free intracavitary thrombus motion correlated with embolization. In the current study, echocardiographic was performed only after embolic events had occurred; we noted such independent thrombus motion in only three patients. Although two of these three patients had had embolic events, eight other patients with immobile thrombi had also had embolic events. In this study, the echocardiographic size of the thrombus, as estimated visually, did not correlate with embolic events. Thus, in our retrospective review of patients with generally remote myocardial infarction and systemic emboli, we did not identify any echocardiographic feature other than the presence of thrombus that correlated with embolization. Acutely formed thrombi may have echocardiographic characteristics predictive of embolization that differ from those of chronically formed thrombi. Prospective studies are needed to define echocardiographic features predictive of embolization in both patient groups.

Minimizing False-positive Diagnoses

The main limitation of the echocardiographic diagnosis of thrombus in this study was that eight of 29
positive or equivocal studies (28%) were falsely positive. Reeder et al.\textsuperscript{4} found three of 14 studies (21%) to be falsely positive. Asinger et al.\textsuperscript{6} noted several echocardiographic features that may falsely suggest a diagnosis of thrombus, including echocardiographic artifact, muscular trabeculae, aneurysmal shelves, chordal structures and prominent papillary muscles.

Detailed review of our eight false-positive cases identified several features that may improve the specificity of echocardiography. Although these guidelines may be helpful in decreasing false-positive studies, no criteria are foolproof. When we were uncertain as to the presence of thrombus, echocardiograms were interpreted as equivocal. Such equivocal studies were more likely to be falsely positive (five of seven, 71%) than studies read as positive (three of 21, 14%) ($p = 0.01$). In this study, if equivocal studies were counted as negative, the predictive value of a positive test improved from 72% to 86%, while the predictive value of a negative test declined only slightly, from 98% to 95%. Thus, equivocal studies should probably be considered negative. In addition, studies in which there was observer disagreement were more likely to be falsely positive (six of eight, 75%) than studies in which there was observer agreement (two of 20, 10%) ($p < 0.01$). In difficult cases, if multiple experienced observers disagree, the study should probably be interpreted as negative.

### Table 5. Clinical Features Associated with Proved Thrombus

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Patients with thrombus (n = 22)</th>
<th>Patients without thrombus (n = 56)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG anterior infarction</td>
<td>86% (19/22)</td>
<td>13% (7/56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ventricular aneurysm by echo</td>
<td>73% (16/22)</td>
<td>5% (3/56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Abnormal wall motion by echo</td>
<td>100% (22/22)</td>
<td>48% (27/56)</td>
<td></td>
</tr>
<tr>
<td>Mean ejection fraction (39 patients)</td>
<td>0.30 ± 0.15</td>
<td>0.38 ± 0.19</td>
<td>0.18</td>
</tr>
<tr>
<td>Clinical emboli</td>
<td>36% (8/22)</td>
<td>7% (4/56)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Clinical or autopsy emboli</td>
<td>45% (10/22)</td>
<td>14% (8/56)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

