Echocardiography in Infective Endocarditis: Reassessment of Prognostic Implications of Vegetation Size Determined by the Transthoracic and the Transesophageal Approach

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In 105 patients with active infective endocarditis, disease-associated complications defined as severe heart failure (New York Heart Association class IV), embolic events and in-hospital death were correlated to the vegetation size determined by both transthoracic and transesophageal echocardiography. A detailed comparison between anatomic and echocardiographic findings, performed in a subgroup of 80 patients undergoing surgery or necropsy, revealed that true valvular vegetations can be reliably identified by echocardiography in the vast majority of patients; the detection rate was significantly higher for the transesophageal (90%) than for the transthoracic (58%) approach, particularly when infected prosthetic valves were evaluated. However, an accurate echocardiographic differentiation between true vegetations and other endocarditis-induced valve destruction (ruptured leaflets or chordae) is impossible.

The correlation of vegetation size with endocarditis-associated complications showed that patients with a vegetation diameter >10 mm had a significantly higher incidence of embolic events than did those with a vegetation diameter ≤10 mm (22 of 47 versus 11 of 58; p < 0.01). Particularly for patients with mitral valve endocarditis, a vegetation diameter >10 mm was highly sensitive in identifying patients at risk for embolic events. Vegetation size, however, was not significantly different in patients with and without severe heart failure or in patients surviving or dying during acute endocarditis. In addition, no significant correlation was found between vegetation size and location of endocarditis or type of infective organism.

These data suggest that the identification of endocarditis-induced vegetations can be improved by transesophageal echocardiography and that patients with a large vegetation at the mitral valve are at increased risk for embolic events. Vegetation size, however, is of minor relevance in relation to the degree of heart failure and patient survival.

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surgery or autopsy were analyzed and correlated with the echocardiographic image of vegetations. Furthermore, the detection rates of vegetations by transthoracic and transesophageal echocardiography were compared.

**Methods**

**Study patients.** Patients meeting the following criteria were selected: acute infective endocarditis documented by clinical signs or histologic findings, or both. Between 1984 and 1987, 105 consecutive patients (75 male, 30 female; mean age 49.7 ± 14.4 years) with clinically (n = 25) or histologically (surgery/autopsy, n = 80) proved infective endocarditis were studied prospectively at the Hannover Medical School. In the 25 patients diagnosed clinically, the clinical criteria for endocarditis were fever (100%), a new regurgitant cardiac murmur (100%) and anemia (100%) associated with bacteremia (80%). In the other 80 patients, histologic specimens were obtained during valve replacement (n = 62) or at necropsy (n = 18). Except for two patients with histologically documented endocarditis, all patients undergoing surgery or autopsy also had clinical signs of infective endocarditis. Patients with vegetations diagnosed by echocardiography alone, but with no clinical signs and no histologic proof of endocarditis were not included. In the 105 patients, a total of 116 valves were diseased (90 native valves [47 aortic, 39 mitral and 4 tricuspid] and 26 prosthetic valves). In total, from 39 aortic, 12 mitral, and 4 tricuspid valves).

**Definition of anatomic findings.** Patients undergoing a detailed physical examination including a personal interview, and their charts were carefully reviewed to detect episodes of pulmonary or systemic arterial embolism. A sudden appearance of neurologic disorders suggestive of cerebral embolism was observed in 28 patients. The diagnosis of cerebral embolism was based on computed tomographic findings (showing a nonhemorrhagic stroke) in 20 patients and could be proved by autopsy in 3 more patients; in the remaining 5 patients, the diagnosis of cerebral embolism was based on clinical signs alone. In addition, embolism to peripheral organs was documented by autopsy or chest X-ray examination in five patients (lung in one, spleen and kidney in one, multiple organs in three). In total, 33 patients had suffered from a major embolic event. Cutaneous manifestations of endocarditis (Osler nodes, petechiae, Janeway lesions, splinter hemorrhages) were not considered to be due to embolic events because their pathogenesis is still questionable and immunologically mediated mechanisms may be involved (13).

Twenty-four patients experienced severe heart failure defined as class IV according to the New York Heart Association classification. Death, defined as inhospital mortality due to endocarditis complications, occurred in 18 patients.

