Prediction of Hemorrhagic Transformation Following Embolic Stroke in Patients with Prosthetic Valve Endocarditis

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Background: Hemorrhagic transformation (HT) of stroke is a disastrous complication in patients with infective endocarditis (IE). In patients with mechanical heart valves complicated by IE, physicians struggle with the appropriateness of anticoagulation administration given the risk of thromboembolism and HT of stroke. In this study, we aimed to define predictive parameters of HT of stroke in patients with prosthetic valve endocarditis (PVE).

Methods: This study was a multicenter, retrospective design. We recruited from 7 institutions a total of 111 patients diagnosed with PVE during May, 2011 to April, 2012.

Results: Complication of stroke was seen in 26/111 patients (23%), and HT of stroke was seen in 11/111 patients (10%). Most patients with HT (9/11, 82%) had supratherapeutic prothrombin times. However, there were no significant differences in clinical and laboratory values between PVE patients without stroke and those patients who had a stroke and with or without concurrent HT. Furthermore, echocardiographic parameters also did not show significant between-group differences.

Conclusion: Even though this was a multicenter study, a limited number of patients was identified and may explain the negative results seen here. However, a large number of PVE patients with stroke also developed HT. Therefore, further studies to define predictive parameters of HT should be implemented in a larger population.

Key Words: Infective endocarditis · Embolization · Hemorrhagic stroke.

Introduction

Systemic embolization occurs in approximately 22-50% of cases of infective endocarditis (IE) and up to 65% of embolic events involve the central nervous system (CNS). Systemic embolism may thus occur more frequently than non-embolic strokes (2–21%). The location, size, and cause of stroke can influence the development of HT, and the use of antithrombotic medications - especially anticoagulant and thrombolytic agents - can increase the likelihood of HT. In general, management of patients with HT depends on the amount of bleeding and clinical symptoms. In patients with native valve IE, anticoagulation is typically

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not recommended as the benefits have never been fully demonstrated. Conversely, in prosthetic valve endocarditis (PVE), some authorities recommend continuation of anticoagulation to prevent thrombotic complications. However, in specific circumstances such as patients with PVE caused by *Staphylococcus aureus* (*S. aureus*) and a recent CNS embolic event, it is generally advised to hold all anticoagulation therapy during the first 2 weeks of antibiotic treatment. Thrombus organizing during this period and discontinuing anticoagulants helps to prevent acute HT. Anticoagulation therapy should then be restarted cautiously, and prothrombin time (PT) should be monitored carefully.

Since HT exacerbates functional disability and worsens overall prognosis for stroke patients, clinicians remain ambivalent about maintaining anticoagulation in cases of ischemic stroke in PVE. However, no consensus exists regarding discontinuation of anticoagulation in PVE complicated by ischemic stroke but with pathogens other than *S. aureus*. Therefore, we evaluated embolic stroke and HT in patients with PVE and investigated clinical and echocardiographic predictors for HT of ischemic stroke in following PVE.

**METHODS**

**PATIENTS**

We retrospectively reviewed clinical records and echocardiographic images of 156 patients from 7 institutions who were diagnosed with PVE during May 2011 to April 2012. Participating centers included Severance Hospital, Seoul National University Hospital, Samsung Medical Center, Pusan National University Hospital, Yeungnam National University Hospital, Bundang CHA Medical Center, and Gangnam Severance Hospital. Patients with bioprosthetic valves (n = 43) or with insufficient medical records (n = 2) were excluded. In total, 111 PVE patients with mechanical valves comprised the study population. Occurrence of redo-valve replacement surgery and in-hospital mortality was checked by reviewing hospital records.

The presence of ischemic stroke and development of HT were diagnosed by imaging studies in symptomatic patients. Brain imaging studies were read by an experienced neuroradiologist with extensive experience in evaluating acute stroke. The brain was divided into 3 vascular territories according to the blood supply: left internal carotid artery, right internal carotid artery, and vertebralbasilar supply. A multivessel stroke was defined as the presence of involvement in more than one vascular territory. HT was defined as secondary bleeding of ischemic stroke, ranging from small areas of petechial hemorrhage to massive space-occupying hematomas.

