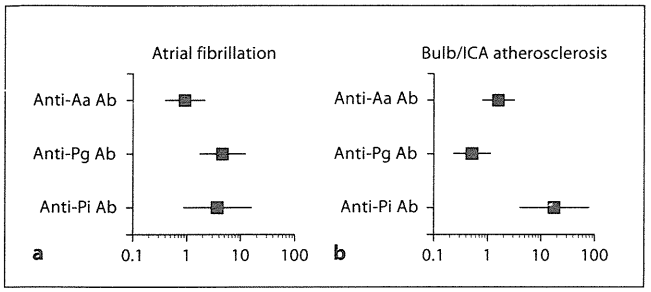

Fig. 2. Association of serum anti-periodontal pathogen antibodies. OR of serum antibody (Ab) levels against Aa, Pg and Pi in association with atrial fibrillation (**a**) including analyses that controlled for age and hypertension, and with bulb/ICA atherosclerosis (**b**) controlled for sex, hypertension, diabetes mellitus, dyslipidemia, drinking and serum hs-CRP levels.

serum anti-Pi antibody, even after controlling for the statistically selected associated factors (overall χ^2 = 46.1, R^2 = 0.18, n = 209, $p < 0.0001$. Anti-Pg antibody: OR 16.58, 95% CI 3.96–78.93, $p < 0.0001$; fig. 2b), but not with the levels of serum antibodies against Aa and Pg.

The association between the levels of serum anti-periodontal-pathogen antibodies and acute ischemic stroke was evaluated. There was no significant difference in the levels of serum antibodies against Aa, Pg and Pi between the patients with acute ischemic stroke and those with no previous stroke (p = 0.104, 0.486 and 0.273, respectively). Considering the subtypes of acute ischemic stroke, there were significant differences in the levels of serum anti-Pi antibody between the patients with atherothrombotic stroke and those with no previous stroke (p = 0.0035, fig. 1i). With a forward stepwise regression forced to include the levels of serum anti-Pi antibody, age, gender, bulb/ICA atherosclerosis, hypertension, diabetes mellitus, drinking, atrial fibrillation and serum hs-CRP levels were selected as factors that associated with atherothrombotic stroke. When we performed a logistic regression analysis with statistically selected associated factors excluding bulb/ICA atherosclerosis, the levels of serum anti-Pi antibody were significantly associated with atherothrombotic stroke (overall $\chi^2 = 77.0$, $R^2 = 0.44$, n = 129, $p < 0.0001$. Anti-Pi antibody: OR 23.6, 95% CI 2.65–298.2, p = 0.008). However, when we included bulb/ICA atherosclerosis into this model, the levels of serum anti-Pi antibody were no longer significantly associated with atherothrombotic stroke (overall $\chi^2 = 98.0$, $R^2 = 0.56$, n = 129, $p < 0.0001$. Anti-Pi antibody: p = 0.107).

Discussion

This study demonstrated that serum hs-CRP levels were independently associated with acute ischemic stroke. The levels of serum antibodies against select periodontal pathogens were significantly higher in the patients with dyslipidemia, drinking habit, atrial fibrillation and bulb/ICA atherosclerosis than in patients without these conditions. No significant association between smoking habits and serum antibody levels against any periodontal pathogen was observed. The levels of serum anti-Pg antibody were significantly associated with atrial fibrillation and the levels of serum anti-Pi antibody were significantly associated with bulb/ICA atherosclerosis, independent of the statistically selected associated factors. The levels of serum anti-Pi antibody were significantly higher in the patients with atherothrombotic stroke and were associated with atherosclerotic stroke through bulb/ICA atherosclerosis.

