Original Article

Factors Associated with Incident Ischemic Stroke in Hospitalized Heart Failure Patients: A Pilot Study

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Stroke is sometimes seen in patients with congestive heart failure (CHF). The factors that best predict incident stroke in hospitalized CHF patients are not well known. We performed this pilot study to explore the clinical markers of incident stroke in CHF patients. We studied 111 hospitalized patients with CHF (mean age, 67±11 years). Ambulatory blood pressure (BP) monitoring, blood tests, and echocardiography were performed in these patients just before they left the hospital, and all cardiovascular events during the study period were followed for an average of 18±9 months. Cox regression analysis was performed to explore the predictors of incident stroke using age, sex, body mass index (BMI), casual and ambulatory systolic BP (SBP), and brain-type natriuretic peptide (BNP). There were 10 stroke events (9%) during the follow-up period. The stroke group had higher nocturnal SBP and plasma BNP levels than the non-stroke group. With Cox regression analysis, both nocturnal SBP and BNP were significant predictors of incident stroke independent of other covariates. When nocturnal BP of 120 mmHg and BNP of 600 pg/mL (75th percentile) were used as cutoffs, nocturnal SBP ≥120 mmHg was associated with a 7-fold increase in the risk of incident stroke, while BNP ≥600 pg/mL was associated with a 46.6-fold increase. However, abnormal circadian BP patterns were not associated with incident stroke. In this pilot study, elevated nocturnal BP and high plasma BNP just before patients left the hospital were significant predictors of stroke events in CHF patients. Further study is needed to confirm this hypothesis. (*Hypertens Res* 2008; 31: 289–294)

***Key Words*: congestive heart failure, stroke, nocturnal blood pressure, brain-type natriuretic peptide**

Introduction

Congestive heart failure (CHF) is commonly seen in elderly populations (*1*), and recent epidemiological studies have shown that its prevalence has been increasing in a growing number of elderly populations (*2*). Despite progress in antihypertensive treatment, the incidence of CHF has not decreased (*3*).

Incident stroke, which sometimes accompanies CHF (*4*, *5*), is one of the most serious complications in the clinical course of CHF. CHF itself has been reported to be associated with a two- to three-fold increased risk of incident stroke (*6*). Various heart diseases that include CHF are described as stroke risk factors in the American Heart Association Stroke Guidelines (*7*). The mechanisms of stroke seen in CHF patients may include intracardiac thrombus caused by left ventricular (LV) dysfunction (*8*), atrial fibrillation, or an atherosclerotic risk factor such as diabetes, hypertension, or hyperlipidemia (*9*). However, the clinical factors most closely associated with incident stroke in hospitalized CHF patients remain unclear. Thus, we performed this pilot study to explore the clinical

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predictors of stroke.

Methods

Study Population

We completed baseline examinations in 117 patients (mean age: 67±11 years; 73 men, 44 women) who were currently hospitalized with a diagnosis of CHF at Jichi Medical University Hospital, Tochigi, Japan. The baseline examinations were performed when the patient condition was stabilized, and in most cases occurred just before the patient left the hospital. The study was performed from July 2002 to March 2004. All of the patients were seen by cardiologists. We excluded patients with renal failure (serum creatinine >3 mg/dL), dementia, cancer, or other severe noncardiovascular disease. Informed consent was obtained from all participants. Six patients lost to follow-up were excluded from the study, and finally 111 patients were analyzed.

Diabetes mellitus was defined by either fasting glucose level ≥126 mg/dL, a random nonfasting glucose level ≥200 mg/dL, or the use of antidiabetic drugs or insulin (*10*). Hyperlipidemia was defined as total cholesterol level >220 mg/dL or the use of an oral lipid-lowering drug. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Electrocardiographically verified LV hypertrophy was defined as an abnormally high voltage of QRS complex (R in V_5 plus S in V_1 >3.5 mV) associated with either flat T-waves (<10% of the R-wave) or ST-segment depression and biphasic T-waves (*11*).

Twenty-Four–Hour Ambulatory Blood Pressure Monitoring

When CHF was stabilized, noninvasive ambulatory blood pressure (BP) was monitored by an automatic system using electric cuff inflation (TM-2425, A&D Co., Tokyo, Japan), which recorded both BP (by the oscillometric method) and pulse rate every 30 min for 24 h. The accuracy of this device was validated previously (*12*). Nocturnal BP was defined as the average of BP measurements during the time the patient was in bed, and awake BP was defined as the average of BP measurements recorded during the rest of the day.