**Definition of anatomic findings.** The macroscopic in situ findings at autopsy or surgery were classified as follows: 1) typical vegetations (valve destruction with thrombotic/infectious material containing platelets, fibrin, erythrocytes and granulocytes), 2) bacterial colonies (a thin layer of thrombotic/infectious material), 3) valve destruction (without thrombotic material as judged by eye inspection and without valve ruptures), 4) ruptured chordae tendineae (with or without macroscopic visible thrombotic material), 5) ruptured valve leaflets (with or without thrombotic material), or 6) no vegetations (although there was histologically proved endocarditis). The anatomy could be evaluated in 80 patients with 91 diseased valves. Acute or postinflammatory lesions proved by histologic examination were present on all 91 valves.

**Echocardiographic examination.** Transthoracic M-mode and two-dimensional echocardiographic studies were performed by standard techniques with use of a 2.25 or 3.5 MHz phased array transducer system. Transesophageal two-dimensional echocardiographic studies were performed with a 3.5 or 5.0 MHz phased array transducer attached to the tip of a modified gastroscope (Diasonics Echoscope, Diasonics Cardiology Inc.; Hewlett-Packard model 21362A). Patients fasted for ≥4 h and received a local pharyngeal anesthetic agent as the only premedication. Informed consent was obtained from all patients. The investigations were carried out without complications with the patient in a left lateral decubitus position. All transesophageal examinations were performed primarily for diagnostic reasons and were usually completed within 5 min.

**Each cardiac valve was evaluated for thickening, calcification, prolapse of the leaflets and, in particular, for the presence or absence of "typical vegetation," defined as a "sessile" or "pendulating" valve-attached mass. A vegetation was considered as "definite" when shaggy echoes in the M-mode study and a corresponding mass without restricted valve motion in the two-dimensional echocardiogram were found. A vegetation was considered as "possible" when the findings were suggestive of a vegetation, but no clear differentiation from a preexisting lesion with thickened or calcified leaflets was possible. A "sessile" vegetation had to be completely attached to the valve, whereas a "mobile" vegetation showed a pedunculating part prolapsing into the ventricle or atrium. The size of vegetations was measured in various planes in the precordial and transesophageal echocardiogram, and the maximal diameter was used for subsequent analysis. The mean size of vegetations was 10.6 mm (range 3 to 28); therefore, vegetations >10 mm in diameter were defined as "large," and those ≥10 mm in diameter were defined as "small."

**Statistical analysis.** For statistical analysis, the chi-square test with Yates' correction for small numbers was used. The association between vegetation size and incidence of embolism, death or severe heart failure was analyzed with use of analysis of variance (ANOVA, SPSS, version X). In patients with more than one diseased valve, the largest vegetation...
Table 1. Comparison Between Echocardiographic and Anatomic Findings in 80 Patients with 91 Diseased Valves (histologically proved endocarditis)

<table>
<thead>
<tr>
<th>Anatomic Findings</th>
<th>Echocardiographic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&quot;Definite&quot; Veg (valves)</td>
</tr>
<tr>
<td>Typical vegetations</td>
<td>52</td>
</tr>
<tr>
<td>Bacterial colonies</td>
<td>7</td>
</tr>
<tr>
<td>Valve destruction</td>
<td>5</td>
</tr>
<tr>
<td>Rupture of chordae tendineae</td>
<td>With vegetations</td>
</tr>
<tr>
<td></td>
<td>Without vegetations</td>
</tr>
<tr>
<td>Rupture of valve leaflets</td>
<td>With vegetations</td>
</tr>
<tr>
<td></td>
<td>Without vegetations</td>
</tr>
<tr>
<td>No vegetations</td>
<td>1</td>
</tr>
</tbody>
</table>

Time interval between the echocardiographic examination and the in situ inspection: 17 ± 2 days. Veg = vegetation.

was used for subsequent analysis. Patients with no vegetation evident on the echocardiogram were evaluated in the group of patients with a small vegetation. A p value < 0.05 was considered as significant. Mean values ± SEM are given unless otherwise noted.

