Brain Embolic Event in Infective Endocarditis: Risk Factor Analysis

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Purpose. Embolic events occur in 30% to 40% of patients with left-sided infective endocarditis. This study is designed to identify the relationship between embolic events, echocardiographic findings, clinical features and patient outcome.

Methods. In this retrospective study, we identified 93 patients with definite infective endocarditis from January 1998 to December 2002 according to modified Duke criteria. The relationships between age, sex, microorganism, major embolic events, involved valve, vegetation size, peak C-reactive protein and in-hospital death were analyzed.

Results. There were 93 patients with infective endocarditis, 28 had major embolic events. The major embolic events included brain emboli, spleen emboli, pulmonary emboli and kidney emboli. There were 8 patients with brain embolism in the non-fatal group (n = 71) and 8 patients in the fatal group (n = 22). The incidence of brain embolism was significantly higher in the fatal group (p = 0.019). The risk factors of brain embolism were mitral valve involvement (p = 0.003) and vegetation size greater than 1 cm in diameter. No significant difference in vegetation size was found between embolisms involving the mitral valve and aortic valves.

Conclusions. Brain embolism is a prognostic predictor of in-hospital mortality in patients with infective endocarditis. Patients are at higher risk of brain emboli in infective endocarditis with mitral valve involvement and vegetation size greater than 1 cm in diameter. **(Mid Taiwan J Med 2005;10:138-43)**

Key words

brain emboli, infective endocarditis, vegetation size

INTRODUCTION

Infective endocarditis (IE) is a serious endovascular infection and has a reported incidence of 1 per 1000 hospital admissions in the United States [1]. Despite major advances in diagnostic technology and antimicrobial treatment, the morbidity and mortality remain high; it has been reported that in-hospital mortality rate is nearly 20% [2-5]. Embolic events occur in 30% to 40% of patients with left-sided IE [6,7]. The utility of the Duke criteria [8,9] for the diagnosis of IE is well recognized [10,11]. Rapid diagnosis, effective treatment, prompt recognition of complication and risk factors for mortality are essential to good outcome. This study is designed to determine whether the echocardiographic findings and clinical features can serve as the risk factors of embolic events.

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MATERIALS AND METHODS

Patient population

From January 1998 to December 2002, we identified 93 patients with definite IE according to modified Duke criteria [6] at the China Medical University Hospital.

For patients with repeat episodes of IE at our institution, only the first episode was included. Patients in which IE involved a prosthetic valve or patients with IE involving more than one valve were excluded.

Table 1. Clinical Characteristics of 93 patients with infective endocarditis

Clinical characteristics	
Age (yr)	40 ± 20
Gender (male/female)	70/23
CHF, Fc III and CHF, Fc IV	20
Intravenous drug abuser	20
Medical death	22
Brain emboli	16
Spleen emboli	3
Pulmonary emboli	9
Kidney emboli	0

Data are presented as the mean value ± SD or number. CHF = congestive heart failure; Fc III = function class III; Fc IV = function class IV.

Table 2. Comparison of clinical features in patients with and without stroke

	Non-stroke (n = 77)	Stroke (n = 16)	*p*
Age (yr)	44 ± 20	47 ± 18	0.6
Gender (M/F)	58/19	12/4	1.0
Medical death	14	8	0.019
CRP (mg/L)	88.3 ± 66.8	96.8 ± 90.2	0.516

Data are presented as the mean value ± SD or number. CRP = C-reactive protein.

Table 3. Comparison of involved valves in patients with and without stroke

	Non-stroke (n = 77)	Stroke (n = 16)	*p*
Mitral valve	25	12	0.003
Aortic valve	25	4	0.768
Tricuspid valve	20	0	0.019
Other	7	0	0.599

The relationships between age, sex, microorganism, major embolic events, involved valve, vegetation size, peak C-reactive protein (CRP) and prognosis (in-hospital death) were analyzed.

Classification of embolic events

An embolic event was defined as the acute onset of organ system dysfunction consistent with ischemia [5]. Determination of major embolic events was made by review of the complete medical record, including brain embolism, pulmonary embolism, spleen embolism and kidney embolism. Patients with immune complex phenomena and microvascular emboli, such as cutaneous microinfarction, were not included in this study.

