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

In-Jeong Cho, MD[1]*, Jin-Sun Kim, MD[2]*, Hyuk-Jae Chang, MD, PhD[1,3], Yong-Jin Kim, MD, PhD[4], Sang-Chol Lee, MD, PhD[5], Jung-Hyun Choi, MD, PhD[6], Sanghoon Shin, MD[1], Chi Young Shim, MD, PhD[1], Geu-Ru Hong, MD, PhD[1], Jong-Won Ha, MD, PhD[1,3] and Namsik Chung, MD, PhD[1]

[1]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Korea
[2]Division of Cardiology, Bundang CHA Medical Center, CHA University, Seongnam, Korea
[3]Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, Korea
[4]Division of Cardiology, Seoul National University College of Medicine, Seoul, Korea
[5]Division of Cardiology, Sungkyunkwan University School of Medicine, Seoul, Korea
[6]Division of Cardiology, Pusan National University Hospital, Busan, Korea

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).[1] In patients with embolic stroke, anticoagulation therapy may lead to hemorrhagic transformation (HT) and consequently worsen prognosis and severity of neurologic symptoms. It has been reported that hemorrhagic events occur in 51-71% of embolic strokes and thus occur more frequently than in non-embolic strokes (2-21%).[2-4] 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.[5][6] 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

• *The authors contributed equally to this work.
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• Address for Correspondence: Hyuk-Jae Chang, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea Tel: +82-2-2228-8454, Fax: +82-2-393-2041, E-mail: hjchang@yuhs.ac

not recommended as the benefits have never been fully demonstrated.[1)3)] Conversely, in prosthetic valve endocarditis (PVE), some authorities recommend continuation of anticoagulation to prevent thrombotic complications.[7)] 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.[1)] Thrombus organizes 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.[3)]

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.[5)8-11)] However, no consensus exists regarding discontinuation of anticoagulation in PVE complicated by ischemic stroke but with pathogens other than *S. aureus*.[12)13)]

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 vertebrobasilar supply. A multivessel stroke was defined as the presence of involvement in more than one vascular territory.[10)] HT was defined as secondary bleeding of ischemic stroke, ranging from small areas of petechial hemorrhage to massive space-occupying hematomas.[11)]

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.[14)] 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 nonhomogeneous appearance.[15)] 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 sec 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 vegetations 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.[16)]

STATISTICAL ANALYSIS

Relevant variables were reported either as percentages or as means ± standard deviations. Groups were compared using χ^2 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 significance 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,

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 *Enterobacter* species, 4 *Pseudomonas* species, 3 *Escherichia coli* species, 2 *Corynebacterium* species, 1 *Acinetobacter baumannii*, 1 *Brucellosis*, 1 *Haemophilus influenza*, 1 *HACEK*, 1 *Micrococcus*, and 1 *Alcaligenes xylosoxidans*. PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time, WBC: white blood cell

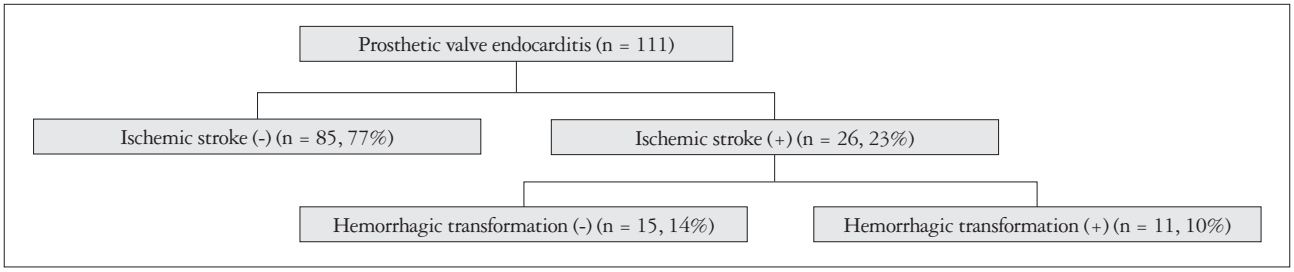

Fig. 1. Study population.

Table 2. Comparison of patient characteristics

	PVE patients without stroke (n = 85)	PVE patients with stroke (n = 26)				*p*-value*
		All (n = 26)	HT (-) (n = 15)	HT (+) (n = 11)	*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 (33)	4 (36)	0.999	0.963
Involved valve					0.875	0.813
Mitral	26 (31)	9 (35)	5 (33)	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						
Systolic blood pressure (mmHg)	112.4 ± 17.6	118.0 ± 15.3	117.7 ± 15.8	118.2 ± 16.3	0.154	0.363
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	0.013
Vital signs and laboratory findings at stroke						
Systolic blood pressure (mmHg)			112.8 ± 10.6	118.9 ± 15.9	0.250	
Diastolic blood pressure (mmHg)			65.7 ± 15.3	70.2 ± 10.7	0.417	
Heart rate (beats/min)			84.0 ± 17.9	82.1 ± 15.8	0.781	
PT/INR			2.1 ± 0.9	2.5 ± 1.6	0.407	
aPTT (sec)			56.6 ± 18.1	57.8 ± 30.7	0.912	
Hemoglobin (g/dL)			9.9 ± 1.8	9.4 ± 2.6	0.657	
WBC (cells/μL)			10.9 ± 4.6	11.5 ± 6.1	0.828	
Platelets (cells/μL)			238 ± 134	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)		
Other‡	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 (33)	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 *Enterobacter* species, 4 *Pseudomonas* species, 3 *Escherichia coli* species, 2 *Corynebacterium* species, 1 *Acinetobacter baumannii*, 1 *Brucellosis*, 1 *Haemophilus influenza*, 1 *HACEK*, 1 *Micrococcus*, 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

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

	PVE patients with stroke (n = 26)		*p*-value
	HT (-) (n = 15)	HT (+) (n = 11)	
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

	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	43 ± 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

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.[17] In the present study, stroke was seen in 23% of PVE patients, a proportion similar to previous reports of IE patients.[9] 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

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.[18][19] 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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