Periodontitis, which is caused by local infections with periodontal pathogens, leads to systemic reactions, such as inflammation, and immunological reactions. In periodontitis, gingival inflammation accompanied by microulceration of the periodontal pocket epithelium and increasing subgingival space for bacterial deposits provide bacteria and their constituents with access to the bloodstream. Local infection in the periodontal pockets triggers a systemic inflammatory response and the release of inflammatory mediators, e.g. CRP. The presence of major periodontal pathogens in subgingival samples was positively associated with elevated CRP levels [12]. The elevation of CRP is directly associated with atherogenesis [13]. Inflammatory markers such as hs-CRP predict myocardial infarction and cerebral infarction, which occur later in life. Systemic or local infection with periodontal pathogens may partially account for the increased serum CRP levels and may be associated with stroke pathogenesis. Our results suggest that serum hs-CRP levels were associated with bulb/ICA atherosclerosis and acute ischemic stroke independent of classical vascular risk factors. These results are supported by many previous reports. Elevated serum hs-CRP levels in acute ischemic stroke are largely caused by inflammation resulting from ischemic insults. No significant associations were observed between the levels of serum antibodies against periodontal pathogens and the serum hs-CRP levels. Thus, inflammation and immunological reactions caused by periodontitis may be independently associated with systemic reactions, e.g. atherosclerosis. Our results support the hypothesis that serum anti-periodontal-

pathogen antibodies levels are associated with atrial fibrillation and bulb/ICA atherosclerosis, independent of serum hs-CRP levels.

In the Framingham Heart Study, the risk factors for atrial fibrillation were identified as age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmurs and heart failure [14]. In addition, atrial fibrillation is associated with inflammation, e.g. CRP [6]. The degeneration of pulmonary veins is an important cause of atrial fibrillation [15]. In this study, we evaluated the possible association of serum anti-periodontal-pathogen antibodies with atrial fibrillation. Our results indicate that the levels of serum anti-Pg antibody were significantly associated with the prevalence of atrial fibrillation, independent of serum hs-CRP levels and the other classical vascular risk factors. To our knowledge, this study is the first to show a possible association between the levels of serum anti-periodontal-pathogen antibodies and atrial fibrillation. Inflammation or immunological responses resulting from periodontitis may lead to the degeneration of pulmonary veins, causing atrial fibrillation.

Chronic infection with *Chlamydia pneumoniae*, *Helicobacter pylori* and cytomegalovirus is associated with cardiovascular disease and atherosclerosis [16–18]. A recent study detected the bacterial DNA of major periodontal pathogens in large-artery atheromatous plaques, showing that 30% of the specimens are positive for *Tannerella forsythus*, 26% are positive for Pg, 18% are positive for Aa and 14% are positive for Pi [19]. In the Oral Infections and Vascular Disease Epidemiology Study (INVEST), a significant association was observed between the levels of tooth loss and the prevalence of carotid artery plaque [20]. Among patients with 0–9 missing teeth, 46% had carotid artery plaque, whereas among those with more than 10 missing teeth, approximately 60% had carotid artery plaque. This cross-sectional study reveals that carotid IMT is regressed on tertiles of periodontal pathogens in the subgingival plaque [21]. Furthermore, the levels of serum antibodies (IgA and IgG) against Aa and Pg were positively correlated with mean IMT [22]. On the other hand, the immunoreactivity to Aa leukotoxin correlates negatively with a future stroke in women, but not in men [23]. Our results show that the levels of serum anti-periodontal-pathogen antibodies, especially against Pi, independently predict large-artery diseases, e.g. carotid artery atherosclerosis.

The risk profiles differ significantly among ischemic stroke subtypes. It is reported that a total of 9.7% patients in the stroke patients had suffered a previous infection within the month before the stroke [24], and previous infection was more frequent in ischemic stroke cases than in intracerebral hemorrhage. A limited number of reports have evaluated the influence of systemic periodontal pathogen infections on stroke. Pussinen et al. [3, 4] demonstrated that IgA seropositivity against Pg is associated with stroke incidence in prospective case-control studies. A recent case-control study revealed that high levels of periodontal clinical attachment loss, gingivitis and radiographic bone loss are independently associated with stroke after adjusting for age, gender, tooth loss and the established cardiovascular risk factors [25]; however, no studies have evaluated the association of the levels of serum anti-periodontal-pathogens antibodies with the subtypes of ischemic stroke. In this study, the levels of serum anti-Pi antibody were significantly higher in the patients with atherothrombotic stroke.

