The Use of Echocardiography in Diagnosing Culture-negative Endocarditis

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SUMMARY We reviewed M-mode and two-dimensional echocardiographic findings in 11 patients with abacteremic endocarditis to study the application of echocardiography in this setting. All patients had negative blood cultures but underwent surgery that confirmed the presence of active infective endocarditis. The infection involved native valves in five patients and prosthetic valves in six patients. Valvular masses were identified in eight patients. The other three patients, who had prosthetic aortic valves, had diastolic mitral valve vibration characteristic of aortic regurgitation. One of these three also showed dehiscence of the prosthesis.

Three patients had poorly defined clinical illnesses and echocardiography was a prime element in the diagnosis because valvular masses were identified. The operation was facilitated by knowledge of the mass indicated by echocardiography in these eight cases. Also, the surgical approach was affected by knowledge of dehiscence and perivalvular abscess formation in two cases each.

THE INABILITY to confirm the presence of infective endocarditis by blood culture often delays institution of therapy while other diagnoses are considered. Even when the diagnosis of endocarditis is strongly suggested on clinical grounds, failure to identify the causative organism makes selecting an effective antimicrobial agent difficult. As a result, culture-negative, or abacteremic, endocarditis is a vexing clinical problem and may carry a poor prognosis. The condition is not rare; nearly all reported series of patients with proved infective endocarditis include such a subgroup, which accounts for 10–25% of cases.1-8

M-mode and two-dimensional echocardiographic techniques are useful in identifying cardiac lesions that may be potential nidi for endocarditis. Both techniques are used to provide direct, noninvasive visualization of valvular vegetations.1-10 At our institution, two patients recently presented with febrile illnesses suggesting infective endocarditis despite persistently negative blood cultures. In both cases, large masses identified by two-dimensional echocardiography greatly strengthened the diagnosis of prosthetic valve endocarditis. We therefore reviewed our clinical records for other cases to elucidate the application of echocardiography in abacteremic endocarditis. This report summarizes these findings in a selected group of patients studied in our laboratory since 1973.

Methods

Patient Selection

The cardiac surgical data base at the Stanford University Medical Center was used to identify patients who underwent valve replacement because of endocarditis between January 1973 and September 1979 and in whom echocardiograms had been obtained within 10 days before operation. After a review of clinical records, patients were selected for inclusion in the study if they met the following criteria: (1) At the time of echocardiogram and subsequent operation, active endocarditis was suggested from clinical signs, including fever, new or changing heart murmur, embolic phenomena or increasing heart failure. (2) Blood cultures obtained preoperatively were negative a minimum of four times. (On the basis of criteria 1 and 2, these patients were diagnosed as having abacteremic endocarditis at the time of operation.) (3) active infective endocarditis was found at operation (characteristic destructive changes, vegetation, or abscess) and microscopic evidence of acute inflammation with or without detectable microorganisms was confirmed independently by a cardiac pathologist, or growth of an organism occurred from the excised valve mass.

Echocardiographic Methods

Patients referred to the Stanford University Medical Center Noninvasive Laboratory for echocardiograms to rule out intracardiac masses, including valvular vegetations, have been evaluated by the two-dimensional technique during the last 5 years. Standard M-mode echocardiograms were also obtained by means of either separate M-mode equipment or the M-mode capabilities of the two-dimensional instruments.

Echocardiographic studies were performed with the patient in the left lateral decubitus position. The M-mode studies were obtained using a Smith Kline Ekoline 20A or Irex System II ultrasonoscope with a 2.25-MHz transducer focused at 7.5 cm. Examinations were recorded on light-sensitive paper using a Honeywell 1856, Ekoline 21 or Irex strip-chart recorder. Two-dimensional echocardiograms were performed with a Varian V-3000 phased-array sector scanner, a Smith Kline Ekosector I mechanical sector
scanner, or a Toshiba SSH 10A phased-array sector scanner. Standard techniques were used to perform the examinations, and the two-dimensional echocardiograms were recorded on videotape.\textsuperscript{11, 12} Each two-dimensional instrument can be used to record standard M-mode echocardiograms using the two-dimensional transducer.

