Risk of Embolism and Death in Infective Endocarditis: Prognostic Value of Echocardiography
A Prospective Multicenter Study

Franck Thuny, MD; Giovanni Disalvo, MD; Olivier Belliard, MD; Jean-François Avierinos, MD; Valeria Pergola, MD; Valerie Rosenberg, MD; Jean-Paul Casalta, MD; Joanny Gouvernet, MD, PhD; Geneviève Derumeaux, MD; Diana Iarussi, MD; Pierre Ambrosi, MD; Raffaello Calabro, MD; Alberto Riberi, MD; Frédéric Collart, MD; Dominique Metras, MD; Hubert Lepidi, MD; Didier Raoult, MD, PhD; Jean-Robert Harle, MD; Pierre-Jean Weiller, MD; Ariel Cohen, MD; Gilbert Habib, MD

Background—The incidence of embolic events (EE) and death is still high in patients with infective endocarditis (IE), and data about predictors of these 2 major complications are conflicting. Moreover, the exact role of echocardiography in risk stratification is not well defined.

Methods and Results—In a multicenter prospective European study, including 384 consecutive patients (aged 57 ± 17 years) with definite IE according to Duke University criteria, we tested clinical, microbiological, and echocardiographic data as potential predictors of EE and 1-year mortality. Transesophageal echocardiography was performed in all patients. Embolism occurred before or after IE diagnosis (total-EE) in 131 patients (34.1%) and after initiation of antibiotic therapy (new-EE) in 28 patients (7.3%).

Staphylococcus aureus and Streptococcus bovis were independently associated with total-EE, whereas vegetation length ≥10 mm and severe vegetation mobility were predictors of new-EE, even after adjustment for S aureus and S bovis. One-year mortality was 20.6%. In multivariable analysis, independently of the other predictors of death (age, female sex, creatinine serum ≥2 mg/L, moderate or severe congestive heart failure, and S aureus) and comorbidity, vegetation length ≥15 mm was a predictor of 1-year mortality (adjusted relative risk = 1.8; 95% CI, 1.10 to 2.82; P = 0.02).

Conclusions—In IE, vegetation length is a strong predictor of new-EE and mortality. In combination with clinical and microbiological findings, echocardiography may identify high-risk patients who will need a more aggressive therapeutic strategy. (Circulation. 2005;112:69-75.)

Key Words: echocardiography ■ embolism ■ endocardium ■ prognosis

Despite recent improvement in diagnostic and therapeutic strategies,2 infective endocarditis (IE) is still associated with high in-hospital mortality, ranging from 16% to 25%,3–5 and a high incidence of embolic events (EE), ranging from 13% to 49%.6 These wide ranges of complications underscore the heterogeneity of the disease and the critical need for baseline risk stratification in order to focus aggressive management toward high-risk subsets of patients. However, previous studies that attempted to identify baseline predictors of mortality5,7–14 and embolism8,10,13,15–19 led to conflicting results. In particular, despite the key role played by echocardiography in IE diagnosis,2 its prognostic value has been questioned, specifically that of vegetation characteristics, namely, vegetation length and mobility. Whereas some authors reported an increased risk of EE and/or mortality in patients with large and mobile vegetation,9,10,13,17–19 others did not find such a correlation.8,11,14–16,20 Several reasons may explain such conflicting results, including the changing pattern of the disease over time,4,21 the retrospective design of some studies,5,7–9,11–16,21 the small number of patients,8–11 the heterogeneous definition of IE,8–12,18 the underutilization of transesophageal echocardiography (TEE),8,9,12,16 which enhances sensitivity of vegetation detection,2 and the inclusion of EE occurring before echocardiography instead of postdiagnosis events.10,13,19 Subsequently, no general agreement emerges from currently available guidelines,22,23 which give discordant recommendations with regard to surgical indications on the basis of vegetation length.