We subclassified the patients as either dippers, nondippers, or risers according to the percentage of nocturnal systolic BP (SBP) reduction ($100 \times (1 - \text{nocturnal SBP/awake SBP})$), as follows: in dippers, the fall was between 10% and 20%; in nondippers it was between 0% and 10%; and in risers it was less than 0%.

Other Examinations

Blood was drawn after 10 min rest in the supine position. Brain-type natriuretic peptide (BNP) was measured from unextracted plasma using highly sensitive, noncompetitive immunoradiometric assays (Shiono-RIA; Shionogi, Osaka, Japan). Transthoracic two-dimensional echocardiography (Sonos 5500, Philips, Andover, USA) was performed in all subjects. The left ventricular ejection fraction (LVEF) was calculated by the Teichholz method (*13*).

Follow-Up and Outcome

A follow-up study was performed from September 1 to December 31, 2005. The mean follow-up period was 18±9 months. The patients' medical records were reviewed when they were followed in the same hospital. When the patients were followed in other hospitals, we interviewed them by mail or telephone. Stroke events were the main outcome of this study, including cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. There were no significant differences between the stroke and non-stroke groups in the duration of the follow-up period. Each stroke event was diagnosed by the physician who was caring for the patient at the time of the event. Independent neurologists reviewed the cases and confirmed the diagnoses of stroke events.

Statistical Analysis

All statistical analyses were carried out with SPSS software, version 11.0 (SPSS, Chicago, USA). The unpaired *t*-test was performed to test mean differences between the stroke and non-stroke groups. The χ^2 test was used to compare proportions. Log-rank statistics were used to test the differences between Kaplan-Meier survival curves. Adjusted hazard ratios (HRs) with 95% confidence intervals (CI) were based on multivariate Cox regression analyses adjusting for age, sex, BMI, and casual SBP. Data were expressed as means±SD or as percentages. Two-tailed $p<0.05$ was considered statistically significant.

Results

Baseline Characteristics

The mean age of the patients was 67±11 years, and 62% were men. Of the 111 study subjects, there were 10 cases of stroke (9%) during the follow-up period. Of these, 7 were ischemic and 3 were hemorrhagic. In the stroke group, the causes of CHF were ischemic heart disease in 4 (40%) and hypertensive heart disease in 6 (60%). Among the 101 patients in the non-stroke group, 32 (31.7%) had ischemic heart disease, 27 (26.7%) had hypertensive heart disease, 16 (15.8%) had dilated cardiomyopathy, 4 (4%) had hypertrophic cardiomyopathy, 22 (21.8%) had valvular heart disease, and 6 (5.9%) had other diseases.

As a preliminary step, we compared the clinical factors between the stroke and non-stroke groups as shown in Table 1. There were no significant differences in demographic or classical risk profiles, or in the severity of CHF evaluated by

Table 1. Baseline Characteristics

Measures	Stroke group ($n=10$)	Non-stroke group ($n=101$)	p
Age, years	67.6	67.5	0.97
Male, %	60	80	0.19
Body mass index, kg/m^2	22.8	22.6	0.90
Diabetes, %	60	40	0.31
Atrial fibrillation, %	10	30	0.28
NYHA III/IV, %	70	75	0.73
Creatinine, mg/mL	1.35	1.18	0.47
Hematocrit, %	42.4	38.9	0.11
BNP geometric mean, pg/mL	650	233	0.02
ECG-LVH, %	20	41	0.17
LVEF, %	43.0	45.3	0.70
Underlying heart disease			
Ischemic heart disease, %	40	32	0.60
Non-ischemic heart disease, %	60	68	0.60
Cardiovascular drugs			
Calcium channel blockers, %	50	44	0.70
ACE inhibitors, %	80	49	0.06
Angiotensin II receptor blockers, %	10	23	0.35
β-Blockers, %	50	38	0.45
α-Blockers, %	0	6	0.43
Diuretics, %	100	86	0.21
Aspirin, %	50	48	0.88
Ticlopidine, %	10	3	0.51
Cilostazol, %	0	1	0.76
Warfarin, %	30	41	0.52
Blood pressures			
Casual SBP, mmHg	139	122	0.02
Casual DBP, mmHg	87	73	0.004
Awake SBP, mmHg	131	120	0.07
Awake DBP, mmHg	80	71	0.11
Nocturnal SBP, mmHg	131	112	0.005
Nocturnal DBP, mmHg	79	67	0.03

NYHA, New York Heart Association; BNP, brain-type natriuretic peptide; ECG-LVH, left ventricular hypertrophy verified by electrocardiography; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure.