### Table 6. Embolic Events in Patients With and Without Left Ventricular Thrombus

<table>
<thead>
<tr>
<th>Pt</th>
<th>Echo Dx of thrombus</th>
<th>Other embolic sources</th>
<th>Clinical emboli</th>
<th>Autopsy emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with thrombus (n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>—</td>
<td>None</td>
<td>Spleen</td>
</tr>
<tr>
<td>2</td>
<td>E</td>
<td>—</td>
<td>Cerebral—TIA</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>—</td>
<td>None</td>
<td>Kidney, aortic bifurcation</td>
</tr>
<tr>
<td>5</td>
<td>E</td>
<td>—</td>
<td>Cerebral—multiple strokes</td>
<td>Brain, kidney</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>—</td>
<td>Cerebral—transient cortical blindness</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>—</td>
<td>Cerebral—multiple infarct dementia</td>
<td>NA</td>
</tr>
<tr>
<td>15</td>
<td>+</td>
<td>—</td>
<td>Cerebral—stroke and TIA</td>
<td>NA</td>
</tr>
<tr>
<td>18</td>
<td>+</td>
<td>—</td>
<td>Cerebral—stroke</td>
<td>NA</td>
</tr>
<tr>
<td>21</td>
<td>+</td>
<td>Bacteremia, ? endocarditis</td>
<td>Cerebral—stroke</td>
<td>NA</td>
</tr>
<tr>
<td>22</td>
<td>—</td>
<td>—</td>
<td>Cerebral—multiple strokes</td>
<td>Brain, kidney</td>
</tr>
<tr>
<td></td>
<td>Patients without thrombus (n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>E</td>
<td>CNS lupus ?</td>
<td>Cerebral ?, TIA</td>
<td>— (brain not examined)</td>
</tr>
<tr>
<td>31</td>
<td>—</td>
<td>Marantic endocarditis</td>
<td>—</td>
<td>Spleen</td>
</tr>
<tr>
<td>32</td>
<td>—</td>
<td>Aortic atherosclerosis</td>
<td>—</td>
<td>Kidney, spleen</td>
</tr>
<tr>
<td>33</td>
<td>—</td>
<td>Bacterial endocarditis</td>
<td>Cerebral—stroke</td>
<td>Kidney, spleen, brain, heart</td>
</tr>
<tr>
<td>34</td>
<td>—</td>
<td>Mitral stenosis, atrial fibrillation</td>
<td>—</td>
<td>Kidney, spleen</td>
</tr>
<tr>
<td>35</td>
<td>—</td>
<td>Atrial fibrillation</td>
<td>Cerebral—stroke</td>
<td>Brain</td>
</tr>
<tr>
<td>36</td>
<td>—</td>
<td>TTP</td>
<td>Cerebral ?, coma</td>
<td>Brain, spleen</td>
</tr>
<tr>
<td>37</td>
<td>—</td>
<td>Marantic endocarditis</td>
<td>—</td>
<td>Kidney</td>
</tr>
</tbody>
</table>

Abbreviations: E = equivocally positive; + = positive; — = not present; CNS = central nervous system; NA = not available; TIA = transient ischemic attack; TTP = thrombotic thrombocytopenic purpura.
Thrombi that appeared small (less than 1.0 cm in the largest dimension) were falsely positive in four of five cases. Thus, assessment of thrombus size may help minimize false-positive diagnoses. Anatomic alterations from ventricular surgery or prominent trabeculation in hypertrophied ventricles may also be misinterpreted as thrombi. In this series, such anatomic variants also presented as small defects. Artificial filling defects originating from reverberations in the near field generally had a convex border bulging into the left ventricular cavity; at least some portion of true thrombi was usually concave. Also, some artifacts simulating thrombi had multiple bright radial lines. When such lines projected beyond the myocardium, they were easily distinguished from thrombus, but when they appeared completely within the ventricle, as in patients with large hearts, distinguishing artifact from thrombus was often difficult. Artifacts did not have motion independent of the ventricular or chest wall, but in our series neither did most proved thrombi. In many false-positive cases, the artifact-blood boundary was not as distinct or sharp as the borders of true thrombi. Thrombi were consistent in size and location from view to view; artifacts often were not. Thus, views using multiple transducer locations with variable gain settings may help distinguish artifact from thrombus (fig. 4).

**Clinical Features Associated with Ventricular Thrombi**

Clinical features that were very common in patients with left ventricular thrombi included transmural anterior myocardial infarction and ventricular aneurysm. In addition, left ventricular ejection fraction tended to be lower in patients with than in those without thrombus, as previously described. These findings are in agreement with earlier clinical and autopsy studies that showed that anterior infarction, transmural infarction, and ventricular aneurysm were associated with ventricular thrombus. Other risk factors include congestive heart failure, multiple infarctions, size of infarction and idiopathic dilated cardiomyopathy. Awareness of these factors may increase the clinical suspicion of thrombus and lead to earlier identification of patients at risk for systemic embolization. In addition, the absence of these clinical features defines a group of patients who are at very low risk for left ventricular thrombus. This group, which is composed of patients without either transmural anterior infarction, left ventricular aneurysm or low ejection fraction, would be very unlikely to benefit from echocardiography performed to rule out left ventricular thrombus.