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From the Departments of Cardiology of La Timone Hospital, Marseille, France (F.T., J.A., J.C., J.G., A.R., F.C., D.M., H.L., D.R., J.H., P.W., G.H.); Saint-Antoine Hospital, Paris, France (O.B., V.R., A.C.); Charles Nicolle Hospital, Rouen, France (G. Derumeaux); and Second University, Naples, Italy (G. Disalvo, V.P., D.L., K.C.).
Correspondence to Dr Gilbert Habib, Département de Cardiologie, Hôtel de la Timone, Boulevard Jean Moulin, 13005, Marseille, France. E-mail gilbert.habib@ap-hm.fr, gilbert.habib@free.fr
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To resolve these issues, we undertook a large multicenter, prospective study of patients with a definite diagnosis of IE by current diagnostic criteria in the contemporary era, with systematic use of TEE, to assess the predictive value of clinical and echocardiographic parameters on the subsequent risk of embolism and death. We hypothesized that in addition to clinical and microbiological variables, echocardiography provides accurate baseline risk stratification of patients diagnosed with IE.

Methods

Patient Sample
From January 1993 to March 2003, all consecutive patients admitted in 4 referral European centers with a suspected diagnosis of IE were eligible for study entry (n=613). The only exclusion criterion was a pacemaker IE (n=34). Written informed consent was obtained from all participating patients, as required by the institutional review board under an approved protocol. Monthly screening of echocardiography and microbiology databases of all patients hospitalized for suspected IE was performed by each center to ensure that a consecutive sample of all definite diagnoses was obtained. Blood cultures, serological assessment, transthoracic echocardiography (TTE), TEE, and cerebral and thoracoabdominal CT scans were systematically performed within 48 hours of admission in all except 7 patients, who underwent abdominal echography and no CT scan because of severe renal insufficiency. Patients with definite diagnosis of IE according to Duke University criteria formed the final prospective cohort (n=384). Antibiotic therapy was started immediately after diagnosis.

Clinical Data
The following clinical and biological parameters were prospectively collected at diagnosis and during hospitalization: age, sex, fever (temperature >38°C), previous heart disease, intravenous drug abuse, HIV infection, diabetes, history of cancer, comorbidity, moderate or severe congestive heart failure (CHF) diagnosed as previously described, and serum creatinine >2 mg/dL. Early surgery was defined as valve replacement or repair performed during the course of antibiotic therapy.

Echocardiography
TTE and TEE were performed in all cases, as previously reported, and were reviewed by 2 experienced echocardiographers, blinded to patients’ clinical status. Echocardiographic data included the presence, maximal length, and mobility of vegetation. Measurements of vegetation length were performed in various planes, and maximal length was used. In the presence of multiple vegetations, the largest length was used for analysis. Mobility was evaluated with the use of a 4-point scale, as follows: absent, fixed vegetation with no detectable independent motion; low, vegetation with a fixed base but with a mobile free edge; moderate, pedunculated vegetation that remains within the same chamber throughout the cardiac cycle; and severe, prolapsing vegetation that crosses the coaptation plane of the leaflets during the cardiac cycle. An abscess was defined as a thickened area or mass with a heterogeneous echogenic or echolucent appearance. Valvular regurgitations were assessed semiquantitatively. Echocardiographic data were stored electronically and used unaltered for subsequent analysis.

End Points
End points were embolic events that occurred before or after initiation of antibiotic therapy (total-EE), embolic events that occurred after initiation of antibiotic therapy (new-EE), and 1-year mortality. Diagnosis of EE was based on clinical or CT scans data or both. CT scans, systematically performed at study entry, were subsequently repeated if clinically indicated. Specific diagnosis of cerebral embolism was eventually confirmed by an experienced neurologist during the clinical course, who was unaware of the microbiological and echocardiographic findings. Cutaneous manifestations and EE occurring after surgery were not included. The outcome at 1 year was obtained by contacting the patients' physicians.

