Echocardiographic Documentation of Vegetative Lesions in Infective Endocarditis: Clinical Implications

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SUMMARY Eighty-seven patients with the clinical syndrome of infective endocarditis were examined by M-mode and two-dimensional echocardiography. Patients were divided into two groups based on the presence or absence of echocardiographically detected vegetative lesions. Group 1 consisted of 47 patients with one or more vegetations. Group 2 consisted of 40 patients without evidence of vegetations. Group 1 patients had a higher rate of complications: emboli, congestive heart failure and the need for surgical intervention. Analysis of morphologic characteristics of the vegetations in group 1 was of no predictive value for complications in individual patients. Two-thirds of the vegetations persisted unaltered well beyond the period of bacteriologic cure without significant complications. No characteristic alteration of the vegetations predicted the efficacy of medical therapy.

Although the detection of vegetations by echocardiography in patients with the clinical syndrome of endocarditis clearly identifies a subgroup at risk for complications, decisions regarding clinical management made solely on the basis of the presence or absence of vegetative lesions are hazardous. Management of such patients must continue to be based on the clinical integration of multiple factors.

ECHOCARDIOGRAPHY contributes to the diagnosis and management of patients with infective endocarditis. Recent studies have suggested a high incidence of embolization, valvular destruction and congestive heart failure in patients with echocardiographically detected vegetations. As many as 90–100% of these patients have been reported to require surgical intervention, a finding that conflicts with our recent experience. At the same time there is little information concerning the ultimate fate of vegetations by echocardiography in patients undergoing successful medical treatment.

This prospective study was undertaken to further clarify the clinical implications of echocardiographically detected vegetations in patients with endocarditis. First, vegetation location, size and morphology were studied on the hypothesis that these factors influence clinical course and outcome. Second, serial changes in vegetation size were evaluated on the hypothesis that such changes are an index of the success or failure of medical therapy.

Methods

Patients

From July 1975 to March 1978, 426 patients, ages 17–75 years, with suspected infective endocarditis were referred for echocardiographic assessment. Echocardiographic examination was part of a routine assessment for all patients admitted or referred to Duke University Medical Center with suspected infective endocarditis. Patients were excluded from the study if they had poor-quality sound transmission characteristics precluding adequate interpretation, prosthetic valves or a history of vegetative endocarditis. Patients who did not meet the clinical and laboratory criteria for the diagnosis of infective endocarditis were also excluded.

Strict clinical and laboratory criteria were used in diagnosing infective endocarditis. Clinical evidence included one or more of the following: persistent fever, intermittent chills, night sweats, arthralgia, cardiac murmur and evidence of peripheral or cutaneous embolization. Laboratory evidence included anemia and elevation of sedimentation rate; all patients had one or more positive blood cultures.

In 333 patients, clinical criteria were not met or some other site of infection was clinically determined. Six patients were excluded from the study because of technically inadequate echocardiographic examinations. The remaining 87 patients constitute our study group. All 87 patients were treated medically on the basis of clinical and laboratory data. The medical records were reviewed for details of antibiotic treatment, the presence or absence of congestive heart failure, embolic phenomena, the necessity for surgical intervention and the ultimate clinical outcome.

Echocardiographic Methods

Time-motion echocardiograms were obtained on all patients using commercially available echocardiographic systems with 2.25-MHz, 13-mm, 7.5-cm focused transducers. Examinations were performed using standard techniques. Two-dimensional echocardiographic examinations were obtained on all patients using previously described and/or commercially available focused, phased-array imaging systems. Images were obtained in the standard cross-sectional planes of the heart, as previously described, and stored on videotape for later playback and analysis.
Echocardiographic Criteria

M-mode detection of valvular vegetations was done according to previously described criteria.\textsuperscript{4, 15, 16} Two-dimensional examinations were considered positive when they showed evidence of mass lesions, sessile or pedunculated, involving the cardiac valves or endocardial surfaces.\textsuperscript{6}

Echocardiographically detected lesions were classified according to location, morphology and size. Location was denoted by single or multiple valve involvement and by the specific valves affected by the vegetative process. Because the vegetative lesions were often amorphous, quantitative sizing at the time of the two-dimensional examination was made by measuring along the longest diameter. Lesions were recorded as small (less than 5 mm), medium (6-10 mm) or large (greater than 10 mm). For purposes of follow-up, lesions that increased or decreased in size were required to move one or more classes (e.g., small to medium) in order to avoid small measurement errors.