Statistical methods

Continuous variables are presented as mean ± SD for data distribution. Statistical testing was performed with the Student's *t* test for continuous variables. The influences of risk factors on the mortality and major embolic events were assessed by Fisher's exact test. Logistic regression modeling and ROC curve were used to determine the relationship between vegetation size and stroke. A p value < 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the 93 patients are listed in Table 1. Patients ranged in age from 3 to 83 years (mean, 44 yr). There was a male predominance (men/women: 75%:25%). Of the 93 patients with IE, 28 had major embolic events. In the non-fatal group (n = 71), a total of 18 patients had major embolic events, including 8 patients with brain embolism, 7 patients with pulmonary embolism and 3 patients with spleen embolism. In the fatal group (in-hospital death, n = 22), a total of 10 patients had major embolic events, including 8 patients with brain embolism and 2 patients with pulmonary embolism. The incidence of brain emboli was significantly higher in the fatal group ($p = 0.019$). We found that a brain embolic event was an independent predictor of death but other embolic events (pulmonary emboli, spleen emboli and kidney emboli) were not. The peak CRP was 60.2 ± 61.4 (mg/L) in the non-fatal group and 149.5 ± 75.3 (mg/L) in the fatal group ($p = 0.004$), indicating that elevation of CRP level was associated with increased risk of mortality in this study.

Stroke was associated with an increased risk of in-hospital death ($p = 0.019$) (Table 2). There was a higher incidence of stroke in IE patients with mitral valve involvement ($p = 0.003$) (Table 3). There were no incidences of stroke in patients with tricuspid infective endocarditis. Microorganisms were not associated with an increased risk of stroke (Table 4). Our data revealed that age, sex, microorganism, aortic

Table 4. Comparison of causative organisms in patients with or without stroke

	Non-stroke (n = 77)	Stroke (n = 16)	*p*
ORSA	7	3	0.37
OSSA	18	3	1.0
Streptococcus viridans	16	5	0.35
Other *Streptococcus*	12	3	0.72

ORSA = oxacillin resistant *Staphylococcus aureus*; OSSA = oxacillin sensitive *Staphylococcus aureus*.

Table 5. Comparison of the size of vegetation on mitral valve and aortic valve

	Aortic valve	Mitral valve	*p*
Length (mm)	8.5 ± 5.7	11.5 ± 7.1	0.139
Width (mm)	5.9 ± 4.1	7.9 ± 5.7	0.201

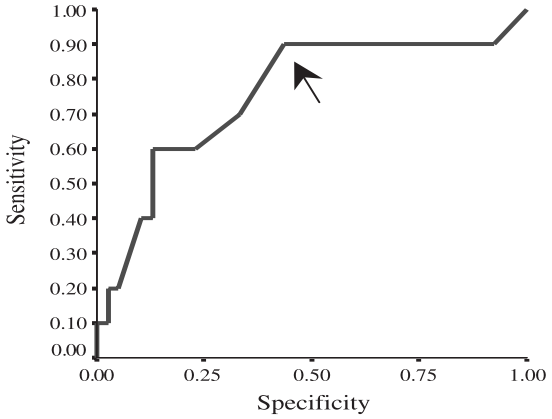

Figure. ROC curve of vegetation size to predict the risk of stroke. There was a higher risk of stroke in IE with the vegetation size greater than 1 cm and its sensitivity was 90% and specificity was 56% ($p = 0.012$) (arrow).

valve endocarditis (AVE), tricuspid valve endocarditis (TVE) and CRP levels were not associated with a higher risk for stroke; however mitral valve endocarditis (MVE) was associated with a higher risk for stroke.

There was a higher risk of stroke in IE patients with vegetation size greater than 1 cm (sensitivity 90%, specificity 56% ($p = 0.012$) (Figure)). With every 1 mm increase in size, the odds ratio of CVA increased by 1.146 ($p = 0.016$ and 95% CI = 1.015 to 1.281). There was no significant difference in vegetation size between mitral valve and aortic valve (Table 5).