Statistical Analysis
For discrete variables, the relation between a variable and an event was studied by χ² test or Fisher exact test (2 tailed) if the expected count in any cell was <5. Mann-Whitney test were used for continuous variables.

For the end point of total-EE, logistic regression analysis was performed with the use of clinical and microbiological variables as previously defined; among echo variables, vegetation length and vegetation mobility were not included in this analysis because these 2 parameters defined at index echo and potentially evolving with time could not be used as predictors of past events. Variables significantly associated with this end point in single-variable analysis (P<0.05) were included as candidate predictors in an ascending stepwise logistic regression analysis.

For the second end point of new-EE, only the echo variables vegetation length and vegetation mobility were tested as potential predictors, first in a single-variable analysis and then after adjustment for predictors of total-EE.

One-year survival was estimated by the Kaplan-Meier method. Baseline clinical, microbiological, and echocardiographic variables were tested as potential predictors of 1-year mortality with Cox proportional hazards modeling. Variables with P<0.10 were included into the multivariable model.

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff value of vegetation length that best predicted end points. P<0.05 was considered significant. All analyses were performed with SPSS for Windows, release 10.0.1999.Chicago (SPSS Inc).

Finally, interobserver variability was good for both vegetation length (κ=0.8) and mobility (κ=0.75).

Results

Patient Characteristics on Admission
Among the 384 patients with a definite diagnosis of IE, 294 had 2 major clinical Duke University criteria, 89 had 1 major and 3 minor criteria, and only 1 patient had 5 minor criteria. Baseline patient features are reported in Table 1, and microbiological data are reported in Table 2.

Mean±SD age was 57±17 years (range, 16 to 94 years), and 26% of patients were older than 70 years. Ninety-eight patients (25%) presented with moderate or severe CHF on admission, and 103 patients (26.8%) had already had an EE, including stroke in 46 patients (12%). A vegetation was identified by TEE in 320 patients (83%) but in only 192 patients (50%) by TTE. An abscess was identified by TEE in 94 patients (24%), and a new moderate to severe regurgitation was identified in 209 (54%).

Indications for Surgery
Early surgery was performed in 201 patients (52.3%) at a median time of 12 days (range, 0 to 50) after institution of antibiotic treatment. One hundred nine patients (28.4%) were operated on in an urgent setting, <15 days after diagnosis and the beginning of antibiotic therapy, 60 (15.6%) between 15 and 30 days, and 32 (8.3%) after 30 days. The indications for surgery included moderate or severe CHF in 72 cases, persistent vegetation after systemic embolization in 56 cases, abscess formation in 77 cases, acute severe aortic or mitral regurgitation without CHF in 29 cases, and early prosthetic valve IE in 9 cases. Forty-three patients with moderate or
severe CHF or abscess or both were not operated on because of severe comorbidity in 41 and refusal in 2. The median duration of hospital stay was 43 days (range, 0 to 167).

Embolic Risk

**Total Embolic Events**

Among 384 patients, 131 (34.1%) had ≥1 total-EE. Sites of embolization were central nervous system (62 cases), spleen (49 cases), kidney (22 cases), lungs (16 cases), peripheral arteries (10 cases), mesentery (3 cases), coronary circulation (2 cases), and eye (1 case). Thirty-three patients (8.6%) presented with ≥1 total-EE. Embolism was silent in 19 patients (4.9%). There was no statistical difference between patients with and without total-EE with regard to age, sex, presence of previous heart disease or prosthetic valve, localization of infection (mitral or aortic), and predisposing factors.