It is important to determine whether different periodontal pathogens or their serum antibodies have different associations with ischemic stroke. The different periodontal pathogens show different levels of association with periodontitis; however, to our knowledge, there are still no data about the different degrees to which periodontal pathogens or their antibodies are associated with cardiovascular disease. This study showed the different degrees to which anti-periodontal-pathogen antibodies are associated with ischemic-stroke subtypes and their risk factors: the levels of serum anti-Pi antibody were higher in the patients with atherothrombotic stroke, the levels of anti-Pi antibody were associated with bulb/ICA atherosclerosis and the levels of anti-Pg antibody were associated with atrial fibrillation. Therefore, the different periodontal pathogens or their antibodies may have different associations with cardiovascular disease.

This study has some limitations. The control group was composed of patients from neurological and neurosurgical clinics with no previous stroke symptomatic or detectable by MRI, in order to avoid possible confounding from anamnestic stroke with a silent infarct. Thus, there was a selection bias favoring nonstroke patients from the general population. In addition, the basic characteristics of the patients with no previous stroke differed significantly from those of the acute ischemic stroke patients. Periodontal disease status was not evaluated in the study; therefore, the relationship between this status and the levels of serum anti-periodontal-pathogen antibodies was not assessed.

In conclusion, our results suggest that anti-Pg antibody may be associated with atrial fibrillation and that anti-Pi antibody may be associated with carotid artery

atherosclerosis. In addition, anti-Pi antibody may be associated with atherothrombotic stroke. Thus, periodontitis may lead to serious systemic diseases. Further studies will be needed to clarify whether intervention against periodontitis could prevent systemic diseases.

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ORIGINAL ARTICLE

The optimal timing of antihypertensive medication administration for morning hypertension in patients with cerebral infarction

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Morning hypertension is an independent risk factor for cardiovascular diseases, particularly stroke. However, the optimal time at which to take antihypertensive medication to treat morning hypertension remains unclear. We prospectively enrolled elderly patients (over 65 years old) with morning hypertension who had suffered an ischemic stroke (or strokes). Additional treatments (one of six arms) were randomly administered for 10 weeks in the morning, in the evening or at bedtime (n=15 for each time point/medication). The patients measured their blood pressure and heart rate at home for 14 days prior to the intervention and for the final 14 days, and recorded the data in a blood pressure diary. The patients' urinary albumin/creatinine ratios were evaluated before and after the 10-week intervention. A total of 270 patients were enrolled in this study (mean age: 75.6 ± 5.8 years; female/male ratio: 125/145). Their morning and evening systolic blood pressures were significantly decreased after following any of the study medication dosing schedules (P<0.001). However, the reductions in the differences between the morning and evening systolic blood pressures were significant only when the medication was taken in the evening or at bedtime (P<0.001 with repeated measures analysis of variance). Furthermore, the recovery rate from morning hypertension was also higher when the medication was taken in the evening (40.0%) or at bedtime (45.6%), rather than in the morning (22.2%; P=0.003 with the χ^2-test). Antihypertensive medication taken in the evening or at bedtime is the most effective in treating morning hypertension when the patient adheres to the medication regimen.
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Keywords: antihypertensive medication; cerebrovascular disease; morning hypertension

INTRODUCTION

Hypertension is a major independent risk factor for cardiovascular diseases, especially stroke, and antihypertensive therapy is effective in preventing cardiovascular events.[1–4] Blood pressure commonly exhibits a diurnal variation, peaking during the morning and then declining, to reach a minimum at approximately midnight. Similarly, there is a marked diurnal variation in the onset of cardiovascular events, with a peak incidence of myocardial infarction, sudden cardiac death, and ischemic and hemorrhagic strokes occurring in the morning (from 0600 hours to noon).[5] Several prospective studies that evaluated self-measured home blood pressure have indicated that morning hypertension, which includes the morning surge, is an important risk factor for stroke and cardiovascular events.[6]

Antihypertensive medication is usually prescribed to be taken once in the morning to increase the likelihood of patient adherence. However, this medication schedule does not satisfactorily decrease morning hypertension. To date, several reports have evaluated the optimal time for taking antihypertensive medication to treat morning hypertension.[7,8] However, those studies either compared morning medication schedules with evening schedules or morning schedules with bedtime schedules but did not compare all three schedules to evaluate their effectiveness at lowering morning hypertension. Therefore, it is still unknown whether taking medications in the evening or at bedtime is better than morning administration to treat morning hypertension. The purpose of this study was to define the optimal dosing schedule for antihypertensive medications to treat morning hypertension.