**TWO-DIMENSIONAL ECHOCARDIOGRAPHY WITH DOPPLER**

Transesophageal echocardiography (TEE) was performed on all patients. Echocardiographic studies were conducted during the acute phase of IE. Two experienced echocardiographers independently reviewed TEE studies without knowledge of patient history or subsequent clinical course. Echocardiographic data were classified using Duke criteria. Echocardiographic characteristics of IE included vegetation, abscess, new partial dehiscence of the prosthetic valve, valve perforation, and new valve regurgitation. Perivalvular abscess was defined as a thickened area or mass in the myocardium or annular region with a non-homogeneous appearance. Transvalvular pressure gradient was measured using continuous wave Doppler. Severe obstruction was defined as mean diastolic pressure gradient > 10 mmHg, peak velocity ≥ 2.5 m/s, and pressure half time > 200 ms in patients with prosthetic mitral valve; and mean systolic pressure gradient > 35 mmHg and peak velocity ≥ 4 m/s in patients with prosthetic aortic valve. Pulmonary hypertension was defined as calculated right ventricular systolic pressure ≥ 35 mmHg.

**ASSESSMENT OF VEGETATIONS**

Vegetation was defined as a fixed or oscillating mass adherent to a leaflet or other cardiac structure with a distinct echogenic appearance and independent motion. The lesion had to be visible in multiple views and detectable during the complete cardiac cycle. Vegetation measurements were obtained in various planes with the maximal length used. When multiple vegetation were present, the largest value was used for analysis. Vegetation mobility was evaluated using a 4-point scale defined as: 0 = fixed vegetation with no detectable independent motion; 1 = vegetation with a fixed base but with a mobile free edge; 2 = pedunculated vegetation that remains within the same chamber throughout the cardiac cycle; and 3 = prolapsing vegetations that cross the coaptation point of the leaflets during the cardiac cycle.

**STATISTICAL ANALYSIS**

Relevant variables were reported either as percentages or as means ± standard deviations. Groups were compared using χ² statistics for categorical variables and Student’s t-tests for continuous variables. If the distributions were skewed, a non-parametric test such as Mann-Whitney U-test and Kruskal-Wallis test were used. A p-value < 0.05 was considered statistically significant.

**RESULTS**

Demographic and clinical characteristics of the study population are shown in Table 1. Mean age was 54 ± 12 years-old, and 54% of the patients were male. Redo-valve replacement surgery was performed in 57 patients, and in-hospital mortality occurred in 12 patients. Among the 111 patients with PVE, 26 patients (23%) suffered ischemic stroke due to IE. HT was observed in 11 of those 26 patients who developed ischemic stroke (Fig. 1).
Clinical characteristics of PVE patients with and without stroke are summarized in Table 2. There were no significant differences in age, gender, prevalence of hypertension, diabetes and atrial fibrillation, involved valve, time interval between operation and diagnosis of IE, duration of hospital stay, initial vital signs and laboratory findings, necessity of redo-valve surgery, mortality, or pathogen type between patients with and without stroke. Platelet count was higher in stroke patients ($p = 0.013$). Redo-valve replacement surgery was performed in 17 patients with stroke; causes for reoperation were persistent fever and vegetation ($n = 7$), valve dehiscence ($n = 6$), perivalvular abscess ($n = 2$), heart failure ($n = 1$), and valve stenosis ($n = 1$). There were 4 deaths including 3 cases of shock due to uncontrolled infection and 1 case with critical intracranial hemorrhage.

We also compared variables between stroke patients with and without HT (Table 2). Stroke with concurrent HT was seen in 8 of 11 patients (73%). There were no significant differences in age, gender, prevalence of hypertension, diabetes and atrial fibrillation, involved valve, time interval between operation and diagnosis of IE, duration of hospital stay, vital signs and laboratory findings at initial presentation and at time of stroke occurrence, and necessity of redo-valve operation. There were no significant differences in the vascular territory of stroke between the groups. In-hospital mortality and S. aureus infections were more common in stroke patients with HT compared with stroke patients without HT, although no statistically significant differences were observed (27% vs. 7%, $p = 0.150$; 36% vs. 13%, $p = 0.381$; respectively). Most stroke patients with HT had supratherapeutic PT values (9/11 patients, 82%), but there was no statistical difference in PT between-groups.