**TABLE 1. Clinical and Laboratory Findings in 384 Cases of IE With and Without Embolic Events Occurring Before or After Initiation of Antibiotic Therapy (Total-EE)**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=384)</th>
<th>Total-EE (n=131)</th>
<th>Without Total-EE (n=253)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>57±17</td>
<td>56±17</td>
<td>57±17</td>
<td>0.53</td>
</tr>
<tr>
<td>Male</td>
<td>274 (71)</td>
<td>92 (70)</td>
<td>182 (72)</td>
<td>0.72</td>
</tr>
<tr>
<td>Valve localization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral</td>
<td>191 (50)</td>
<td>70 (53)</td>
<td>121 (48)</td>
<td>0.33</td>
</tr>
<tr>
<td>Aortic</td>
<td>214 (53)</td>
<td>67 (51)</td>
<td>147 (58)</td>
<td>0.20</td>
</tr>
<tr>
<td>Prosthetic valves</td>
<td>91 (24)</td>
<td>28 (21)</td>
<td>63 (25)</td>
<td>0.70</td>
</tr>
<tr>
<td>Multivalvular†</td>
<td>60 (16)</td>
<td>24 (18)</td>
<td>36 (14)</td>
<td>0.30</td>
</tr>
<tr>
<td>Right-heart IE‡</td>
<td>34 (9)</td>
<td>18 (14)</td>
<td>16 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous heart disease§</td>
<td>180 (47)</td>
<td>54 (41)</td>
<td>126 (50)</td>
<td>0.13</td>
</tr>
<tr>
<td>IVDA</td>
<td>24 (6)</td>
<td>13 (10)</td>
<td>11 (4)</td>
<td>0.04</td>
</tr>
<tr>
<td>HIV infection</td>
<td>13 (3)</td>
<td>4 (3)</td>
<td>9 (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>History of cancer</td>
<td>23 (6)</td>
<td>8 (6)</td>
<td>15 (6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27 (7)</td>
<td>12 (9)</td>
<td>15 (6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Comorbidity index &gt;2</td>
<td>69 (18)</td>
<td>26 (20)</td>
<td>43 (17)</td>
<td>0.49</td>
</tr>
<tr>
<td>Moderate or severe CHF</td>
<td>98 (25)</td>
<td>37 (28)</td>
<td>61 (24)</td>
<td>0.38</td>
</tr>
<tr>
<td>Serum creatinine &gt;2 mg/L</td>
<td>70 (18)</td>
<td>28 (21)</td>
<td>42 (17)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Values are number (%). IVDA indicates intravenous drug abuse.

*Comparison between total-EE group and without total-EE group. Bold values are significant.
†At least 2 locations.
‡Only right heart localization.
§Including 91 patients with prosthetic valve, 33 congenital heart disease (27 bicuspid aortic valves, 3 interventricular septal defects, 2 Fallot, and 1 quadricuspid aortic valve), 27 mitral valve diseases, 26 aortic valve diseases, 3 obstructive cardiomyopathies.
||Charlson comorbidity scale.

**TABLE 2. Microbiological Findings in 384 Cases of IE With and Without Embolic Events Occurring Before or After Initiation of Antibiotic Therapy (Total-EE)**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=384)</th>
<th>Total-EE (n=131)</th>
<th>Without Total-EE (n=253)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>S bovis</td>
<td>63 (16)</td>
<td>32 (24)</td>
<td>31 (12)</td>
<td>0.003</td>
</tr>
<tr>
<td>Enterococci</td>
<td>28 (7)</td>
<td>14 (11)</td>
<td>14 (5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Oral streptococci</td>
<td>95 (25)</td>
<td>24 (18)</td>
<td>71 (28)</td>
<td>0.045</td>
</tr>
<tr>
<td>S aureus</td>
<td>82 (21)</td>
<td>37 (28)</td>
<td>45 (18)</td>
<td>0.03</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>17 (4)</td>
<td>4 (3)</td>
<td>13 (5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Others†</td>
<td>40 (10)</td>
<td>15 (19)</td>
<td>25 (10)</td>
<td>1</td>
</tr>
<tr>
<td>Negative blood cultures‡</td>
<td>76 (20)</td>
<td>15 (11)</td>
<td>61 (24)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are number (%).