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METHODS

Study design and patients

We prospectively enrolled elderly patients (over 65 years old) with morning hypertension who had a history of ischemic stroke (or strokes), could record their home blood pressure consistently and could visit the outpatient clinic at Kagawa University School of Medicine Hospital or Osaka Neurosurgical Hospital from April 2008 to December 2009. We excluded patients who had poor medication adherence (<95% of doses taken at the proper time). In addition, patients were also excluded if they were not good candidates to receive an additional antihypertensive medicine because of severe carotid stenosis (more than 75% stenosis according to the North American Symptomatic Carotid Endarterectomy Trial criteria[9]), liver dysfunction (aspartate aminotransferase $\geqslant 100\,IU\,l^{-1}$ or alanine aminotransferase $\geqslant 100\,IU\,l^{-1}$), renal dysfunction (creatinine $\geqslant 1.5\,mg\,dl^{-1}$) or an allergy to the medicine. All the patients who enrolled in this study provided their informed consent to participate. Our protocol was approved by the ethics review committee of the Kagawa University School of Medicine Hospital, Kagawa, Japan. The study protocol was registered on a clinical trials registration site (University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR: #UMIN000001764)).

First, we evaluated the subjects' self-measured home blood pressure and heart rate for 14 days. The patients were asked to record these values in a blood pressure diary. Then each patient was randomly assigned to receive one of the interventional treatments (the calcium channel blocker amlodipine 5 mg per day; the angiotensin-converting enzyme inhibitor perindopril 4 mg per day; or the angiotensin II receptor blocker candesartan 8 mg per day, olmesartan 20 mg per day, valsartan 80 mg per day or telmisartan 40 mg per day) for 10 weeks. Patients were not administered a medication from the same class as one of their current antihypertensive drugs, and the interventional treatment was added to each patient's current antihypertensive medication(s) in the morning (after breakfast), in the evening (after dinner) or at bedtime (n=15 for each time point/medication).

We also assessed the presence of diabetes mellitus and dyslipidemia. Diabetes mellitus was defined as a fasting blood glucose level $\geqslant 126\,mg\,dl^{-1}$ or the use of any antidiabetes drugs. Dyslipidemia was defined as a low-density lipoprotein cholesterol level $\geqslant 140\,mg\,dl^{-1}$, a triglyceride level $\geqslant 150\,mg\,dl^{-1}$, a high-density lipoprotein cholesterol level $<40\,mg\,dl^{-1}$ or the use of any antihyperlipidemia drugs. We also recorded the class(es) of patients' original antihypertensive medication(s).

Home blood pressure

Home blood pressure was measured according to the Japanese Society of Hypertension guidelines for the self-monitoring of blood pressure at home.[10] Home blood pressure was measured with an electrical sphygmomanometer in a standardized manner following 10 min of rest in a sitting position. The blood pressure was measured three times with more than 1 min between samplings in the morning (within 30 min of awakening and prior to doing anything else except going to the restroom) and in the evening (before dinner). The median value of these three blood pressure measurements was used in the subsequent analyses. The home blood pressure and heart rate values were collected for 14 days prior to the intervention and during the final 14 days of the observational period, beginning 8 weeks after starting the intervention. The mean home blood pressure and heart rate values from the 14 days of measurement were used for analysis.