Follow-up Examinations

Echocardiographic evaluation was performed before or during the initiation of antimicrobial therapy in all 87 patients. In the patients with echocardiographically detected vegetations (group 1), serial evaluations were performed in the first, middle and last third of medical therapy. Treatment courses ran from 4-6 weeks, depending on the organism involved. Multiple echocardiographic evaluations were performed during convalescence and, for the purposes of this presentation, intervals were defined by less than 1 month, 1-6 months and more than 6 months after therapy.

Group 1 is the main study group of this report. Clinical follow-up of the patients without echocardiographically detected vegetations (group 2) was maintained; however, serial echocardiographic follow-up of patients in this group was sporadic and only occasionally complete. Data derived from this group are used only where appropriate.

Results

Initial Echocardiographic Observations

Forty-seven of the 87 patients (54\%) had echocardiographically demonstrable valvular or endocardial lesions consistent with vegetative endocarditis (group 1). The remaining 40 patients had no vegetative lesions by echocardiography (group 2). Sixty-three vegetations were found in the 47 group 1 patients; the location and morphologic characteristics of the vegetations are summarized in tables 1 and 2. Four patients had nonvalvular endocardial lesions involving left ventricular mural endocardium or chordae tendineae, as well as vegetative involvement of either the aortic or mitral valve.

Follow-up Echocardiographic Studies

The number of group 1 patients who had serial echocardiographic examinations is shown in table 3.

All 47 patients had examinations spanning at least two of the three time periods during treatment, regardless of clinical disposition. Twenty-nine patients had examinations spanning two or more convalescent time periods, although six were ultimately operated. One hundred seventy-nine two-dimensional examinations were available for review.

The fate of echocardiographically detected lesions with respect to changes in size classification is summarized in table 4 (fig. 1). Echocardiographic follow-up in group 1 patients ranged from 2 weeks to 36 months (mean 16 months).

Clinical follow-up regarding late medical death and occurrence of new emboli or congestive heart failure was complete in all 47 group 1 patients. The nine transferred patients were followed by telephone or mail contact. Similar means were used for clinical follow-up in group 2.

Clinical Correlations

Embolic events occurred in 14 of 47 patients (30%) in group 1, six during antimicrobial therapy and eight after completion of therapy. Cerebrovascular emboli was the most frequently observed embolic event. Congestive heart failure developed in 15 of 47 patients (30%). Nine patients developed heart failure during antimicrobial therapy and six patients developed heart

<table>
<thead>
<tr>
<th>Location of Vegetative Lesions</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single valve involved (n = 36, 77%)</td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>18</td>
</tr>
<tr>
<td>Mitral</td>
<td>12</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>6</td>
</tr>
<tr>
<td>Two valves involved (n = 10, 21%)</td>
<td></td>
</tr>
<tr>
<td>Aortic and mitral</td>
<td>8</td>
</tr>
<tr>
<td>Tricuspid and mitral</td>
<td>2</td>
</tr>
<tr>
<td>Three valves involved (n = 1, 2%)</td>
<td></td>
</tr>
<tr>
<td>Aortic, mitral and tricuspid</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
</tr>
<tr>
<td>Additional nonvalvular involvement*</td>
<td>4</td>
</tr>
</tbody>
</table>

*See text.

<table>
<thead>
<tr>
<th>Morphologic Characteristics of Lesions</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive variable</td>
<td>n</td>
</tr>
<tr>
<td>Size (n = 63)</td>
<td></td>
</tr>
<tr>
<td>Small (0-5 mm)</td>
<td>26</td>
</tr>
<tr>
<td>Medium (6-10 mm)</td>
<td>27</td>
</tr>
<tr>
<td>Large (&gt; 10 mm)</td>
<td>10</td>
</tr>
<tr>
<td>Morphology (n = 63)</td>
<td></td>
</tr>
<tr>
<td>Sessile</td>
<td>28</td>
</tr>
<tr>
<td>Pedunculated</td>
<td>35</td>
</tr>
</tbody>
</table>
Table 3.  