New York Heart Association (NYHA) class between the groups. There were no significant differences between the groups in the cause of heart failure (ischemic *vs.* nonischemic) or in cardiovascular medications. However, there were some differences: plasma BNP and nocturnal BP were higher in the stroke group than in the non-stroke group. Therefore, we tested the tentative hypothesis that baseline plasma BNP and nocturnal BP are associated with a future incidence of stroke in our patients.

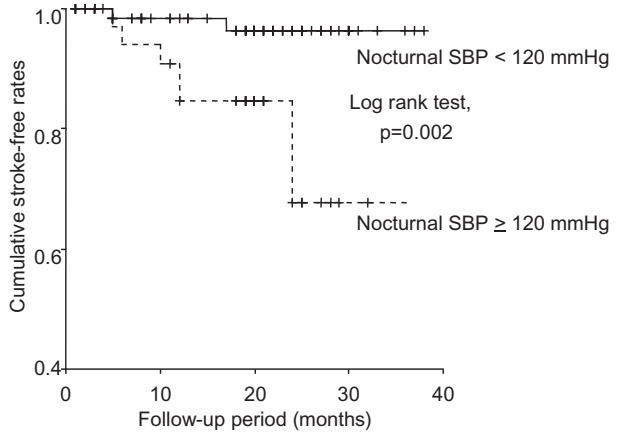

Fig. 1. *Kaplan-Meier curves for the incidence of stroke by nocturnal SBP. Patients were divided into two groups: those with nocturnal SBP ≥120 mmHg (n = 37) and those with nocturnal SBP < 120 mmHg (n = 72). The cumulative stroke-free rates were 68% in the nocturnal SBP ≥120 mmHg group and 96% in the nocturnal SBP < 120 mmHg group.*

Outcome

First, we performed the Kaplan-Meier analysis using two categories of nocturnal SBP (nocturnal SBP <120 mmHg, and ≥120 mmHg) as shown in Fig. 1. The cutoff value of nocturnal SBP 120 mmHg was based on multiple hypertension guidelines (*14–16*). The higher nocturnal SBP group had a significantly higher incidence of stroke than the lower nocturnal SBP group (log-rank 9.88, $p=0.002$). We then performed another Kaplan-Meier analysis using two categories of BNP divided by the 75th percentile of BNP (600 pg/mL) (Fig. 2). The Kaplan-Meier curves show that the patients with BNP ≥600 pg/mL had a significantly higher incidence of stroke than the lower-BNP group (log-rank 28.6, $p=0.0001$). In multivariate Cox regression analysis adjusting for age, sex, BMI, and casual SBP, a 1 mmHg increase in nocturnal SBP was associated with a 6% increase in the likelihood of stroke, and nocturnal SBP ≥120 mmHg was associated with a 7.5-fold higher likelihood of having a stroke independent of other covariates (Table 2). On the other hand, increased BNP was associated with increased risk of incident stroke, and patients with BNP ≥600 pg/mL had a 47-fold higher likelihood of stroke than those in the lower-BNP group independent of other covariates. However, abnormal circadian BP patterns, such as nondipping and rising, were not associated with the incidence of stroke.

Discussion

In this pilot study, higher levels of nocturnal BP and plasma BNP were independent predictors of stroke in CHF patients. The risk factors for stroke in CHF patients reported previ-

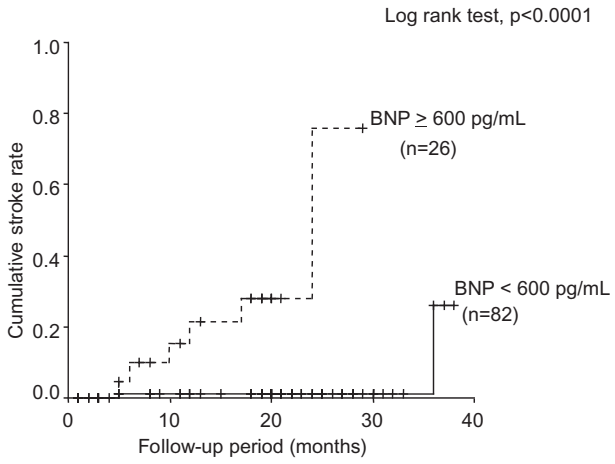

Fig. 2. *Kaplan-Meier curves for the incidence of stroke by BNP. Patients were divided into two groups: those with BNP ≥600 pg/mL and those with BNP < 600 pg/mL. The cumulative stroke rates were 74% in the BNP ≥600 pg/mL group and 24% in the BNP < 600 pg/mL group.*