The echocardiograms were interpreted by more than one observer who was aware of the clinical features of each case. The echocardiograms were clear enough to allow unequivocally positive identification by each observer.

In the appropriate clinical setting, two-dimensional echocardiographic findings that we consider indicative of infective endocarditis include discrete mobile masses contiguous with valvar leaflets or prosthetic valve structures and circumscribed echo-free areas adjacent to valves suggestive of perivalvular abscess formation. Prosthetic valve dehiscence is also consistent with infective endocarditis. The M-mode criteria for infective endocarditis used in this study have been described.\textsuperscript{4-6, 10}

Results

A summary of the salient clinical features, echocardiographic interpretations and operative findings for each patient is shown in Table 1.

Echocardiographic Data

Both M-mode and two-dimensional echocardiograms were obtained in eight of the 11 patients. In three patients, only M-mode echocardiographic examinations were obtained.

Five of the 11 M-mode studies performed (45%) were positive for valvar masses. The lesions were characterized by rapidly oscillating masses of “fluffy” or “shaggy” echoes. These masses usually did not interfere with normal leaflet motion. Such findings are compatible with valvar vegetations described by others.\textsuperscript{4-4, 10} The six remaining M-mode studies were interpreted as showing high-frequency oscillation of the mitral valve suggestive of aortic regurgitation without associated valvar masses (patients 3, 7, 8 and 9) or abnormalities not specific for endocarditis (diffusely increased echoes in the region of prosthetic valve leaflets, case 11), or were considered normal (case 6). Two-dimensional echocardiograms were positive in all eight patients examined with this technique. Abnormalities identified on these studies included valvar masses characterized as shaggy groups of mobile, bright echoes adherent to, replacing or protruding from normal leaflet tissue; annular or myocardial abscesses seen as abnormal echo-free spaces adjacent to affected valves; and dehiscence of prosthetic valves characterized by abnormal rocking motion or displacement of the prosthesis in the presence or absence of a mass (figs. 1–4).

Prosthetic Valve Endocarditis

Two-dimensional echocardiographic study of patients 6 and 7 showed abnormal rocking motion of the aortic prosthetic valve stents during systole and diastole, compatible with dehiscence. A mass involving the anterior portion of the valve ring and stent was also seen in patient 6 (fig. 3). This abnormal group of echoes appeared to move into the left ventricular outflow tract during diastole. The two-dimensional echocardiograms of patients 10 and 11 showed large, mobile, pedunculated masses adherent to the leaflets of the porcine heterograft mitral valves. Figure 4 (patient 10) shows dense, bright echoes within the mitral heterograft that move into the left atrium in systole.

In none of the four cases involving prosthetic aortic valves was a definite mass lesion, abscess or valve dehiscence identified on the M-mode study. Three of the patients had high-frequency oscillations of the anterior mitral leaflet consistent with aortic regurgitation. A mitral heterograft valve in patient 10 showed multiple, shaggy, mobile echoes between the stents of the valve, consistent with a vegetation on M-mode. The M-mode study of the other patient with a heterograft mitral valve was not considered characteristic of a mass.

Anatomic Correlation with the Echocardiogram

The operative findings in each of the 11 patients are listed in Table 1. The echocardiograms correctly predicted the presence, site and relative size of vegetations in each of the eight patients where these were present. In the patients in whom prosthetic valve dehiscence or abscess formation was identified on the echocardiogram, these findings were confirmed at operation.

Echocardiography in Relation to Therapy

In three of the 11 patients the clinical illness was not well defined, but echocardiographic examination identified a valvar mass in each case that sharply focused attention toward the diagnosis of endocarditis. Antibiotic therapy had been started empirically before echocardiography in these patients. In the other eight patients, the diagnosis of infective endocarditis was strongly suspected from the history, physical findings and clinical course before echocardiography. High-dose, broad-spectrum antibiotic therapy had been started before echocardiography in six of these cases. The remaining two cases went to surgery without prior antibiotic therapy. The existing plan for surgical intervention was supported by echocardiographic identification of major unsuspected complications of infection in four cases: two with dehiscence of a prosthetic valve and two with perivalvular abscess involving a native aortic valve.