Table 3 shows the comparison of echocardiographic parameters between stroke patients with and without HT. There were no significant differences between-groups in number, size, and mobility of vegetations. Left ventricular ejection fraction, severe valve dysfunction, and complications of IE including perivalvular abscess and valve dehiscence were not statistically different between-groups. Pulmonary hypertension was more common in stroke patients with HT, although it did not achieve statistical significance (64% vs. 27%, $p = 0.059$).

Comparisons between stroke patients caused by S. aureus or by other organisms are shown in Table 4. There were no significant differences in reoperation, duration of hospital stay.

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**Table 1. Patient characteristics**

| Characteristics                        | Value       |
|----------------------------------------|-------------|
| Number of patients                     | 111         |
| Age (yr)                               | 54 ± 12     |
| Males                                  | 60 (54)     |
| Hypertension                           | 15 (14)     |
| Diabetes mellitus                      | 10 (90)     |
| Atrial fibrillation                    | 38 (34)     |
| Involved valve                         |             |
| Mitral                                 | 35 (32)     |
| Aortic                                 | 30 (27)     |
| Combined mitral and aortic             | 40 (36)     |
| Other                                  | 6 (5)       |
| Time interval between operation and diagnosis of infective endocarditis |    |
| < 60 days                              | 17 (15)     |
| ≥ 60 days                              | 94 (85)     |
| Mean time interval (months)            | 95.2 ± 95.3 |
| Duration of hospital stay (days)       | 42.8 ± 25.7 |
| Initial vital signs                    |             |
| Systolic blood pressure (mmHg)         | 113.8 ± 17.3|
| Diastolic blood pressure (mmHg)        | 66.8 ± 13.7 |
| Heart rate (beats/min)                 | 85.3 ± 19.7 |
| Initial PT/INR                         | 2.77 ± 2.26 |
| Initial aPTT (sec)                     | 59.6 ± 26.3 |
| Hemoglobin (g/dL)                      | 10.7 ± 2.2  |
| WBC (cells/µL)                         | 11.9 ± 7.8  |
| Platelets (cells/µL)                   | 200 ± 103   |
| Reoperation                            | 57 (51)     |
| In-hospital mortality                  | 12 (11)     |
| Pathogen type                          |             |
| Staphylococcus aureus                  | 18 (16)     |
| Other*                                 | 56 (51)     |
| Negative blood cultures                | 36 (33)     |
| Stroke                                 | 26 (23)     |
| Hemorrhagic transformation             | 11 (10)     |

Data are presented as n (% of population) or mean ± standard deviation.

*Includes 12 other Staphylococcus species, 23 Streptococcus species, 6 Enterococcus species, 4 Pseudomonas species, 3 Eubacterioides species, 2 Corynebacterium species, 1 Acinetobacter baumannii, 1 Brucella, 1 Haemophilus influenza, 1 HACEK, 3 Micrococcus, and 1 Alcaligenes xylosoxidans. PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time, WBC: white blood cell.

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**Fig. 1. Study population.**
**Table 2. Comparison of patient characteristics**