The diagnosis of morning hypertension was based on the home blood pressures recorded for 14 days prior to the intervention; patients were determined to have morning hypertension when the average of their morning and evening systolic blood pressures was $\geqslant 135$ mm Hg and the difference between the morning and evening systolic blood pressure (morning systolic blood pressure−evening systolic blood pressure) was $\geqslant 15$ mm Hg, as described elsewhere.[8]

Microalbuminuria

The urinary albumin/creatinine ratio (UACR, $mg\,g^{-1}$) was evaluated using fasting morning spot-urine tests conducted prior to the intervention and 10 weeks after starting the intervention. Urinary albumin levels were measured with the immunoturbidimetric method, and urinary creatinine levels were measured with the enzymatic method. UACR was calculated as described elsewhere.[11]

Statistical analysis

The data are expressed as the means ± s.d. for continuous variables and as frequencies and percentages for discrete variables. Univariate analyses were performed to evaluate the differences between groups with respect to baseline characteristics, current medication and UACR. The clinical characteristics of the groups were compared using a one-way analysis of variance (ANOVA, for continuous variables) or Fisher's exact test (for discrete variables). Changes between the morning and evening systolic blood pressures during the interventional treatment period and changes in the UACR were examined using repeated measures ANOVA. The reduction rates of them were calculated with the formula (pre-value–post-value)/pre-value. Then, the differences of reduction rates between the each dosing schedules were examined using a one-way ANOVA. The rates of recovery from morning hypertension were examined using the χ^2-test. When the P-value was <0.05 by ANOVA, Turkey-Kramer's Honestly Significant Difference test or Bonferroni's correction for multiple comparisons was applied to evaluate whether the differences in each between-groups were significant. The difference of systolic blood pressure, diastolic blood pressure, the level of difference between the morning and evening systolic blood pressure (morning systolic blood pressure−evening systolic blood pressure), and UACR between the pre- and postinterventional treatment periods were evaluated for each medication dosing schedule using a paired t-test. The statistical analyses were performed using JMP software version 9.0 or StatView version 5.0 for Macintosh (SAS, Cary, NC, USA). All the analyses were two-tailed, and a value of $P<0.05$ was considered statistically significant.

RESULTS

Patient characteristics

The subjects' clinical characteristics, morning and evening systolic blood pressures, diastolic blood pressures, heart rates and baseline UACRs grouped according to morning, evening and bedtime antihypertensive medication schedules (n=90) are listed in Table 1. There were no significant differences in clinical characteristics between the different medication schedule groups.

The appropriate timing of antihypertensive medication to treat morning hypertension

There were no significant differences in the morning and evening systolic blood pressures, the diastolic blood pressures and the heart rates before the interventions between the different medication schedule groups (Table 1). All of the studied dosing schedules of antihypertensive medications effectively reduced morning and evening systolic blood pressures ($P<0.001$ using two-way repeated measures ANOVA, Figure 1). There were no significant differences in the changes of the morning and evening systolic blood pressures among the groups on different dosing schedules (P=0.29 and 0.86 using two-way repeated measures ANOVA, respectively). The reduction rates of morning systolic blood pressure with the morning, evening or bedtime dosing schedule were 0.119 ± 0.023, 0.121 ± 0.018 or 0.126 ± 0.025, respectively (P=0.026, using one-way ANOVA). It was significantly higher in the bedtime medication schedule than that in the morning medication schedule (P=0.021). Moreover, the reduction rates of evening systolic blood pressure with either medication schedules were 0.088 ± 0.041, 0.059 ± 0.059 or 0.059 ± 0.054, respectively ($P<0.001$, using one-way ANOVA). It was significantly higher in the morning medication schedule than that in the evening and bedtime medication schedule (P=0.001 and $P<0.001$, respectively). In contrast, the difference between the morning and evening systolic blood pressure (morning systolic blood pressure–evening systolic blood pressure) was reduced significantly with the evening and

