The risk of stroke and death in patients with aortic and mitral valve endocarditis

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Background Previous studies have generated inconsistent results when attempting to define predictors of stroke and death in patients with endocarditis. We sought to examine the relationship between vegetation 2-dimensional size and stroke in those with infective endocarditis (IE) and to identify differences between aortic valve (AV) and mitral valve (MV) IE with regard to clinical characteristics, echocardiographic findings, stroke, and death.

Methods We used the Duke Endocarditis Database to examine 145 episodes of definite IE involving the AV, n = 62, or MV, n = 83. A logistic regression model was developed to analyze important variables in predicting stroke, and a Cox proportional hazards model was used in predicting mortality.

Results The mitral valve was infected in 57% of the cases. Vegetations were more commonly detected in patients with MV IE (92.8% vs 66.1%, P = .001) and these MV vegetations were significantly larger (P < .05). Thirty-four of 145 episodes (23.4%) were complicated by stroke. MV IE was associated with a greater stroke rate, 32.5% versus 11.3% (P = .003). Strokes tended to occur early in the course of illness, particularly in MV IE. In the multivariable model, the independent predictors of stroke were MV IE (P = .04) and vegetation length (P = .03). Independent predictors of 1-year mortality were age (P = .02) and vegetation area (P = .048).

Conclusion Stroke is more common in patients with MV IE. Vegetation 2-dimensional size and characteristics are important predictors of stroke and mortality. These findings may lead to predictive models that allow physicians to identify high-risk patients who need aggressive treatment strategies to prevent long-term morbidity and mortality. [Am Heart J 2001;142:75-80.]

Since 1885 when Osler1 first emphasized the relationship between infective endocarditis (IE) and central nervous system (CNS) complications, it has been known that embolic stroke is a major cause of morbidity in patients with IE. Advances in echocardiographic technology and valve surgery have now made it possible to select high-risk patients and pursue early surgical therapy to prevent stroke. However, identifying patients at high risk remains elusive.

The pathogenic relationship between vegetation size and the risk of neurologic complications is controversial.2–8 The authors of several studies reported an increase in embolic risk in patients with vegetations visualized by transthoracic echocardiography,9–17 whereas other studies found no such increase.18–23 Intuitively, patients with larger vegetations should be at higher risk for embolization,12–15 this finding has not been consistent.20–22 There are a number of potential explanations for the lack of consensus among these studies. These explanations include small sample size in individual studies, the lack of use of validated diagnostic criteria for IE, inclusion of heterogeneous groups, the inclusion of patients studied by echocardiography after stroke has occurred, and the limited use of transesophageal echocardiography to evaluate patients at risk. Because the studies cited above have suffered from some or all the preceding methodologic problems, the relationship between vegetation location and embolic risk has not been properly examined. Moreover, only one of the preceding studies focused specifically on stroke in patients with IE.6

To clarify the relationships among vegetation size,
stroke, and death, we performed an evaluation of consecutive cases of definite IE entered into the Duke University Medical Center endocarditis database over a 9-year period. We sought to examine the relationship between vegetation size and stroke in those with IE. In addition, we sought to identify differences between aortic valve (AV) and mitral valve (MV) IE with regard to clinical characteristics, echocardiographic findings, stroke, and death.

**Methods**

**Patient selection**

A total of 2114 consecutive patients who underwent a transthoracic (TTE) or a transesophageal echocardiogram (TEE) for suspicion of endocarditis during the period from Jan 1, 1991, through Dec 31, 1999, were evaluated. Patients were enrolled if they were suspected to have IE and were not rejected by the Duke criteria.23 Demographic, clinical, microbiologic, pathologic, and echocardiographic data were collected from each patient’s medical record and clinical course. Of the 450 patients with definite or possible IE, 228 patients fulfilled criteria for definite IE. Patients were excluded (n = 85) for the following reasons: multivalvular involvement (n = 19), tricuspid valvular disease (n = 16), and inability to localize the infected valve by echocardiogram (n = 48). Therefore 145 patients with definite MV or AV IE were included in the study. The study received Institutional Review Board approval.

**Echocardiographic assessment**

Echocardiograms were performed as previously described.21,25 TEEs were performed with biplane or multiplane transducers in fasting patients with use of topical pharyngeal anesthesia and conscious sedation. Informed consent was obtained from all patients, or their surrogates, before TEE. Images were recorded on one-half-inch super VHS videocassette and in digital loop display format (EchoNet, Heartlab, Westerly, RI, or EnConcert, Agilent Technologies, Andover, Mass).