The frequency with which ventricular thrombi cause clinically significant embolic events is unknown. Several studies in which left ventricular thrombus was diagnosed during life by either contrast angiography or echocardiography have suggested that less than 25% of patients with ventricular thrombus have clinically detected embolization. In the present series, 36% of patients with ventricular thrombus had a history of probable or definite clinical embolic events, and 45% of patients with thrombus had either clinical or autopsy evidence of embolization. Our findings are in agreement with autopsy studies in which 33–64% of patients with cardiac thrombus had autopsy evidence of systemic embolization, although many embolic events were clinically silent.

Several reports of relatively small numbers of patients suggest that anticoagulation may prevent left ventricular thrombus formation or lead to thrombus resolution. At least seven of the 22 patients with thrombus in this series had been fully anticoagulated after infarction for up to 2 years before the diagnosis of thrombus. Thus, anticoagulant therapy does not prevent thrombus formation or lead to resolution in all patients. The influence of anticoagulation on ventricular thrombus formation, resolution or embolization remains to be determined prospectively.

**Study Limitations**

This study represents a retrospective analysis of echocardiograms from patients who had another independent definitive diagnostic procedure. One inherent weakness is that the population was not representative of all patients who undergo echocardiography. For example, our study group included only one patient with an idiopathic cardiomyopathy who had a thrombus and only one patient who had a recent myocardial infarction. Thus, our results may not be applicable to all patient groups.

Because this study was retrospective, there was often a delay between the echocardiogram and the definitive diagnostic procedure, which averaged 4.5 weeks for all 78 patients. Some thrombi could have developed, resolved, or embolized during this interval. None of the eight patients with false-positive echocardiograms had evidence of systemic embolization between echocardiography and autopsy or cardiac operation to account for disappearance of thrombus, and only patient 23 had received anticoagulation during this interval. However, the interval between echocardiography and the definitive diagnosis was significantly longer in patients with false-positive studies (9.3 ± 11.1 weeks) than in patients with true-positive studies (1.8 ± 5.2 weeks, p = 0.02). Thus, some thrombi may have resolved spontaneously. Also, the one patient with hypercoagulability and a false-negative echocardiogram (patient 22) may have developed a thrombus during the 3 weeks between echocardiography and autopsy.

Fifteen patients were included in this study on the basis of having a thrombus identified by indium-111 platelet imaging. Neither we nor others have ever noted a platelet imaging study falsely positive for thrombus. Nonetheless, the number of positive platelet scans with autopsy or operative confirmation remains small. Platelet imaging may detect only relatively large ventricular thrombi, which, because of their size, may be easily detectable by echocardiography. However, echocardiography detected a similar proportion of thrombi defined by platelet imaging (15 of 15) as by autopsy or cardiac operation (six of seven). Because
this was a retrospective study in which many patients with thrombus did not have surgery or autopsy, information on the actual size of many of the thrombi detected by echocardiography is limited. Although our arbitrary system for visually grading thrombus size appeared helpful in identifying false-positive studies, we do not have adequate data to determine the reliability with which echocardiography measures thrombus size.

Only two two-dimensional echocardiographic instruments were used; most of the patients with proved thrombus were studied by a phased-array scanner. Instrument design characteristics may alter the appearance of ventricular thrombi. Phased-array transducers generally have more near-field transducer artifacts and, because of their smaller elements, generate more side lobes. Mechanical scanners, on the other hand, are often less easily applied to the apical window, and the near-field resolution of their large-dimension elements is not ideal. In this series, we did not study the same patients with different instruments. Different results might have been obtained with different instruments.

Clinical Implications

Several clinical features define a group of patients who are most likely to benefit from echocardiography to detect left ventricular thrombus. In patients with clinically suspected left ventricular thrombus, two-dimensional echocardiography is our initial procedure of choice for determining the presence or absence of thrombus. Most patients with left ventricular thrombus can be reliably detected by two-dimensional echocardiography, which has a high sensitivity (95%) but a somewhat lower specificity (86%). Attention to several echocardiographic details, including the size, shape and margin of the thrombus, may help minimize false-positive diagnoses. In patients in whom the echocardiogram is technically inadequate or equivocal, platelet imaging may be helpful. Further studies using these improved noninvasive diagnostic techniques for the detection of thrombi are needed to define the natural history of left ventricular thrombi and the role of anticoagulant and antiplatelet drugs.