The association between embolic episodes (Emb) and echocardiographically detected "large" vegetations (Veg) > 10 mm in diameter was determined by calculating sensitivity, specificity, positive and negative predictive values as follows:

\[
\text{Sensitivity} = \frac{\text{Emb with Veg} > 10 \text{ mm}}{\text{Emb with Veg} > 10 \text{ mm} + \text{Emb with Veg} \leq 10 \text{ mm}}
\]

\[
\text{Specificity} = \frac{\text{No Emb with Veg} \leq 10 \text{ mm}}{\text{no Emb with Veg} \leq 10 \text{ mm} + \text{Emb with Veg} > 10 \text{ mm}}
\]

\[
\text{Predictive value (+)} = \frac{\text{Emb with Veg} > 10 \text{ mm}}{\text{Emb with Veg} > 10 \text{ mm} + \text{no Emb with Veg} > 10 \text{ mm}}
\]

\[
\text{Predictive value (-)} = \frac{\text{No Emb with Veg} \leq 10 \text{ mm}}{\text{No Emb with Veg} \leq 10 \text{ mm} + \text{Emb with Veg} \leq 10 \text{ mm}}
\]

Results

Comparison of echocardiographic and anatomic findings (Table 1). In 80 patients with endocarditis of 91 valves proved by surgery or autopsy, the macroscopic appearance of the diseased valves could be compared with the findings obtained by echocardiography. In these 80 patients, the echocardiographic studies were performed 17 ± 2 days before surgery or autopsy. In 62 (97%) of 64 diseased valves with anatomically documented vegetations, echocardiography detected a "definite" vegetation (considered as a "typical" vegetation [n = 54] or a vegetation associated with ruptured chordae tendineae [n = 4] or ruptured leaflets [n = 6]). However, echocardiography could not differentiate precisely between vegetations and rupture of leaflets or chordae tendineae found in seven valves without additional vegetations at surgery or autopsy. In 18 other cases where the involved anatomic site revealed "bacterial colonies" (n = 11) or "valve destruction" (n = 7), the echocardiogram showed "definite" (n = 12) or "possible" (n = 4) vegetations or none (n = 2). The one patient with a "definite" vegetation on the echocardiogram, but no corresponding findings during anatomic inspection, had suffered from brain embolism in the interval between the echocardiographic study and surgery.

Comparison of transthoracic and transesophageal echocardiography (Table 2). In the same subgroup of 80 patients with histologically proved endocarditis, the transthoracic and the transesophageal echocardiographic findings regarding the detection of a vegetation or valve destruction, or both, were compared. Transthoracic echocardiography was able to visualize a "definite" vegetation in 53 (58%) of 91 infected valves; 17 valves (19%) were considered as showing a "possible" vegetation. In contrast, transesophageal echocardiography visualized a "definite" vegetation in 82 (90%) of 91 valves; on 6 valves (6%) findings were suggestive of a vegetation (p < 0.05). The relatively low detection rate of the

Table 2. Detection of Vegetations by Transthoracic and Transesophageal Echocardiography in 80 Patients With 91 Diseased Valves

<table>
<thead>
<tr>
<th>Valve</th>
<th>Transthoracic Echo</th>
<th>Transesophageal Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&quot;Definite&quot; Veg</td>
<td>&quot;Possible&quot; Veg</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Tricuspid valve</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Total (%)</td>
<td>91</td>
<td>53 (58%)</td>
</tr>
</tbody>
</table>

Veg = vegetation; Echo = echocardiography.
Echocardiography in infective endocarditis

The transthoracic technique is mainly due to the high number of prosthetic valves in which the difference between the two echocardiographic approaches was most striking.

Prognostic implications of vegetation size (Fig. 1 to 7). In the total study group of 105 patients, the size of vegetations in the echocardiogram was compared in patients with and without severe heart failure (Fig. 1), in patients surviving or dying during the acute phase of endocarditis (Fig. 2) and in patients with or without major embolism (Fig. 3). Only the latter comparison showed a significant difference: 47 patients with a large vegetation (>10 mm in diameter) had a higher incidence of embolic events (46.8%) than those of the 49 patients with a small or the 9 patients with no vegetation (18.9%; p < 0.05). In 16 patients, the echocardiographic examination was performed after one or more embolic events; in the remaining 17 cases, embolism occurred after the initial echocardiographic study. Because an embolic event might decrease the size of vegetations, statistical analysis was repeated after exclusion of the 16 patients who had an embolic episode before the echocardiographic study. This second analysis, including the remaining 89 patients, also revealed that the incidence rate of embolism was lower (6%) in the 50 patients with a small vegetation than the rate (36%) in the 39 patients with a large vegetation (p < 0.05). The average size of vegetations in the 17 patients with an embolic event after the echocardiographic examination was 14 ± 7 mm compared with 9 ± 5 mm in the 72 patients without embolism. Sensitivity, specificity and positive and negative predictive values of a vegetation size > 10 mm for detection of patients with embolism are shown in Table 3.