Vegetations were defined as irregularly shaped echogenic masses attached to cardiac surfaces including valve structures, myocardium, and intracardiac devices. Only vegetations attached to the mitral or aortic valves were analyzed. In addition, for those patients with definite IE by clinical criteria but no clear vegetation, additional echocardiographic information was used to localize infection. This information included the presence and location of a prosthetic valve, valve perforation, or moderate-to-severe paravalvular regurgitation. Oscillating vegetations were defined as masses with high-frequency movement independent of the associated valvular motion. Myocardial abscess was defined as thickened areas or masses within the myocardium or annular region with a nonhomogeneous echogenic or echoluent appearance. The presence of blood flow within the thickened space as visualized by color flow imaging was used as supporting evidence for abscess formation. Vegetations were measured in 2 orthogonal dimensions at the point in the cardiac cycle where the vegetation appeared the largest. The greatest length and width were recorded and the vegetation 2-dimensional (2D) size was computed as length × width. Dehiscence of a prosthetic valve was defined as a rocking motion of the prosthetic valve with excursion greater than 15 degrees in at least one direction.

Because 86% of our patient population had both a TTE and a TEE, only the most diagnostic echocardiogram was used for each patient for analyses. To determine the most diagnostic echocardiogram, a scoring system was created giving 1 point for each significant finding (vegetation, dehiscence, and perforation), 1 point for each increased grade of regurgitation, 1 point for each increased grade of paravalvular regurgitation, and 1 point for each millimeter in vegetation length and width. For each patient the echocardiogram with the highest score was used for all analyses. A cardiologist trained in echocardiography read all echocardiograms, and this information was available to the clinicians taking care of the patient. Additionally, echocardiograms were read blindly by a cardiologist on the endocarditis team specifically to characterize vegetations.

**Assessment of stroke**

Stroke was defined as the rapid onset of a focal neurologic deficit consisting of a motor deficit (dysarthria, weakness, or paralysis), visual field loss, or aphasia that either did not resolve within 24 hours or that resulted in death.26 Neurologic symptoms attributable to a tumor of the brain, trauma, severe metabolic disorder, or chronic degenerative neurologic disease were excluded. Time to stroke was defined as the time (in days) from the admission date at Duke Medical Center to the date of stroke. The group of strokes was divided into preventable and nonpreventable strokes. Nonpreventable strokes were defined as strokes that occurred as the presenting symptom or before admission and those that occurred after cardiac surgery. All other strokes were considered preventable. Time to preventable stroke was defined as the time (in days) from the admission date at Duke Medical Center to the date of stroke.

**Follow-up**

Data concerning death or last known date alive was obtained on all patients by assessing the medical record to determine dates of clinic visits, admissions, and death at Duke Medical Center. To determine vital status at 1 year after the index hospitalization, a national death index search was performed for those patients without documentation of death at Duke Medical Center and for whom there was no clinic visit or admission date greater than 1 year from the index hospitalization.

**Data analysis**

Descriptive statistics are presented as percentages for discrete variables. Continuous variables are presented as mean ± SD for data distributed normally; for data not distributed normally, median with interquartile ranges were calculated. Statistical testing was performed with the Student t test or the Wilcoxon rank sum test for continuous variables. Discrete variables were compared with the χ² test. Logistic regression modeling was used to determine predictors of stroke and Cox proportional hazards modeling was used to determine predictors of mortality. A 2-sided P value of less than .05 was considered significant for all statistical tests. All statistical analyses were done with the use of the Statistical Analysis System (SAS Institute, Cary, NC).
Results

Demographic features

There were 145 patients with definite IE and isolated MV or AV involvement. The mean age of the cohort was 54.5 years (Table I). More than one half of patients were white (56.3%) and male (60.7%). Intravenous drug abuse (IVDA) and human immunodeficiency (HIV) infection were uncommon, as were a history of cancer and immunosuppression. The presence of a prosthetic valve was common (42.8%) and the majority of patients were transferred from outside facilities (62.8%).

When basic demographic features were compared between patients with MV IE and AV IE there were significant differences (Table II). Prosthetic valve infection was 1.5 times more common in patients with AV IE compared with MV IE (53.2% vs 34.9%, \( P = .03 \)). Although the overall prevalence of cancer was low, a history of cancer was more likely in patients with MV IE (10.8% vs 1.6%, \( P = .03 \)). In addition, there was a trend toward more dialysis in those with AV IE (21.0% vs 10.8%, \( P = .09 \)).