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total*</th>
<th>Died</th>
<th>Operated</th>
<th>Transferred</th>
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</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>47</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Convalescence</td>
<td>29</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

*Number of patients in whom serial studies were available.

failure during convalescence. Four patients with echocardiographic evidence of valvular disruption (flail mitral, tricuspid or aortic leaflets) and three patients with mitral valve preclosure had congestive heart failure.

Twelve of 47 patients in group 1 (25%) required surgical intervention, six patients during antimicrobial therapy and six during convalescence after bacteriologic cure. Refractory congestive heart failure, the clinical indication for surgical intervention in 11 of the 12 patients, was caused by aortic regurgitation in eight cases and mitral insufficiency secondary to flail mitral leaflet in three cases. The other patient underwent surgery because of persistent bacteremia and a resistant organism and had a large tricuspid valve vegetation and tricuspid insufficiency. Eight of the 12 patients underwent surgery on the basis of echocardiographic and clinical findings without prior cardiac catheterization. Seven patients had aortic valve, three mitral, one tricuspid and one aortic and mitral valve replacements.

Mortality in group 1 was 11% (five of 47). All five deaths occurred during antimicrobial therapy. Two patients died during or immediately after surgical intervention, both from low cardiac output syndromes. Three medically treated patients died, and in each case the patient was considered inoperable on the basis of refractory congestive heart failure, coexistent coronary artery disease and/or renal failure.

Size, morphology and location of vegetations did not relate to the presence or absence of embolic events, congestive heart failure, medical/surgical death or the need for surgical intervention in group 1 patients.

Among the 40 group 2 patients, embolic events occurred in four (10%), congestive heart failure in one (2%) and death during medical therapy in two (5%). In addition, two group 2 patients were operated for persistent bacteremia and both were found to have valve ring abscesses but not valvular vegetations.

Pathologic Correlations

Bacteriologic findings in group 1 patients are presented in table 5. *Staphylococcus aureus* was the most frequent organism in this series, followed by *Streptococcus viridans*. Staphylococcal infections were present in five of the 12 patients requiring surgical intervention and were involved in three of the five deaths (one surgical and two medical). A streptococcal infection and an unidentified organism accounted for the other two deaths.

Pathologic material was available for examination in all 14 surgically treated patients (twelve group 1 patients and two group 2 patients). An additional three patients underwent autopsy (two group 1 patients and one group 2 patient). The results of echocardiography agreed with those obtained by gross inspection in all cases.

Discussion

Presence of Vegetative Lesions

Previous autopsy studies have reported vegetative valvular lesions in 53% of patients who died of active infective endocarditis. The present study found echocardiographically demonstrable valvular vegetations in 54% of the patients. Obviously, pathologic studies involve populations with 100% mortality, while in the present series mortality was only 11%. The di-

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Table 4. Changes in Echocardiographically Detected Vegetations During Therapy and Convalescence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>New</th>
<th>Increased in size</th>
<th>Decreased in size</th>
<th>Stable</th>
<th>Gone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Convalescence</td>
<td>0</td>
<td>7</td>
<td>4</td>
<td>34</td>
<td>2</td>
</tr>
</tbody>
</table>

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Figure 1. Stop-frame and accompanying schematic drawings in the long axis of the left ventricle with a mitral vegetative mass at the onset of treatment (panels A and B) and 10 weeks later (panels C and D). The size of the lesion is unchanged after completion of successful medical therapy. The image was obtained with a phased-array device operating in the compound-scan format, which accounts for the double origin of the arrays in each image. LV = left ventricle; LA = left atrium.
crepancy is explained when risk factors other than the presence of vegetations are considered.\textsuperscript{17-19} In the autopsy series, congestive heart failure was present in as many as 75\% of the patients, compared with 32\% in the present series. In addition, 76\% of patients in the autopsy series were infected with highly virulent organisms (staphylococcal infections occurred in 55\% of patients), while 67\% had predisposing factors such as heroin addiction, alcoholism, malignancy or cardiac surgery. The frequency of infection with virulent organisms in the present series was noticeably less (staphylococcal infection occurred in 27\% of group 1 patients) and the predisposing factors seen in the pathologic series were uncommon in the present series. Thus, factors other than the presence of vegetative lesions are important in determining clinical outcome.