|                               | PVE patients without stroke (n = 85) | PVE patients with stroke (n = 26) | p-value* | p-value† |
|-------------------------------|--------------------------------------|-----------------------------------|----------|----------|
|                               | All (n = 26) | HT (-) (n = 15) | HT (+) (n = 11) | p-value* | p-value† |
| Age (yr)                      | 53.7 ± 12.9 | 54.5 ± 9.5 | 53.5 ± 8.2 | 55.8 ± 11.2 | 0.782 | 0.856 |
| Males                         | 47 (55) | 13 (50) | 8 (53) | 5 (46) | 0.635 | 0.826 |
| Hypertension                  | 9 (11) | 6 (23) | 2 (13) | 4 (36) | 0.348 | 0.103 |
| Diabetes mellitus             | 8 (9) | 2 (8) | 1 (7) | 1 (9) | 0.999 | 0.789 |
| Atrial fibrillation           | 29 (34) | 9 (35) | 5 (35) | 4 (36) | 0.999 | 0.965 |
| Involved valve                |          |          |          |          | 0.875 | 0.813 |
| Mitral                        | 26 (31) | 9 (35) | 5 (35) | 4 (36) |          |          |
| Aortic                        | 22 (26) | 8 (31) | 6 (40) | 2 (18) |          |          |
| Combined mitral and aortic    | 32 (38) | 8 (31) | 4 (27) | 4 (36) |          |          |
| Other                         | 5 (6) | 1 (4) | 0 (0) | 1 (9) |          |          |
| Time interval between operation and diagnosis of infective endocarditis |          |          |          |          |          |          |
| < 60 days                     | 13 (15) | 4 (15) | 3 (20) | 1 (9) | 0.603 | 0.747 |
| ≥ 60 days                     | 72 (85) | 22 (85) | 12 (80) | 10 (91) |          |          |
| Mean time interval (months)   | 97.2 ± 96.6 | 88.8 ± 89.8 | 80.9 ± 85.2 | 99.6 ± 99.0 | 0.695 | 0.820 |
| Duration of hospital stay (days) | 40.4 ± 25.9 | 50.1 ± 24.1 | 47.1 ± 22.0 | 54.1 ± 27.3 | 0.095 | 0.197 |
| Initial vital signs and laboratory findings at stroke |          |          |          |          |          |          |
| Systolic blood pressure (mmHg) | 112.4 ± 17.6 | 118.0 ± 15.3 | 117.7 ± 15.8 | 118.2 ± 16.3 | 0.154 | 0.365 |
| Diastolic blood pressure (mmHg) | 66.7 ± 13.6 | 67.5 ± 14.1 | 66.6 ± 16.2 | 67.5 ± 11.7 | 0.802 | 0.969 |
| Heart rate (beats/min)        | 86.7 ± 19.9 | 81.2 ± 18.6 | 85.9 ± 18.8 | 76.5 ± 18.6 | 0.237 | 0.281 |
| PT/INR                        | 2.80 ± 2.44 | 2.64 ± 1.53 | 2.63 ± 0.98 | 2.77 ± 2.11 | 0.760 | 0.926 |
| aPTT (sec)                    | 61.8 ± 28.1 | 51.8 ± 17.6 | 50.9 ± 14.2 | 54.0 ± 27.8 | 0.097 | 0.239 |
| Hemoglobin (g/dL)             | 10.9 ± 2.2 | 9.9 ± 1.9 | 10.0 ± 1.6 | 9.8 ± 2.2 | 0.073 | 0.198 |
| WBC (cells/µL)                | 11.9 ± 8.4 | 11.7 ± 4.8 | 10.8 ± 3.5 | 12.7 ± 6.0 | 0.914 | 0.844 |
| Platelets (cells/µL)          | 185 ± 86 | 257 ± 141 | 255 ± 117 | 260 ± 173 | 0.742 | 0.015 |
| Vital signs and laboratory findings at stroke |          |          |          |          |          |          |
| Systolic blood pressure (mmHg) | 112.8 ± 10.6 | 118.9 ± 15.9 | 118.2 ± 16.3 | 0.250 |          |          |
| Diastolic blood pressure (mmHg) | 65.7 ± 15.3 | 70.2 ± 10.7 | 70.2 ± 10.7 | 0.417 |          |          |
| Heart rate (beats/min)        | 84.0 ± 17.9 | 82.1 ± 15.8 | 82.1 ± 15.8 | 0.781 |          |          |
| PT/INR                        | 2.1 ± 0.9 | 2.5 ± 1.6 | 2.5 ± 1.6 | 0.407 |          |          |
| aPTT (sec)                    | 56.6 ± 18.1 | 57.8 ± 30.7 | 57.8 ± 30.7 | 0.912 |          |          |
| Hemoglobin (g/dL)             | 9.9 ± 1.8 | 9.4 ± 2.6 | 9.4 ± 2.6 | 0.657 |          |          |
| WBC (cells/µL)                | 10.9 ± 4.6 | 11.5 ± 6.1 | 11.5 ± 6.1 | 0.828 |          |          |
| Platelets (cells/µL)          | 238 ± 134 | 219 ± 161 | 219 ± 161 | 0.739 |          |          |
| Reoperation                   | 40 (47) | 17 (65) | 11 (73) | 6 (55) | 0.102 | 0.168 |
| In-hospital mortality         | 8 (9) | 4 (15) | 1 (7) | 3 (27) | 0.391 | 0.171 |
| Pathogen type                 |          |          |          |          | 0.381 | 0.460 |
| *Staphylococcus aureus*       | 12 (14) | 6 (23) | 2 (13) | 4 (36) |          |          |
| Other1                        | 44 (52) | 12 (46) | 8 (53) | 4 (36) |          |          |
| Negative blood cultures       | 28 (33) | 8 (31) | 5 (33) | 3 (27) |          |          |
| Vascular territory of stroke  |          |          |          |          | 0.617 |          |
| Left internal carotid artery  | 5 (35) | 2 (18) |          |          |          |          |
| Right internal carotid artery | 3 (20) | 1 (9) |          |          |          |          |
| Vertebrobasilar artery        | 1 (7) | 1 (9) |          |          |          |          |
| Multivessel territory         | 6 (40) | 7 (64) |          |          |          |          |