Discussion

The 11 patients presented in this report constitute a consecutive series of patients selected retrospectively by strict criteria. Because all of our patients underwent valve replacement, they may have been more acutely ill than other infective endocarditis patients. Alternatively, surgery may have been facilitated once
the extent of cardiac damage was delineated on the echocardiogram. In reviewing the cases, we attempted to assess whether visualization of the abnormalities detected by echocardiography caused any alteration in therapy, such as a shift from antibiotic to surgical therapy. In our cases the decision to initiate antibiotic therapy appeared to have been made before the echocardiographic findings. Valve replacement surgery was performed for hemodynamic deterioration or obvious failure of medical therapy to decrease fever, reduce heart rate or emboli. Knowledge of the presence of a definite valvular mass, valve dehiscence,

Table 1. Patient Data

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Cardiac history</th>
<th>Clinical signs</th>
<th>M-mode echo</th>
<th>2-D echo</th>
<th>Operative findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Native aortic valves</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>None</td>
<td>Fever, AR murmur</td>
<td>Mass on AV; AR on MV</td>
<td>NA</td>
<td>Perforated cusp, vegetation*</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>F</td>
<td>Flow murmur</td>
<td>Fever, AR murmur</td>
<td>Mass on AV; AR on MV</td>
<td>Mass on AV; abscess</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>M</td>
<td>None</td>
<td>Fever, AR murmur</td>
<td>AR on MV</td>
<td>Mass on AV</td>
<td>Vegetation</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>M</td>
<td>None</td>
<td>Fever, AR murmur</td>
<td>Mass on AV; AR on MV</td>
<td>Mass on AV; abscess</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Native mitral valve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>M</td>
<td>None</td>
<td>Fever, CVA</td>
<td>Mass on MV</td>
<td>Mass on MV</td>
<td>Vegetation</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>M</td>
<td>RHD, AVR</td>
<td>Fever, AR murmur</td>
<td>Normal</td>
<td>Dehiscence; mass on AV</td>
<td>Dehiscence, vegetation</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>M</td>
<td>IE, AVR</td>
<td>CHF, AR murmur</td>
<td>AR on MV</td>
<td>Dehiscence</td>
<td>Dehiscence</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>M</td>
<td>AS, AVR</td>
<td>Fever, AR murmur</td>
<td>AR on MV</td>
<td>NA</td>
<td>Dehiscence, abscess</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>M</td>
<td>Bicuspid AV, AVR</td>
<td>Fever, AV block, AR murmur</td>
<td>AR on MV</td>
<td>NA</td>
<td>Dehiscence, abscess</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>F</td>
<td>RHD, MVR</td>
<td>Fever, systolic murmur</td>
<td>Mass on MV</td>
<td>Mass on MV</td>
<td>Vegetation</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>F</td>
<td>RHD, MVR</td>
<td>Fever, systolic murmur</td>
<td>MV leaflet thickening</td>
<td>Mass on MV</td>
<td>Vegetation</td>
</tr>
</tbody>
</table>


Abbreviations: AR = aortic regurgitation; MV = mitral valve; AVR = aortic valve replacement; AV = aortic valve; NA = not obtained; MVR = mitral valve replacement; IE = infective endocarditis; RHD = rheumatic heart disease; CVA = stroke; CHF = congestive heart failure; AV = atriocentric.

Figure 1. Long- and short-axis two-dimensional echocardiograms from patient 4, who had a native aortic valve vegetation and a subannular abscess. Note the discrete mass of echoes (arrows) adherent to the right aortic leaflet, consistent with a vegetation. An abnormal echo-free space (asterisk) contiguous with the right sinus of Valsalva was identified as an abscess cavity at operation. RV = right ventricle; LV = left ventricle; LA = left atrium; Ao = aorta; RVOT = right ventricular outflow tract; RA = right atrium.
or abscess provided by the echocardiogram probably aided the decision to intervene surgically at an early stage in each patient's course, but this is difficult to document by chart review.