The distribution of valvular involvement by the vegetative process in the present series closely approximated that in the autopsy series.\textsuperscript{17} Ventricular endocardial lesions were observed in four cases, associated in each instance with primary aortic or mitral valve involvement. Presumably, these represent contiguous spread from a mitral lesion to the chords or “seeding” from an aortic lesion to the ventricular endocardial surface.\textsuperscript{18, 20} Isolated endocardial involvement without primary valvular lesions has been described pathologically in patients with ventricular septal defect or immunologic compromise.\textsuperscript{18} Patients in this series with endocardial and/or multiple valvular involvement tended to have a more complicated course: four of these patients required surgical intervention early in the course of therapy. The prognostic significance of these findings should be interpreted with caution because of the small number of patients.

Results from the current series support published data regarding the ability of two-dimensional echocardiography to assess the location, size and morphology of vegetative lesions.\textsuperscript{8} Of particular interest was the echocardiographic absence of vegetative lesions in the three group 2 patients who came to surgery or autopsy. Two of these patients were treated surgically and had ring abscesses but no discernible valvular vegetations. The other patient died of septicemia and myocardial infarction. At postmortem examination no vegetative lesions were found and the site of infection was determined to be renal.

**Influence of Medical Therapy on Vegetation Size and Morphology**

Reports in which echocardiographically detected vegetations were followed during therapy and convalescence are sparse. Isolated reports documenting no change, an increase or decrease in size or complete disappearance of the vegetations at varying intervals have been published.\textsuperscript{5, 11, 12, 21} These reports had small numbers of patients who were examined on fewer occasions at widely varying intervals in relation to antimicrobial therapy. The majority of these findings were based on M-mode observations alone, and the vegetative lesions were not classified by size or morphologic characteristics.

In the present series, almost two-thirds of the echocardiographically detected vegetations remained stable with respect to size and morphology throughout therapy and for as long as 36 months after bacteriologic cure. Complete disappearance was noted in five of 63 (8\%), three during antimicrobial therapy and two during convalescence. Lesion disappearance correlated with embolic events in only two cases, each from the tricuspid valve during therapy.

There was no relationship between change in lesion size or morphology and efficacy of antimicrobial therapy. In addition, classification of the vegetative lesions according to size was of little value in predicting associated clinical phenomena: infection with particular organisms, occurrence of embolic events or necessity for surgical intervention. Patients with small vegetations were as likely to develop complications as those with larger vegetations. Thus, evaluating change in the appearance of the vegetation as an approach to evaluating the efficacy of medical therapy seems limited.

**Complications and Need for Surgical Intervention**

Embolic phenomena are common in infective endocarditis. Before antimicrobial therapy, embolic rates ranged from 20-80\%; with effective antibiotic treatment, embolic rates decreased to 15-30\%.\textsuperscript{22, 23} Among the highest rates of embolization in echocardiographic series is 43\% reported by Roy.\textsuperscript{8} Isolated instances in which clinically occurring embolic events were closely related to echocardiographic disappearance of the vegetation have also been reported.\textsuperscript{5, 10}

Embolic events occurred in 30\% of group 1 patients, with the highest frequency occurring after completion of antimicrobial therapy. Embolic events occurred in fewer than 10\% of group 2 patients. Weinstein noted...
that successful bacteriologic cure does not preclude the occurrence of embolic disease as long as several years after successful antimicrobial therapy. Extended duration of illness and highly virulent organisms have predisposed to embolic episodes. The patient with an echocardiographically detected vegetation is at higher risk for an embolic event than the patient without evidence of vegetative lesions. On the other hand, failure to detect such lesions does not protect against the occurrence of an embolic event. Unfortunately, analysis of location, size and morphologic characteristics of the detected vegetation was of little aid in identifying patients who were more likely to have an embolus.