Data are presented as n (% of population) or mean ± standard deviation. *Statistical significance of values between prosthetic valve endocarditis with and without stroke, †Statistical significance of values between stroke patients with and without hemorrhagic transformation, ‡Includes 12 other Staphylococcus species, 23 Streptococcus species, 6 Enterococcus species, 4 Pseudomonas species, 5 Esherichia coli species, 2 Corynebacterium species, 1 Acinetobacter baumannii, 1 Bordetella, 1 Haemophilus influenza, 1 HACEK, 1 Moraxella, and 1 Alcaligenes xylosoxidans. PVE: prosthetic valve endocarditis, HT: hemorrhagic transformation, PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time, WBC: white blood cell.
white blood cell count, PT, and activated partial thromboplastin time between-groups. Platelet count was significantly lower in PVE patients caused by *S. aureus* (*p* = 0.039). HT was more common and hemoglobin level was lower in the *S. aureus* group, but no statistically significant differences were identified (67% vs. 35%, *p* = 0.169; 11.2 mg/dL vs. 9.4 mg/dL, *p* = 0.050, respectively).

**Discussion**

The current study demonstrated that 1) embolic stroke was seen in about a quarter of patients with PVE (26/111 patients, 23%), 2) nearly half of embolic strokes in PVE patients were accompanied by HT (11/26 patients, 42%), 3) in-hospital mortality of PVE patients with embolic stroke was 15% (4/26 patients), 4) in-hospital mortality appeared higher in patients with HT compared to those without HT (27% vs. 7%), although statistically significant differences were not identified likely due to the limited number of patients identified for study, and 5) predictors for HT of ischemic stroke were not identified from the present study, even though we recruited patients through a multicenter study.

Stroke remains a debilitating complication of left-sided IE in 20–40% of patients and has been associated with poor outcomes.

In the present study, stroke was seen in 23% of PVE patients, a proportion similar to previous reports of IE patients. As a result, we speculate that the risk of stroke may not be influenced by the type of infected valve (native vs. prosthetic). Not surprisingly, HT was observed in nearly half of embolic patients as prior evidence demonstrated increased frequency of HT in embolic stroke than in non-embolic stroke patients. Mortality rate for our overall data was 11% and 15% in stroke patients. Interestingly, mortality rate of stroke patients without HT appeared much lower than stroke patients with HT (7% vs. 37%). Therefore, stroke following IE of mechanical heart valves might represent a poor prognostic factor, specifically when associated with HT.

PT values were not different between stroke patients with and without HT both at the onset of IE and at stroke presentation. Although most of the patients with HT had supratherapeutic PT values (PT/INR > 3), HT also occurred in 2 patients with suboptimal PT levels. Therefore, other factors yet to be uncovered may also be associated with the development of HT in PVE. PT levels remained prolonged even after discontinuing anticoagulation in most of our patients - perhaps due to uncontrolled infection - suggesting that the clinical benefits of stopping anticoagulants in PVE patients with elevated PT values remain unknown. In our population, 8 of 11 stroke patients (73%) were complicated with HT at the time of onset.