Microbiology

Similar proportions of pathogens caused MV and AV IE in our study group (Table III). *Staphylococcus aureus* was the most common organism isolated. There was a nonsignificant trend toward more infections caused by methicillin-sensitive *S. aureus* in patients with AV IE (24.2% vs 12.0%, \( P = .06 \)). *Staphylococcus epidermidis* was more common than typical causes of endocarditis such as viridans group streptococci.
Echocardiographic features

The echocardiographic findings were different in patients with MV IE compared with those with AV IE (Table IV). Vegetations were 1.4 times more common in patients with MV IE (92.8% vs 66.1%, \(P = 0.001\)), whereas abscess was more common in AV IE (35.5% vs 10.8%, \(P = 0.001\)). Perforation, dehiscence, and moderate-to-severe paravalvular regurgitation were uncommon, and the incidence of these complications was not different between groups.

Vegetation characteristics such as 2D size were not statistically different depending on the type of organism. For instance, the mean vegetation length for those IE patients with \(S\) aureus and coagulase-negative staphylococcus was 8.22 mm and 7.65 mm, respectively. In addition, abscess appeared to be more common in those with \(S\) aureus and enterococcus infection (22.5% and 40.9%), but the absolute numbers were too small to detect statistical differences.

TEE was the most diagnostic echocardiogram in 75% of cases regardless of location of infection. When vegetations were present, there were significant differences in the 2D size dimensions of vegetations between patients with MV and AV infections (Table IV). MV IE vegetations were larger in each measured dimension.

Surgery, stroke, and death

Four major outcomes were assessed: valve surgery during initial hospitalization for IE, stroke, 30-day mortality, and mortality at 1 year (Table V). Patients with MV IE and AV IE had the same rate of surgery during the initial hospitalization, but the rate of stroke was nearly 3 times more common in cases of MV IE compared with cases of AV IE (32.5% vs 11.3%, \(P = 0.003\)). Mortality in MV IE, both at 30 days (18.1% vs 16.1%) and 1 year (42.2% vs 32.8%), was not statistically different from mortality in cases of AV IE.

Table V. Outcome comparisons between cases of AV and MV endocarditis

<table>
<thead>
<tr>
<th></th>
<th>MV</th>
<th>AV</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery this hospitalization</td>
<td>n = 83</td>
<td>n = 62</td>
<td>.80</td>
</tr>
<tr>
<td>Stroke</td>
<td>23 [27.7%]</td>
<td>16 [25.8%]</td>
<td>.31</td>
</tr>
<tr>
<td>Mortality</td>
<td>27 [32.5%]</td>
<td>7 [11.3%]</td>
<td>.003</td>
</tr>
<tr>
<td>30-day</td>
<td>15 [18.1%]</td>
<td>10 [16.1%]</td>
<td>.76</td>
</tr>
<tr>
<td>1-year</td>
<td>35 [42.2%]</td>
<td>20 [33.3%]</td>
<td>.22</td>
</tr>
<tr>
<td>Stroke at admission</td>
<td>15 [55.6%]</td>
<td>3 [42.9%]</td>
<td>.55</td>
</tr>
<tr>
<td>Time to stroke</td>
<td>0 [0%]</td>
<td>1 [-2, 16%]</td>
<td>.76</td>
</tr>
<tr>
<td>Time to preventable stroke</td>
<td>2 [1,4]</td>
<td>11 [3.5, 46]</td>
<td>.31</td>
</tr>
</tbody>
</table>

Discrete variables reported as absolute number and percentage. Continuous variables reported as median and interquartile range.

Of the 34 strokes, 18 (53%) occurred at or before admission at our medical center, whereas 2 occurred after intracardiac surgery (Table V). For all 34 patients with stroke the median time from onset of stroke to admission at our center was less than 1 day and did not differ between patients with MV IE and AV IE. In the group of preventable strokes (n = 14) there was a difference in time to stroke. In patients with MV IE the median time to preventable stroke was 2 days, whereas in AV IE patients it was 11 days. Because the frequency of preventable strokes was low and the variation high, especially in the AV IE group, the difference was not statistically different (\(P = .31\)).

Predictors of stroke and death

There was a no statistical difference in the rate of stroke between native valve and prosthetic valve infections (26.5% vs 19.4%, \(P = .32\)). In patients with prosthetic valves, cases of MV IE did not have a statistically higher rate of stroke than cases of AV IE (24.1% vs 15.2%, \(P = .37\)) In contrast, in native valve infections, patients with MV IE had a much higher rate of stroke than those with AV IE (37.0% vs 6.9%, \(P = .003\)).