When vegetation size was analyzed according to the various underlying bacteria isolated in at least two different blood cultures, the data of 97 patients could be evaluated (8 patients had blood cultures with more than one or different bacteria and were therefore excluded from the analysis). Statistical evaluation showed no significant differences between the bacteriologic groups (Fig. 4).

The mean size of vegetation was compared in all 116 diseased valves. The mean vegetation size in native aortic and mitral valves did not differ significantly (Fig. 5). In contrast, vegetations of the tricuspid valve were significantly
Table 3. Association Between Embolic Events and Vegetation Size >10 mm in 105 Patients With Infective Endocarditis

<table>
<thead>
<tr>
<th></th>
<th>Total Collective (n = 105)</th>
<th>Patients Without Emb Before Echo (n = 89)</th>
<th>Patients With Mitral Valve Endo (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emb with Veg &gt;10 mm</td>
<td>22</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>No Emb with Veg &gt;10 mm</td>
<td>25</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>No Emb with Veg ≤10 mm</td>
<td>47</td>
<td>47</td>
<td>13</td>
</tr>
<tr>
<td>Emb with Veg ≤10 mm</td>
<td>11</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>66.7%</td>
<td>82.3%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>65.3%</td>
<td>65.3%</td>
<td>65.0%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>46.8%</td>
<td>35.9%</td>
<td>61.1%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>81.0%</td>
<td>94.0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Echo = echocardiography; Emb = embolic episodes; Endo = endocarditis; Veg = vegetations.

larger, and vegetations of a prosthetic device were significantly smaller on the average than were vegetations of native aortic and mitral valves (variance analysis: p < 0.01) (Fig. 5).

The incidence of embolism was evaluated separately for the various locations of the diseased valves as well as for native and prosthetic valves (Fig. 6). The evaluation included 45 patients with native aortic endocarditis (11 with embolism), 31 patients with native mitral valve endocarditis (11 with embolism) and 25 patients with prosthetic valve endocarditis (10 with embolism); the 4 patients with native tricuspid valve endocarditis (1 patient with embolism) were excluded because of the small number of cases. There was no significant difference in risk of embolic episodes between patients with a small or large vegetation, as long as endocarditis was confined to a native aortic valve or a prosthetic valve (in either the aortic or the mitral position). However, among patients with a vegetation at the mitral valve, those with a large vegetation had a significantly higher incidence of embolism than did patients with a small vegetation (p < 0.001). The association between vegetation size and embolic risk in patients with mitral valve endocarditis is included in Table 3; sensitivity and negative predictive value reached a level of 100% in this series of patients.

Patients with a "mobile" vegetation had a significantly higher incidence of embolic episodes than did patients with a "sessile" vegetation (Fig. 7). However, the mobility of vegetations was not a further independent variable to discriminate the risk of patients for embolism because 40 (85%)...
of the 47 patients with a "large" vegetation also had a "mobile" vegetation whereas only 28 (48%) of the 58 patients with a small vegetation had a mobile vegetation (p < 0.001).

**Discussion**

**Identification of vegetations by echocardiography.** Echocardiography is the only noninvasive method available today allowing direct visualization of endocarditis-induced lesions. The detection rate for valvular vegetations depends on the approach used. Use of M-mode echocardiography alone allows the identification of vegetations in about 57% of cases (evaluation of 14 studies with 332 positive results in 583 patients (3,5,6,12,14-23)). The combined use of M-mode and two-dimensional imaging increases the detection rate to about 73% (550 positive results in 755 patients (4,7-11,24-34)). In our subgroup of 80 patients with endocarditis proved at surgery or autopsy, a "definite" or "possible" vegetation was found in about 77% (70 of 91 diseased valves) with use of transthoracic M-mode and two-dimensional echocardiography. Recently, the diagnostic value of echocardiography has been further improved by the introduction of the transesophageal approach. This technique is of particular importance in patients in whom transthoracic echocardiography fails to provide an adequate imaging quality, as in patients who have advanced obesity, chest deformity or emphysema, or who are seen early after thoracic surgery or under artificial ventilation. In addition, the transesophageal approach identified a vegetation or endocarditis-induced valve destruction, or both, in about 96% (88 of 91 diseased valves). A similar high detection rate using transesophageal echocardiography was recently reported by Erbel et al. (39).