Table 2. Cox Regression Analysis for Stroke

Variables	Hazard ratio (95% CI)*	*p* value
24 h SBP (mmHg)	1.03 (0.99–1.08)	0.16
Nocturnal SBP (mmHg)	1.06 (1.01–1.12)	0.03
Nondipper (yes or no)	2.80 (0.66–11.9)	0.17
Riser (yes or no)	2.63 (0.61–11.3)	0.19
log (BNP pg/mL)	6.58 (2.33–18.6)	0.0004
Nocturnal SBP ≥120 (mmHg)	7.47 (1.26–44.5)	0.03
BNP ≥600 (pg/mL)**	46.6 (4.41–492.2)	0.001

These variables were entered one-by-one in this model. Adjusted by age, sex, BMI and casual SBP. *Adjusted by age, sex, BMI and casual SBP. **This cutoff value was 75 percentile of BNP. CI, confidence interval; SBP, systolic blood pressure; BNP, brain-type natriuretic peptide; BMI, body mass index.

ously were hemostatic abnormality (*8*) and impaired cerebral blood flow, both of which were associated with cardiac dysfunction (*9*). However, none of these reports has shown the significance of BP as a risk factor for stroke. Our finding of BNP as a risk factor for stroke also has not been reported before.

Cardiomyopathy and valvular heart disease can be risk factors for stroke in cardiac diseases (*8, 17*). However, these two were not present in the stroke group. Therefore, cardiomyopathy and valvular heart disease as underlying risk factors for heart disease may not have influenced our results.

Nocturnal BP and Stroke

In our study, nocturnal BP, as a continuous variable, was significantly associated with incident stroke independent of other confounders, including casual BP. Nocturnal BP ≥120 mmHg was associated with a 7.5-fold increase in incident stroke. Because the reported BP in moderate to severe CHF patients was usually low, high BP has rarely been reported as a risk for complications (*18*). In a study of severe CHF (NYHA class IV), the average BP was 108.2±13.4/72.2±8.1 mmHg (*19*). On the other hand, the patients in our study were completely different from those in previous reports because only mild to moderate CHF patients who were able to leave the hospital were enrolled in our study. There are also limited data on ambulatory BP monitoring in CHF patients; only the blunted circadian variability of BP (*i.e.*, nondipping) in CHF patients has been reported (*20*). Therefore, this is the first study to show a significant relationship between high nocturnal BP and incident stroke. Nocturnal high BP (or nondipping) is a well-known predictor of cardiovascular events in hypertensive patients (*21–27*). Our study expands the previous findings of nocturnal BP in hypertensive patients to risk stratification for CHF patients. Because the significant association of nocturnal BP was independent of casual BP in our study, ambulatory BP will be necessary for stroke prevention. On the other hand, neither nondipping nor rising was associated with future stroke, probably because our ambulatory BP monitoring was performed in a hospital setting, which could influence physical inactivity in the daytime and result in a high percentage of nondipping patterns. Further study, involving ambulatory CHF patients, is needed.

Severity of CHF and Stroke

In our study, increased plasma BNP level was a significant predictor of stroke. Especially, a high BNP level (≥600 pg/mL) was associated with a 47-fold increased risk of stroke. This is not surprising, since a previous report has shown that the severity of CHF strongly predicted cardiac morbidity and mortality in CHF patients (*28*). However, no report has shown that a single measurement of plasma BNP in a stable CHF condition could predict the incidence of stroke. A previous study showed that decreased LV function was associated with stroke in CHF patients (*29*), but LV function in our population was not severely decreased. Because the number of CHF patients with preserved LV function has been increasing (*30*), our finding—that plasma BNP just before leaving the hospital can predict stroke—is important and can be applied to stroke prevention strategy in CHF patients.

Study Limitations

There are some limitations to this study. First, the number of subjects was small. Therefore, some clinical factors might have been underpowered. Second, the results of this study can be applied only to those subjects who were able to leave the hospital. Third, ambulatory BP monitoring was performed

while the patients were taking cardiovascular drugs. Therefore, the results of ambulatory BP levels and circadian BP rhythm could have been influenced to some extent. Fourth, the frequency of anticoagulation therapy was similar between the stroke group and the non-stroke group, but the data on anticoagulation therapy were obtained only in the hospital, and the control status of anticoagulation therapy was not available from our database. Finally, we did not perform a comprehensive approach, which would have included an assessment of hemostatic abnormality or brain scanning.

Conclusion

In our pilot study of hospitalized CHF patients, high nocturnal BP and high plasma BNP were independent predictors of stroke. To prevent stroke in hospitalized CHF patients, it is necessary to aggressively control nocturnal BP guided by ambulatory BP monitoring and to sufficiently lower BNP through multiple strategies. A further interventional study using a larger number of patients is going to be performed to confirm the findings.

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