*Comparison between total-EE group and without total-EE group. Bold values are significant.
†Including Q fever (n=9), HACEK group (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella [n=6]), Candida species (n=6), Escherichia coli (n=4), Enterobacter cloacae (n=2), Gemella morbillorum (n=3), Corynebacterium (n=3), Bartonella quintana (n=2), Bartonella henselae (n=2), Strepococcus agalactiae (n=1), Mycoplasma hominis (n=1), Propionibacterium acnes (n=1).
‡Definite IE diagnosis using clinical Duke criteria: 1 major and 3 minor criteria (n=75), 5 minor criteria (n=1).
TABLE 3. Predictors of Embolic Events in Multivariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>P</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-EE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S bovis</td>
<td>&lt;0.001</td>
<td>3.9</td>
<td>1.86–8.21</td>
</tr>
<tr>
<td>S aureus</td>
<td>0.002</td>
<td>2.4</td>
<td>1.15–4.83</td>
</tr>
<tr>
<td>New-EE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetation length &gt;10 mm</td>
<td>0.004</td>
<td>9</td>
<td>1.98–40.8</td>
</tr>
<tr>
<td>Severe vegetation mobility</td>
<td>0.04</td>
<td>2.4</td>
<td>1.02–5.42</td>
</tr>
<tr>
<td>S bovis</td>
<td>0.19</td>
<td>1.9</td>
<td>0.73–4.74</td>
</tr>
<tr>
<td>S aureus</td>
<td>0.12</td>
<td>2</td>
<td>0.84–4.76</td>
</tr>
</tbody>
</table>

Embolic Events During Antibiotic Therapy

New-EE occurred in 28 patients (7.3%). Sites of embolization were central nervous system (14 cases), spleen (9 cases), kidney (5 cases), peripheral arteries (5 cases), eye (2 cases), coronary circulation (2 cases), and pulmonary circulation (2 cases). These events occurred at a median time of 7 days (range, 1 to 38) after institution of adequate antibiotic therapy (20 [71.4%] in the first 15 days).

By single-variable analysis, vegetation length was predictive of new-EE (P<0.001). Vegetation length (median) was larger in patients with new-EE than in those without (15.5 mm [range, 0 to 40] versus 9 mm [range, 0 to 50], respectively; P<0.001). A vegetation length threshold of 10 mm was identified as having the highest predictive value for new-EE by ROC curve analysis. New-EE occurred more frequently in patients with vegetation length >10 mm than in those with vegetation length ≤10 mm (13.7% [26/190] versus 1% [2/194]; P<0.001). New-EE were also more frequent among 117 patients with severe vegetation mobility (16.2% [19/117] versus 3.4% [9/267]; P<0.001). Conversely, new-EE occurred in only 2 patients with both vegetation length <10 mm and no severe mobility. After adjustment for the 2 multivariate predictors of total-EE, ie, S aureus and S bovis, vegetation length >10 mm and severe vegetation mobility remained the only predictors of new-EE (Table 3).

In the subgroup of 14 patients with new cerebral embolism, vegetation length was >10 mm in all 14 patients. In those patients, vegetation mobility was severe in 12 patients.

Mortality

Incidence and Causes of Death

One-year mortality was 20.6%. Thirty-seven patients (9.6%) died during their hospital stay at a median time of 16 days (range, 0 to 73) after institution of antibiotic therapy. The causes for death were severe CHF (10 cases), multigang failure (9 cases), cerebral embolism (9 cases), septic shock (6 cases), cerebral hemorrhage (3 cases), atrioventricular block (1 case), and myocardial infarction (1 case). Forty-two patients died after dismissal. The cause for late death was a direct consequence of the cardiac lesions induced by IE in 26 patients (severe valve regurgitation in 21 and postoperative left ventricular dysfunction in 5). In the remaining 16 patients, the cause for late death was not directly related to cardiac lesions, including stroke in 2 patients, myocardial infarction in 1, IE recurrence in 1, noncardiac cause in 8, and unknown in 4.