**Advantages of transesophageal echocardiography.** Because analysis of the impact of vegetation size on prognosis in patients with infective endocarditis requires optimal imaging quality of valve structures, this study involved transesophageal echocardiography in addition to the precordial approach. Imaging of the heart from the esophagus provides a clear visualization of virtually all cardiac structures that is not disturbed by bones, lungs and the precordial chest wall (40,41). In addition, because of the close relation between the esophagus and the heart, higher transducer frequencies can be applied, thereafter leading to improved resolution and more accurate measurement of vegetation size. As shown by earlier studies from our laboratory (35,42), transesophageal echocardiography, although accompanied by minor discomfort, can also be performed easily in conscious patients at almost no risk.

**Comparison with anatomic findings.** The comparison between the anatomic findings documented at surgery or autopsy and the echocardiographic results showed that vegetations attached to diseased valves can be identified on the echocardiogram in the vast majority of patients. A reliable differentiation between vegetations and other endocarditis-induced lesions, such as rupture of leaflets or the valve apparatus, is generally not possible. This point is only of minor clinical relevance regarding the echocardiographic assessment of the diagnosis; it is, however, of major importance concerning the associated embolic risk because ruptured leaflets, in contrast to vegetations, usually do not
embolize. In this regard, previous studies did not provide sufficient information about the true anatomic findings. This anatomic inhomogeneity of echocardiographically detected “vegetations” in earlier studies may contribute to the controversies concerning the prognostic implications.

**Prognostic implications.** The present study clearly shows that vegetations >10 mm in diameter are associated with a higher incidence of embolic episodes. Although this association was significant in our total study group, further detailed analysis revealed that it was based on the subgroup of patients with a vegetation on a native mitral valve. Earlier studies that did (7,8,9,12,26) or did not (4,10) find an increased embolic risk in patients with vegetations focused only on the presence and size of vegetations but not on their location. Our findings may therefore partially explain previous discrepancies concerning the prognostic implications of echocardiographically detected vegetations.

In all studies published to date, a certain percentage of patients underwent echocardiographic examination after an embolic event had already taken place; this increases the number of patients with embolic events in the subgroup with a small (or even no) vegetation and may obscure a possible significant difference in the embolic risk. In the present study, we classified our patients with embolic events into those with embolism before and those with embolism after the echocardiographic examination. This classification permitted improved sensitivity and negative predictive value of echocardiographically detected vegetations >10 mm in relation to identification of patients with increased embolic risk.

Other endocarditis-associated complications, such as severe heart failure and death, showed no significant dependence on vegetation size. These results are in agreement with two previous reports (4,10), but Wong et al. (28) found an increased need for surgery in patients with a large vegetation and recommended early surgery in patients with vegetations >10 mm. However, their study included only 31 patients studied by two-dimensional echocardiography, and most patients had mitral and tricuspid valve disease (n = 22). In our study group, there was an approximately equal distribution of infected aortic and mitral valves in the patients with large or small vegetations (Fig. 5).

Our data indicate that there is no clear association between vegetation size and the common underlying infective organisms (Fig. 4). However, because specific organisms like fungi were rare in the present series, this lack of association may not be true for all bacteria.

**Limitations of the study.** This study like earlier reported studies, has certain limitations that seem to be unavoidable. First, there is a remaining uncertainty regarding the true vegetation size when measurements are based on echocardiographic images. The additional use of transesophageal echocardiography improves the detection rate of vegetations and, because of better visualization, probably also improves the accuracy of measurements. However, it was not the aim of the present study to address these questions. Second, it is well known (43) that some embolic events during the course of infective endocarditis remain clinically silent. Therefore, the true number of embolic events remains unknown in this as well as in comparable studies. Furthermore, the natural course of patients with a large vegetation can only be partially assessed in studies of this type. A certain percentage of patients undergo surgery before a potential embolic event because of refractory septicemia or advanced heart failure. Thus, some patients with a possible late embolic episode may be missed.

**Clinical implications.** Although the present study as well as previous reports cannot avoid certain limitations, our results indicate that the echocardiographic identification of endocarditis-induced vegetations can be improved by the transesophageal approach and that patients with a vegetation >10 mm at the mitral valve are exposed to an increased risk for embolic episodes. In these patients, we recommend early surgery independent of the degree of heart failure and responsiveness of septicemia to medical therapy.

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**References**