Because nonoperated patients were not included in this series we cannot advocate, or suggest withholding, surgical therapy on the basis of the echocardiographic findings. Other series have shown that patients with echocardiographically definable masses during infection may do well on medical therapy alone.6-10

Indications for surgical intervention in acute endocarditis are under scrutiny. There appears to be a trend toward earlier valve replacement, particularly in patients with heart failure, embolic complications, evidence of progressive spread of intracardiac infection (conduction system abnormalities, aneurysm or fistula formation), any degree of dehiscence of prosthetic valves or lack of improvement in clinical state after 7 days of antibiotics.10 Echocardiography is being used more often to document some of these situations.

In early reported series of patients with infective endocarditis, the sensitivity of echocardiography in diagnosing vegetations was estimated to be 30-50%.4, 8 These studies relied exclusively on the M-mode technique, which is inferior for spatial orientation and permits a less comprehensive evaluation of cardiac structure and function, compared with two-dimensional echocardiography. Reports of the use of two-dimensional echocardiography alone and in combination with M-mode recordings suggest that diagnostic abnormalities may be identified in 80% or more of cases.7, 8, 15-18 In some studies, the sensitivity of M-mode and two-dimensional echocardiography have been comparable in identifying “vegetations” in endocarditis patients.15, 18 Our experience shows that two-dimensional echocardiography is superior for this purpose, but the sensitivity of M-mode echocardiography is improved when the M-mode beam is guided to particular structures (i.e., parts of valves) by the two-dimensional images. Strict criteria for identification of a valvular mass or prosthetic valve dehiscence by echocardiography have not been formulated. We have found that a discrete circular or irregular mass of echoes not corresponding to known anatomic structures, or a mass of echoes apparently attached to a valve leaflet, does not often lead to equivocation in interpretation of two-dimensional studies.8 The ability to display a broad dynamic range (multiple amplitudes of returning echoes) giving a gray scale presentation helps in subjectively separating masses, which have varying echo intensity, from more uniform leaflet tissue. Schapira et al. formulated diagnostic criteria for the normal bioprosthetic valve and emphasized the need to focus attention on the stents, sewing ring, ring motion and leaflets to accurately assess valve structure and function.9
Dillon et al. presented data indicating that a mass diameter of at least 2 mm is required for echocardiographic identification. We often find bright, echogenic areas on the porcine valve leaflets (mainly associated with atheromata) on aortic leaflets in patients older than 50 years of age in the absence of endocarditis. In the clinical setting compatible with endocarditis, such findings could lead to a false-positive echocardiographic diagnosis. Alternatively, infective endocarditis may be present without a valvular mass of sufficient size to be resolved by current echocardiographic protocols. The likelihood that some false-positive and false-negative diagnoses may be made emphasizes the necessity for correlation of the echocardiographic findings with routine clinical and laboratory methods. We have not attempted to assess the sensitivity of echocardiography in the diagnosis of abacterial endocarditis on the basis of this study.

These patients illustrate that echocardiography may detect complications of the infective process in patients with abacterial endocarditis. Dehiscence of prosthetic valves was identified in two patients and in two additional patients, perivalvular abscesses were visualized as echo-free spaces adjacent to involved valvular structures. Some investigators have reported that two-dimensional echocardiography can be used to identify myocardial abscesses. In the appropriate clinical setting, we considered the identification of valvular dehiscence or abscess formation by echocardiography was evidence of endocarditis, even in the absence of a valvular mass.

A recent review of 52 cases of abacterial endocarditis emphasizes that prompt effective antimicrobial and appropriately timed surgical therapy are essential to prevent excessive mortality in this condition. Patients who failed to become afebrile within 1 week after antibiotic therapy was started had only a 50% survival, compared with 92% survival when antibiotic therapy was started. In the management of these high-risk patients with suspected abacterial endocarditis, a presumptive diagnosis should be established promptly and the clinical response to therapy should be monitored closely. The clear potential of echocardiography for identifying masses representing valvular vegetations and defining other complications of endocarditis appears to have particular application in patients with negative blood cultures.

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