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Assessment of Myocardial Perfusion Abnormalities with Contrast-enhanced Two-dimensional Echocardiography

WILLIAM F. ARMSTRONG, M.D., THOMAS M. MUELLER, M.D., EVLIN L. KINNEY, M.D.,
E. GLENN TICKNER, M.S., JAMES C. DILLON, M.D., AND HARVEY FEIGENBAUM, M.D.

SUMMARY A new echocardiographic contrast agent, gelatin-encapsulated microbubbles, that produces
an intramyocardial contrast effect, was evaluated as a marker for the detection of regions of abnormal
myocardial perfusion in nine open-chest dogs. The gelatin-encapsulated microbubbles were injected into
the aortic root under control conditions and during circumflex coronary artery occlusion. Myocardial
perfusion was simultaneously assessed with radioactive microspheres. Echocardiographic contrast en-
hancement (ECE) was measured in footlamberts (Fl-L) from the videoscreen of an off-line playback system,
using a commercially available light meter. A single short-axis section of the left ventricle was divided into
octants to analyze myocardial perfusion. The equivalent regions of the echocardiographic image were
analyzed for contrast enhancement and wall motion. An ECE > 0.3 Fl-L was seen in all 120 octants
analyzed before circumflex coronary artery occlusion and in 48 of 51 (94%) octants with > 50% of the
normal zone flow during circumflex artery occlusion. An ECE < 0.3 Fl-L identified 19 of 21 octants (90%)
with 50% normal zone flow and all 13 octants with 25% normal zone flow during coronary artery
occlusion. In contrast, wall motion abnormalities (akinesis or dyskinesia) were seen in 13 of 51 octants
(25%) with > 50% normal zone flow, and normal wall motion was seen in two of 21 octants (10%) with
blood flow 50% of normal zone flow during circumflex coronary artery occlusion. We could not
demonstrate a linear correlation between ECE and the absolute level of myocardial blood flow. We feel this
was due to the limitations imposed by imaging an open-chest animal preparation, variation in the number
of gelatin-encapsulated microbubbles used for each injection and variations in the echocardiographic gain
settings among experiments. We conclude that contrast-enhanced two-dimensional echocardiography with
gelatin-encapsulated microbubbles can accurately identify ischemic regions of the left ventricular myocar-
dium. This technique is more accurate than wall motion analysis for detecting myocardial ischemia.

A NEW CLASS of ultrasound contrast agents has been
developed that offer the possibility of determining the
distribution of myocardial blood flow with two-dimen-
sional echocardiography. These agents are encapsulat-
ed gas microbubbles, which are highly reflectant and
are the source of ultrasonic contrast effect. When in-
jected into the circulation, these microbubbles produce
an intense contrast effect that lasts several seconds to
several minutes. The degree of contrast enhancement is
considerably greater than that provided by agents
such as indocyanine green dye and saline. When
injected into the coronary circulation, the microbub-
bles reproducibly and markedly increase the intensity
of the echocardiographic image of the myocardium
(fig. 1). This effect is not seen after injecting standard
contrast agents. To test whether one of these agents,
gelatin-encapsulated microbubbles, could serve as a
marker for left ventricular perfusion, we compared
two-dimensional echocardiographic videodensity after
the injection of gelatin-encapsulated microbubbles
with myocardial blood flow measured with radiola-
beled microspheres. The presence or absence of con-
current wall motion abnormalities was also evaluated
as a marker for myocardial ischemia, and compared
with results of contrast echocardiography and myocar-
dial perfusion studies.

From the Krannert Institute of Cardiology, the Department of Medi-
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Dr. Kinney is recipient of a Clinical Scientist award from the Ameri-
can Heart Association.

Address for correspondence: William F. Armstrong, M.D., Indiana
University School of Medicine, Hospital N56Z, 1100 West
Michigan Street, Indianapolis, Indiana 46223.

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