DISCUSSION

In this retrospective study, there were 31 patients whose conditions were diagnosed by transesophageal echocardiography (TEE). The results demonstrated that brain embolism was an independent predictor of in-hospital mortality. Heiro et al found that death during the acute phase of IE occurred in 24% of patients with neurologic complications and in 10% of patients without neurologic complications ($p < 0.03$) [12]. Chao et al demonstrated that neurologic complications were important prognostic predictors of in-hospital mortality in patients with IE [13]. Di Salvo et al reported that the risk factors for in-hospital mortality were age, prosthetic valve and cerebral embolism [14]. However, Vivian et al found that embolic events were independent predictors of death, although they demonstrated that any stroke (at time of admission or during hospitalization) was associated with an increased risk of death, and the occurrence of other embolic events (excluding stroke) was significantly more common in patients who died during hospitalization [15].

Anderson et al found that patients with mitral valve endocarditis have a greater risk of stroke than patients with aortic valve endocarditis. They demonstrated that the increased risk of stroke in MVE may be in part due to larger vegetations in these patients [16]; however, our data did not support that finding. Despite this difference in stroke risk between patients with MVE and AVE, no differences were detected in stroke severity, stroke subtype, vascular distribution, length of hospitalization, or survival [16]. Previous studies have evaluated predictors of major embolic events in IE. Durante et al demonstrated that young IE patients and/or IE patients with large vegetation and/or high serum CRP levels were at increased risk of major embolic complications during the in-hospital course of the disease [17].

Jaffe et al found that there was a higher risk of embolization in patients with vegetation

> 10 mm in size [18]. Tischler et al also demonstrated that left-sided vegetation > 10 mm on echocardiograms poses a significantly increased risk of systemic embolization [19]. James et al demonstrated that the presence of vegetation on echocardiograms was not associated with a significantly higher risk for embolism in patients with left-sided native valve IE. The relative risk for embolic events associated with echocardiographically visualized vegetations may be microorganism dependent, with a significantly increased risk seen only in patients with *Streptococcus viridans* infection [6]. However, in our study, that microorganism was not associated with a higher risk for stroke.

In our study, elevation of CRP level was associated with increased risk of mortality (p = 0.004) but not associated with an increased risk of stroke (p = 0.516). This discrepancy may be due to the possibility that the CRP level used for analysis was not the real peak CRP level in the stroke group.

A number of limitations should be noted in interpreting the results of this study. Brain embolism was noted by retrospective chart review. Some patients with strokes that presented with mild or atypical signs and symptoms may not have been included. Many factors related to stroke, including old age, cholesterol, hypertension, diabetes mellitus and atrial fibrillation were not evaluated in this study. Vegetation size was measured by two dimensional echocardiography and may not have represented the actual size of vegetation.

In conclusion, brain embolism was a prognostic predictor of in-hospital mortality in patients with IE. We found a higher incidence of brain emboli in IE patients with mitral valve involvement and in IE patients with vegetation greater than 1 cm. There was no significant difference in the vegetation size between mitral or aortic valves. Age, sex, CRP level, and causative organisms were not predictors of brain emboli. Physicians should aggressively treat IE patients with mitral valve involvement and large vegetation.

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感染性心內膜炎患者併發腦栓塞之危險因子分析

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目的　栓塞的發生是感染性心內膜炎的併發症之一，且造成不良的生活品質，但在臺灣卻很少有關於超音波的診斷、臨床表現及栓塞預後的相關性研究，本研究主要是探討感染性心內膜炎患者併發腦栓塞的危險因子。

方法　收集了從1998年1月至2002年12月發生感染性心內膜炎的病例，分析其年齡、性別、菌種、栓塞的發生、感染的瓣膜、贅生物大小、發炎指數和死亡率及相關性。

結果　此回溯性的研究，共收集93個病例，其中28人發生了栓塞。而發生栓塞的病例中有10人死亡，其中腦栓塞的發生率明顯較高，另外感染二尖瓣的心內膜炎及贅生物大於1公分者，其發生腦栓塞比例也明顯升高。

結論　腦栓塞是發生感染性心內膜炎死亡的重要因子，而感染二尖瓣的心內膜炎及贅生物大於1公分者，則爲發生腦栓塞的危險因子。（**中台灣醫誌 2005;10:138-43**）

關鍵詞

腦栓塞，感染性心內膜炎，贅生物大小

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