Factors associated with 1-year mortality are summarized in Table 4. Vegetation length was predictive of 1-year mortality (relative risk [RR]=1.03 per millimeter; 95% CI, 1.01 to 1.06; P=0.01), and ROC curve demonstrated vegetation length >15 mm to have the best predictive value (RR=2.1; 95% CI, 1.34 to 3.26; P=0.001). The Figure shows 1-year survival curves according to vegetation length.

By multivariable analysis, baseline predictors of 1-year mortality were vegetation length >15 mm (adjusted RR=1.7; 95% CI, 1.10 to 2.64; P=0.03), age (adjusted RR=1.02; 95% CI, 1.01 to 1.06; P=0.01), and ROC curve demonstrated vegetation length >15 mm to have the best predictive value (RR=2.1; 95% CI, 1.34 to 3.26; P=0.001). The Figure shows 1-year survival curves according to vegetation length.

TABLE 4. Predictors of 1-Year Mortality (Cox Single-Variable Analysis)

<table>
<thead>
<tr>
<th>Factor</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.01–1.04</td>
<td>0.0003</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.8</td>
<td>1.16–2.86</td>
<td>0.009</td>
</tr>
<tr>
<td>Comorbidity index &gt;2</td>
<td>1.8</td>
<td>1.10–2.90</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum creatinine &gt;2 mg/L</td>
<td>2.9</td>
<td>1.80–4.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>1.6</td>
<td>0.99–2.58</td>
<td>0.05</td>
</tr>
<tr>
<td>S aureus IE</td>
<td>2.1</td>
<td>1.35–3.39</td>
<td>0.002</td>
</tr>
<tr>
<td>Cerebral embolism</td>
<td>1.4</td>
<td>0.83–2.48</td>
<td>0.2</td>
</tr>
<tr>
<td>Moderate or severe CHF</td>
<td>1.9</td>
<td>1.21–3.01</td>
<td>0.005</td>
</tr>
<tr>
<td>Abscess</td>
<td>1.2</td>
<td>0.72–1.92</td>
<td>0.53</td>
</tr>
<tr>
<td>Moderate or severe regurgitation</td>
<td>1.1</td>
<td>0.72–1.75</td>
<td>0.61</td>
</tr>
<tr>
<td>Vegetation length, mm</td>
<td>1.03</td>
<td>1.01–1.06</td>
<td>0.01</td>
</tr>
<tr>
<td>Vegetation length &gt;15 mm</td>
<td>2.1</td>
<td>1.34–3.26</td>
<td>0.001</td>
</tr>
</tbody>
</table>

TABLE 5. Predictors of 1-Year Mortality (Cox Multivariable Analysis)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01–1.04</td>
<td>0.007</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.6</td>
<td>1.01–2.58</td>
<td>0.048</td>
</tr>
<tr>
<td>Comorbidity index &gt;2</td>
<td>1.6</td>
<td>0.92–2.64</td>
<td>0.1</td>
</tr>
<tr>
<td>Serum creatinine &gt;2 mg/L</td>
<td>1.9</td>
<td>1.16–3.23</td>
<td>0.01</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>2</td>
<td>1.19–3.24</td>
<td>0.001</td>
</tr>
<tr>
<td>Moderate or severe CHF</td>
<td>1.6</td>
<td>1.02–1.54</td>
<td>0.04</td>
</tr>
<tr>
<td>Vegetation length &gt;15 mm</td>
<td>1.8</td>
<td>1.10–2.82</td>
<td>0.02</td>
</tr>
</tbody>
</table>
The exact role of echocardiography in predicting embolism has been largely debated, and past studies gave conflicting results. The causes for these discrepancies are well known. Limitations of past studies include small sample size, use of TTE alone, inclusion of EE occurring before echocardiography, and poor standardization of diagnostic criteria. The present study overcomes all these limitations because it included prospectively a large cohort of patients with definite IE according to Duke University criteria, with special attention to new-EE. In addition, this is the largest study in which vegetation characteristics were prospectively collected and TEE was systematically performed. The main result is that the echocardiographic characteristics of vegetation are clearly associated with the embolic risk. In a previous study from our center, 178 patients with IE were included, and a significant correlation was found between EE and vegetation size and mobility. However, a limitation of this study was the inclusion of patients with previous EE and the relative small number of new-EE. The present large multicenter study was initiated to overcome these limitations and allowed us both to include a larger number of patients and to analyze a more significant number of new-EE. The results of the present study confirm that large vegetations >10 mm or severe vegetation mobility or both are associated with an increased embolic risk. Conversely, new-EE were infrequent in a low-risk subgroup of patients with both vegetation length <10 mm and no severe mobility.