With use of univariable analyses, the following characteristics were assessed to determine the predictors of stroke: vegetation characteristics (oscillation, location, dimensions, and 2D size), age, and prosthetic valve infection. The presence of MV vegetations (odds ratio [OR] 3.6, 95% confidence interval [CI] 1.1-11.6) and length >7 mm (OR 2.5, 95% CI 1.01-6.3) were the only predictors of stroke. With use of a multivariable logistic regression analysis, valve location and length were added to a model including width, 2D size, and prosthetic valve infection. The independent predictors of stroke: vegetation characteristics (oscillation, location, dimensions, and 2D size), age, and prosthetic valve infection. The presence of MV vegetations (odds ratio [OR] 3.6, 95% confidence interval [CI] 1.1-11.6) and length >7 mm (OR 2.5, 95% CI 1.01-6.3) were the only predictors of stroke. With use of a multivariable logistic regression analysis, valve location and length were added to a model including width, 2D size, and prosthetic valve infection. The independent predictors of stroke were mitral valve infection (OR 1.74, 95% CI 1.03-1.91) and vegetation length (OR 1.21, 95% CI 1.02-1.44).

The following characteristics were assessed in a multivariable analysis of 30-day mortality: age, valve location, stroke, surgery during hospitalization, vegetation 2D size, and intracardiac abscess. Only vegetation 2D size was an independent predictor of 30-day mortality (\(P < .001\)).

The following characteristics were assessed in a multivariable analysis of 1-year mortality: age, valve location, dialysis, prosthetic valve, stroke, surgery during hospitalization, vegetation 2D size, history of cancer, and intracardiac abscess. Only age (\(P = .02\)) and vegetation 2D size (\(P = .048\)) were independent predictors of death at 1 year.

Discussion

There are important differences in the demographic characteristics and echocardiographic findings between cases of MV IE and cases of AV IE. These differences
include the risk of stroke. Stroke is 1.5 times more common in all patients with MV IE and more than 5 times more common in cases of native MV IE. In addition, preventable strokes tend to occur much earlier in patients with MV IE. In a multivariable analysis, valve location and vegetation length were the only independent predictors of stroke. Vegetation characteristics were also important in predicting mortality. Vegetation 2D size was the only significant predictor of 30-day mortality and, along with age, vegetation 2D size was an independent predictor of mortality at 1 year.

Although other studies have examined embolic complications in IE, our study focused on a distinct population of patients with definite AV IE or MV IE and carefully examined the risk of stroke and death. Previous studies have not been adequately powered to examine the specific relationships between infected location, vegetation characteristics, and stroke. We used a validated set of diagnostic criteria and all patients were evaluated with echocardiography, 85% of whom were evaluated with TEE. This is in contrast to previous studies that were performed before the existence of validated criteria or TEE.2-7,9-14,18-20

This study has several limitations. It is a retrospective cohort study where population differences may only be controlled by statistical adjustment instead of random allocation. In addition, our database consists of patients that have been admitted to a large tertiary care referral center. It is likely that they represent a proportion of patients that have a high severity of illness compared with the general IE population. Patients were not prospectively evaluated for neurologic symptoms and thus small CNS emboli may have been missed. It is possible that certain organisms (ie, S. aureus and the HACEK group [Haemophilus aphrophilus, Haemophilus parainfluenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae]) may increase the risk of stroke, but this study had insufficient power to examine this variable. In addition, because 53% of the patients presented with stroke, it is possible that our findings underestimate the correlation between vegetation characteristics and stroke. Finally, because treatment decisions are complex, it is difficult to statistically control for all factors that may relate to outcomes.

The predictors of stroke and mortality that we have found should be viewed as hypothesis generating and need further verification with larger patient populations. Future studies of stroke in patients with IE should include the following: sufficient sample size to adequately power the analysis, classification of stroke with validated criteria, prospective serial examinations to detect small strokes with confirmatory neuroimaging studies, and exclusion of strokes before the echocardiographic determination of vegetation characteristics.

The reduction in adverse outcomes, particularly the rate of stroke and mortality, is the leading clinical imperative in the modern management of IE. From this work it appears that vegetation location and 2D size are important predictors of stroke and death. In addition, some strokes related to IE may be preventable if models can be developed that help clinicians predict those at risk. The presence of MV IE, particularly on native valves, and vegetation length are two such predictors. It is possible that patients with MV IE, specifically those with large vegetations, could benefit from aggressive early valve debridement or valve replacement. Further work needs to be done to delineate and verify predictors of stroke and death. Once clinically useful predictors of stroke are identified in patients with IE, then studies can evaluate an aggressive treatment strategy in high-risk patients to decrease long-term morbidity and mortality.

References


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