Table 1 Clinical characteristics of the study cohort

	All subjects (n=270)	*Morning* (n=90)	*Evening* (n=90)	*Bedtime* (n=90)	P-value
Age, years	75.6±5.8	75.7±6.1	75.0±5.5	76.2±5.9	0.37
Gender (female/male)	125/145	37/53	44/46	44/46	0.48
Dyslipidemia, *n* (%)	101 (37.4)	35 (37.8)	33 (36.7)	33 (36.7)	0.94
Diabetes mellitus, *n* (%)	55 (20.4)	17 (18.9)	17 (18.9)	21(23.3)	0.69
Ischemic stroke subtypes					
Lacunar, *n* (%)	101 (37.4)	32 (35.6)	33 (36.7)	36 (40.0)	0.99
Atherothrombotic, *n* (%)	75 (27.8)	23 (25.6)	26 (28.9)	26 (28.9)	
Cardioembolic, *n* (%)	45 (16.7)	18 (20.0)	14 (15.6)	13 (14.4)	
Other, *n* (%)	30 (11.1)	10 (11.1)	11 (12.2)	9 (10.0)	
Undetermined, *n* (%)	19 (7.0)	7 (7.8)	6 (6.7)	6 (6.7)	
Prior medication					
CCB, *n* (%)	200 (74.1)	68 (75.6)	65 (72.2)	67 (74.4)	0.87
ARB, *n* (%)	50 (18.5)	18 (20.0)	15 (16.7)	17 (18.9)	0.84
ACEI, *n* (%)	11 (4.1)	4 (4.4)	4 (4.4)	3 (3.3)	0.91
Morning SBP, mm Hg	152.8±9.5	153.1±9.5	152.1±9.4	153.2±9.6	0.70
Morning DBP, mm Hg	84.4±10.6	85.3±10.8	83.3±10.3	84.5±10.7	0.43
Morning heart rate, per min	68.1±7.6	67.8±6.8	68.8±7.9	67.8±8.0	0.56
Evening SBP, mm Hg	134.2±9.4	135.2±9.6	133.8±9.5	133.8±9.3	0.54
Evening DBP, mm Hg	79.9±10.8	81.0±11.1	79.4±10.4	79.4±11.0	0.50
Evening heart rate, per min	70.9±8.2	69.6±7.2	71.6±9.0	71.5±8.2	0.19
UACR, mgg^{-1}	32.4±21.2	33.1±20.9	30.9±19.5	33.1±23.0	0.71

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

bedtime dosing schedule groups ($P<0.001$, using two-way repeated measures ANOVA with Bonferroni's corrections, respectively, Figure 1). There were significant reductions in the changes of the difference between the morning and evening systolic blood pressure with the evening and bedtime medication schedules compared with the morning medication schedule ($P<0.001$). The reduction rates of the difference between the morning and evening systolic blood pressure with the morning, evening or bedtime dosing schedule were -0.345 ± 1.05, 0.387 ± 0.908 or 0.596 ± 1.360, respectively ($P<0.001$, using one-way ANOVA). It was significantly higher in the evening and bedtime medication schedules than that in the morning medication schedule ($P<0.001$). In addition, the proportion of patients who recovered from morning hypertension was evaluated with respect to the timing of antihypertensive medication administration (Figure 2). Recovery from morning hypertension was defined as the attainment of the following follow-up home blood pressure measurements for 14 days: morning and evening systolic blood pressures averaging <135 mm Hg and the difference between the morning and evening systolic blood pressure (morning systolic blood pressure–evening systolic blood pressure) averaging <15 mm Hg. The rates of recovery from morning hypertension were higher among the patients who took their medications in the evening or at bedtime (40.0 and 45.6%, respectively) compared with those on the morning schedule (22.2%; $P=0.003$ with the χ^2-test).

The appropriate arms of antihypertensive medication to treat morning hypertension

There are significant differences in the reduction of the morning and evening systolic blood pressure among the medication arms ($P<0.001$, using two-way repeated measures ANOVA). Among the medication arms used in this study, amlodipine significantly reduced the morning and evening systolic blood pressure compared with the other arms ($P<0.001$). However, there was no significant difference in the difference between the morning and evening systolic blood pressure among the medication arms ($P=0.85$, using two-way repeated measures ANOVA).