Predictors other than vegetation characteristics were identified by several studies. For example, antiphospholipid antibodies, coagulation parameters, and endothelial cell activation have been associated with an increased embolic risk.30 Bacteriologic factors and localization of IE have also been previously reported to influence the incidence of EE. For example, S aureus and S bovis have been associated with an increased embolic risk. In our study, S aureus and S bovis infection were associated with an increased risk of total-EE. However, in regard to the occurrence of new-EE, vegetation length and mobility remained the only predictors after adjustment for these microbiological variables. Finally, our study did not confirm the previously reported higher incidence of EE in mitral valve IE.

**Embolic Risk in IE**

Embolic risk represents one of the most frequent and severe complications of IE and has been reported to occur in 13% to 49% with IE.6 If the total risk of embolism associated with IE is very high, the risk of new embolism occurring after initiation of therapy is much lower, from 6% to 21% in past series and 7.3% in the present series. The risk of embolism seems particularly high during the first 2 weeks after diagnosis, and this point was confirmed by the present study because 71.4% of new-EE occurred during the first 15 days after diagnosis.

Discussion

The present study shows that echocardiography, performed early in the course of IE, has a strong prognostic value. Along with baseline clinical and microbiological features, the assessment of vegetation characteristics (length and mobility) allows identification of patients who are at highest risk for new-EE and death.

**Risk of Embolism and Death in Prosthetic Versus Native Valve Endocarditis**

**Embolic Risk**

New-EE were observed in 22 (7.5%) among the 293 patients with native valve IE and in 6 (6.5%) among the 91 patients with prosthetic valve IE. Vegetation length and mobility remained predictors of new-EE in native valve IE subgroup (vegetation length >10 mm [odds ratio = 5.9; P = 0.006] and severe vegetation mobility [odds ratio = 3.5; P = 0.03]) but not in prosthetic valve IE subgroup.

**Mortality**

One-year mortality was 18.4% and 27.5% in the subgroups of patients with native and prosthetic valve IE, respectively. Vegetation length >15 mm remained associated with death (RR = 2.2; 95% CI, 1.27 to 3.71; P = 0.004) in the native valve IE subgroup but not in the prosthetic valve IE subgroup, in which only S aureus was predictive of death (RR = 2.9; 95% CI, 1.30 to 6.67; P = 0.009).

**Mortality**

Mortality is still high in IE, although it has declined in recent years. The low mortality rate observed in our study may be related to a more aggressive surgical approach (28.4% of all patients underwent surgery before the 15th day of antibiotic therapy) and a lower incidence of S aureus IE compared
with the most recent American studies. In addition, a high incidence of S. bovis IE was observed in our study, and IE caused by this microorganism has been associated with a good prognosis.

Mortality in IE may be related to factors related to the patient or to factors related to the disease, the former being potentially preventable. Thus, the identification of factors associated with increased mortality is a crucial challenge because it will allow the identification of high-risk patients in whom an aggressive strategy will be potentially useful.