Data from the present series suggest that the presence of echocardiographically manifest vegetative lesions does not imply as high a patient risk as previously reported. Wann noted valvular disruption in 54%, congestive heart failure in 100% and death or the need for surgical intervention in 91% of patients with lesions by M-mode echocardiography. These rates are considerably higher than those of 15%, 32% and 25%, respectively, reported in the current series.

The reasons why patients in Wann's series appeared more ill and had a higher prevalence of more virulent organisms are not readily apparent. Patterns of patient referral might differ between institutions, resulting in less severely ill patients being incorporated into the present series. Although not likely, different echocardiographic criteria for the presence of vegetative lesions might have been used. Differences in ultrasonic diagnostic instrumentation (M-mode vs two-dimensional) may also be a factor. Another unlikely possibility is that regimens of medical therapy or indications for surgical intervention may differ between institutions.

Such differences in complication rates between series should not be distracting. As in the series of Wann and others, patients in the current study with echocardiographically detected vegetations who had convective heart failure almost invariably required surgical intervention. The need for surgery in such patients remains irrefutable.

Seventy percent of patients in the present series completed successful medical treatment and entered convalescence with remaining vegetative lesions. These data indicate that surgery based solely on the presence of echocardiographically detected lesions in patients with endocarditis is unwarranted. They also support Wann's suspicion that a decision for surgery should be based on a combination of factors, especially the presence of refractory heart failure. The mere presence of vegetations should not imply that all patients will have valve leaflet destruction. In an autopsy series, Buchbinder and Roberts showed that 35% of patients with aortic valve vegetations and 63% of patients with mitral valve vegetations had no evidence of valvular disruption. In group 1, 87% of patients with aortic and 85% with mitral involvement had no echocardiographic evidence of disruption. When vegetations are present, aortic cusp fenestration or avulsion and mitral chordal rupture or flail leaflet may be difficult to evaluate by echocardiography.

Echocardiographically detected vegetations adversely affect prognosis when they are associated with flail aortic or mitral leaflets, significant aortic regurgitation with mitral valve preclosure, vegetations on more than one left-sided valve and/or involvement of mitral chordae and left ventricular endocardium, or infection with more virulent organisms. The prognostic significance of the majority of these findings agrees with published observations.

Echocardiographic Limitations

Only 54% of patients in the present series had echocardiographically detectable vegetations despite firm clinical and laboratory evidence of infective endocarditis. This apparent lack of sensitivity has been reported by other investigators. It is not clear why some patients with endocarditis develop vegetations while others do not. The fact that autopsy series reveal a similar occurrence of vegetations suggests that either two forms of endocarditis exist (one with and one without vegetations) or that the clinical diagnosis of vegetative endocarditis may often be misapplied. Further study of the endocarditis syndrome is warranted.

The size of the vegetation is an important factor in its echocardiographic detection. Most vegetations in this study were smaller than 10 mm. The largest vegetations tended to be associated with right-sided endocarditis, confirming the observation of others. Given the present resolution characteristics of echocardiographic equipment, it is unlikely that vegetations smaller than 2 mm will be easily differentiated from surrounding leaflet or endocardial surfaces. Thomson et al., however, detected 1–2 mm lesions when they were calcified.

The type of echocardiographic examination performed may also be important. Because of its wider field of view, two-dimensional echocardiography may be more suitable for the initial detection of vegetations. In the experience of this laboratory, such lesions detected by one echocardiographic method may easily be detected by the other. Examinations are begun by the two-dimensional approach and suspected lesions are identified. This method is helpful in directing M-mode examination toward documentation of all lesions, particularly when they are small or located in remote areas not commonly interrogated during a routine M-mode examination. Because of the high pulse repetition rate and display format, M-mode is superior to two-dimensional methods for documenting the rapid oscillations typical of vegetative endocardial lesions.

The timing of examination may be another important factor determining sensitivity. A review of reported cases indicates that vegetative lesions are rarely detected until 2 weeks after the onset of symptoms. Lesions may also develop after institution of antimicrobial therapy, as shown by the appearance of five new lesions during the course of therapy in the
present series. Other reasons for lack of sensitivity have been reported,\textsuperscript{4, 7, 16} including inadequate visualization of cardiac structures due to poor sound transmission characteristics, improper instrument settings and difficulty in detecting vegetations on markedly abnormal or prosthetic valves.