### Table 3. Comparison of echocardiographic variables between stroke patients with and without hemorrhagic stroke

| Variable                        | HT (-) (n = 15) | HT (+) (n = 11) | *p*-value |
|---------------------------------|-----------------|----------------|-----------|
| Ejection fraction < 55%         | 4 (27)          | 4 (36)         | 0.597     |
| Number of vegetation(s)        | 1.8 ± 1.1       | 1.4 ± 0.9      | 0.317     |
| Vegetation size (mm)            | 11 ± 4          | 10 ± 4         | 0.554     |
| Mobility scale of vegetation    | 2.0 ± 0.8       | 2.0 ± 0.7      | 0.800     |
| Perivalvular abscess            | 5 (33)          | 2 (18)         | 0.390     |
| Valve dehiscence                | 3 (20)          | 3 (27)         | 0.664     |
| Severe valve regurgitation      | 2 (13)          | 1 (9)          | 0.738     |
| Severe valve obstruction        | 1 (7)           | 0 (0)          | 0.382     |
| Pulmonary artery hypertension   | 4 (27)          | 7 (64)         | 0.059     |

Data are presented as n (% of population) or mean ± standard deviation. PVE: prosthetic valve endocarditis, HT: hemorrhagic transformation.

### Table 4. Comparison between stroke patients caused by *Staphylococcus aureus* and other organisms

| Variable                        | S. aureus (n = 6) | Other organisms (n = 20) | *p*-value |
|---------------------------------|-------------------|-------------------------|-----------|
| Hemorrhagic transformation      | 4 (67)            | 7 (35)                  | 0.169     |
| Reoperation                     | 4 (67)            | 13 (65)                 | 0.940     |
| In-hospital mortality           | 2 (33)            | 10 (10)                 | 0.165     |
| Duration of hospital stay (days)| 61 ± 32           | 52 ± 22                 | 0.639     |
| Hemoglobin (g/dL)               | 11.2 ± 0.9        | 9.4 ± 1.9               | 0.050     |
| WBC (cells/µL)                  | 13.1 ± 6.8        | 11.7 ± 4.6              | 0.914     |
| Platelets (cells/µL)            | 144 ± 57          | 275 ± 145               | 0.039     |
| PT/INR                          | 2.2 ± 0.8         | 2.5 ± 1.2               | 0.779     |
| aPTT (sec)                      | 49 ± 8            | 45 ± 9                  | 0.160     |

Data are presented as n (% of population) or mean ± standard deviation. WBC: white blood cell, PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time.
stroke diagnosis, demonstrating the difficulty in preventing HT by discontinuing anticoagulation.

IE caused by S. aureus has the worst prognosis and has a high rate of embolic episodes with subsequent neurologic involvement. Therefore, we compared differences between stroke patients with S. aureus infection and stroke patients infected by other organisms. HT of ischemic stroke was seen more commonly in PVE caused by S. aureus than by other pathogens (67% vs. 35%). Platelet count was much lower with S. aureus infection, which may indicate a possible role of sepsis in the development of HT of ischemic stroke. Therefore, results from the present study support the discontinuation of anticoagulant therapy in patients with PVE caused by S. aureus due to the high occurrence of HT of embolic stroke seen in our data.

The main limitation of this study was the small patient population and retrospective analysis. Limited number of cases may have caused the negative results seen here. Clinical detection alone of embolic stroke clearly underestimates the true prevalence. Furthermore, many of the patients diagnosed with IE and ischemic stroke simultaneously at the time of hospital admission likely had echocardiographic examinations performed at varying stages of endocarditis development. Therefore, the predictive value of echocardiography for stroke and HT may be limited. Further prospective studies to define parameters of HT should be implemented in a larger population to help clarify the optimal care of PVE patients with ischemic stroke.

In conclusion, although we identified patients through a multicenter study, a limited number of cases likely impacted the negative results seen here. However, a large number of patients with PVE who suffered a stroke subsequently had HT. Therefore, further studies to define predictive parameters of HT should be implemented in a larger population.

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