Several markers have previously been identified in past studies, including age, occurrence of complications, staphylococcal infection, and prosthetic valve IE. Other studies found different results; for example, Netzer et al. found that only neurological symptoms, arthralgia, and weight loss were independent predictors of mortality, and Wallace et al. found that clinical indices such as abnormal white cell count, serum albumin concentration, serum creatinine concentration, or visible vegetation were the best predictors of bad prognosis.

The most comprehensive study has recently been published by Hasbun et al. They studied 6-month mortality in a series of 513 patients with complicated IE. They found that comorbidity, abnormal mental status, moderate to severe CHF, staphylococcal infection, and medical therapy were independent predictors of mortality. In these series, the presence of vegetation was not associated with increased mortality, but the vegetation size and mobility were not specifically analyzed. In addition, the presence of vegetation was considered a criterion for “complicated IE” in this study, and only patients with complicated IE were included; thus, some patients without vegetation were probably not included, and this may explain why the presence of vegetation did not predict mortality in this study. Similarly, in the recent study of Chu et al., early echocardiographic findings were not predictive of death, but in this report, which included possible and definite diagnosis of IE, TEE was performed in only 66% of patients, and data on vegetation size were not prospectively collected.

In our study several factors were associated with a poor prognosis, including age, female sex, serum creatinine, S. aureus, and moderate or severe CHF. More importantly, we also found vegetation length >15 mm to be a predictor of 1-year mortality, even after adjustment for the other predictors and comorbidity. Older series failed to give a prognostic value to the presence or size of vegetation, probably because of the small number of patients studied or use of TTE alone. However, our results are in agreement with the recent series of Cabell et al., who found a direct relationship between vegetation size and mortality at 30 days and 1 year. Finally, the fact that very large vegetations were independently associated with a worse prognosis is not surprising because this feature is frequently associated with severe valve destruction and a high embolic risk. Interestingly, among the patients with vegetation length >15 mm, 34% had no other indication for surgery and would have been identified as high-risk patients by echocardiography before standard indications for surgery were met.

Study Limitations
This study has several limitations. First, it was subject to a referral bias because it was performed in referral centers. The early surgery policy of these centers could have reduced the incidence of new-EE. Moreover, a repeated CT scan was not systematically performed after antibiotic therapy in all patients, and therefore the exact incidence of new silent EE may have been underestimated. In addition, the incidence of EE was low in the subgroup of patients with prosthetic valve IE, and therefore no definite conclusion can be drawn concerning the value of TEE in predicting EE in this particular subgroup.

The rate of negative blood cultures was relatively high in our study. The causes for negative blood cultures may include prior antibiotic therapy and a relatively high incidence of Q fever endocarditis in our countries, as previously reported. It is our policy to perform a systematic serological assessment of multiple microorganisms in case of suspected IE, allowing identification of a high rate of “atypical” microorganisms (Coxiella burnetii, Bartonella species, Mycoplasma species) consistent with IE and not identified by blood cultures.

Conclusion
Echocardiography has a strong predictive value in IE. Independently of other baseline characteristics, vegetation length has major prognostic implications by predicting both EE under antibiotic therapy and mortality. Thus, the measurement of vegetation length at the time of diagnosis of IE is strongly recommended as part of the initial risk stratification. Patients with the largest vegetations should be considered at high risk for subsequent serious complications. Whether a more aggressive therapeutic strategy (ie, early surgery) is required in those patients requires further prospective studies.

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In the article, “Risk of Embolism and Death in Infective Endocarditis: Prognostic Value of Echocardiography: A Prospective Multicenter Study,” by Thuny et al, which appeared in the July 5, 2005, issue of the journal (Circulation. 2005;112:69–75), the names of two of the authors were incorrect.

“Giovanni Disalvo” should be “Giovanni Di Salvo,” and “Raffaello Calabro” should be “Raffaele Calabró.”

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