False-positive examinations, although less frequent, may also occur.\textsuperscript{4, 16, 28} Myxomatous valvular degeneration as seen with mitral valve prolapse, tumors such as myxomas and/or ruptured chordae tendineae of other etiologies may all present false-positive indicators for vegetative endocarditis.

The persistence of vegetations despite bacteriologic cure poses a particularly difficult problem. The present study as well as previous reports, documents the persistence of such lesions well beyond the period of bacteriologic cure.\textsuperscript{4, 6, 7, 16} Present findings agree with the reported observation that disease activity cannot as yet be ascertained by any echocardiographic characteristics of these lesions.

Utility of Echocardiography

The results of this study assign echocardiography a reasonable role in the clinical decision-making process in patients with vegetative endocarditis. Although it is a good method for documenting the presence or absence of vegetations, it is unreasonable to use echocardiography as a routine method for establishing a diagnosis in this disorder. Only half of the patients with clinical criteria for endocarditis manifest lesions by echocardiography. Because lesions do not involve rapidly, echocardiography may be of little diagnostic value in patients with a history of endocarditis. Caution must always be exercised in interpreting echocardiographic data when other causes for valvular thickening or disruption are present, as in mitral prolapse.

When clinical criteria are uncertain, however, echocardiographic data will play a more critical role in establishing the diagnosis of vegetative endocarditis. It is curious that many patients are assigned the clinical diagnosis of endocarditis without anatomic (echocardiographic, surgical or autopsy) confirmation of lesions. Further study may show the usefulness of documenting lesions to establish the diagnosis of endocarditis and/or direct therapeutic regimens.

Once the presence of lesions is established by echocardiography, patients are at higher risk for embolic events, valvular disruption and congestive heart failure than those without lesions. Data from the patients in group 2 indicate that complications may arise in patients without vegetations. Extrapolation of risk to a given patient based on the presence or absence of vegetations is hazardous.

Serial echocardiography during acute phases of clinical endocarditis is probably of value, although no recommendation as to its routine use can be made. Reports in the literature concerning progressive leaflet damage,\textsuperscript{10, 27} compromise of coronary ostia by mass lesions affecting the aortic valve, and progressive impairment of ventricular function indicate areas where this technique may be most profitably applied. Data from the present series indicate little hope for the use of this technique for assessing the effects of medical therapy by evaluating the regression in lesion size or morphology.

The use of echocardiographic data in evaluating the hemodynamic status of a given patient must be tempered by the observation of this and other studies.\textsuperscript{9} That clinical evidence of congestive heart failure is invariably present in patients with echocardiographic signs of leaflet disruption or mitral preclosure. Thus, echocardiography may play an important role in delineating the cause of clinically evident hemodynamic impairment.

There may be an investigative role for echocardiography in patients recovering from clinical endocarditis. Roberts and Buchbinder\textsuperscript{10} reported focal areas of fibrosis or calcification as residua of vegetations in a postmortem series when examinations were performed an average of 16 years after episodes of endocarditis. When compared with the echocardiographic data during the early convalescent period from the present study it is obvious that lesions undergo some involutorial process over the course of years. Conclusions about the natural history of such a process as it regards patient care and ultimate outcome are yet to be determined.

The presence of congestive heart failure, rather than specific echocardiographic findings, remains the paramount indication when considering patients for surgical intervention, but echocardiographic data are clearly important. Localization of lesions, evaluation of leaflet integrity and estimation of ventricular size and contractility are all possible by echocardiography and are helpful in selecting patients for surgery and directing the surgical procedure. Such information obviates the need for risky cardiac catheterization\textsuperscript{6, 7, 28} in these patients.

Acknowledgments

We wish to thank Colleen Gray for her long-suffering secretarial assistance and Sondra Myers, Robyn Haney, Janet Moore and Melvinia Parker for their superlative technical expertise in obtaining the necessary echocardiographic examinations.

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Echocardiographic documentation of vegetative lesions in infective endocarditis: clinical implications.

J A Stewart, D Silimperi, P Harris, N K Wise, T D Fraker, Jr and J A Kisslo

Circulation. 1980;61:374-380
doi: 10.1161/01.CIR.61.2.374

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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