Decreases in the UACR in each dosing schedule

We evaluated the effects of the different dosing schedules of antihypertensive medications on lowering the UACR. There were no significant differences in the UACRs before the interventions between the different medication schedule groups (Table 1). All of the dosing schedules produced effective reductions in the UACR ($P<0.001$, using two-way repeated measures ANOVA, Figure 3). However, there were no significant differences in the amount of UACR reduction among the different schedules ($P=0.59$, using two-way repeated measures ANOVA). The reduction rates of UACR with the morning, evening or bedtime medication schedules were 0.148 ± 0.068, 0.167 ± 0.169 or 0.178 ± 0.127, respectively ($P=0.28$, using one-way ANOVA). In addition, there was no significant difference among the medication arms in the reduction of UACR ($P=0.14$, using two-way repeated measures ANOVA).

DISCUSSION

In this study, the optimal medication dosing schedule for the most effective treatment of morning hypertension was prospectively evaluated using six antihypertensive medications. Our results indicate that to reduce the difference between morning and evening blood pressures, antihypertensive medication should be taken in the evening or at bedtime and that evening or bedtime administration of these

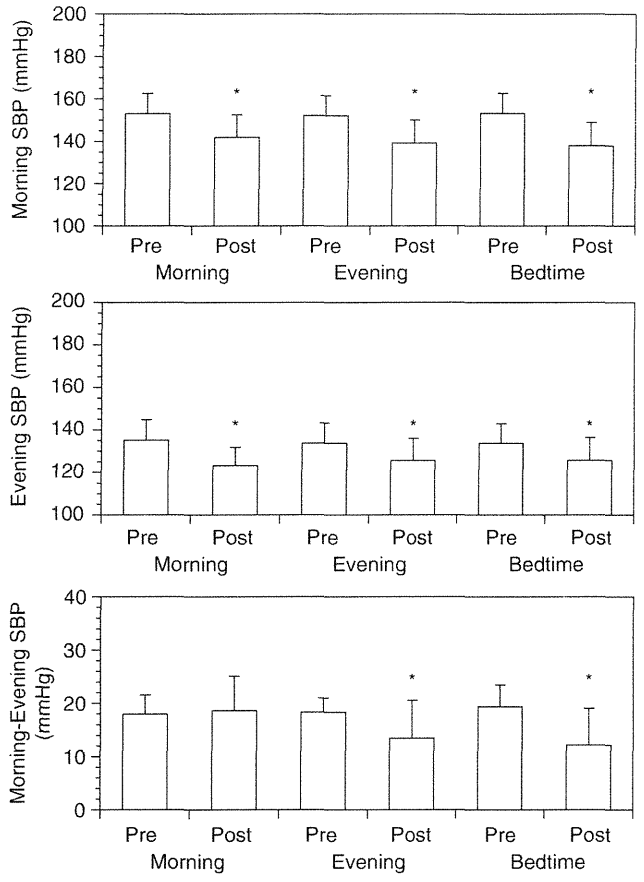

Figure 1 Differences in blood pressure reduction with different medication dosing schedules. Although there were no significant differences between the dosing schedules in terms of the levels of reduction of morning and evening SBPs, the difference between the morning and evening systolic blood pressure (morning–evening SBP) was significantly reduced in the groups that received evening or bedtime medications, but not in the group assigned to morning medications. SBP, systolic blood pressure. *$P<0.001$ compared with preintervention.

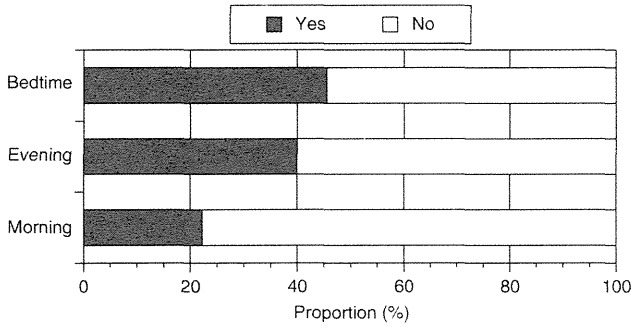

Figure 2 Recovery from morning hypertension according to the timing of medication administration. The recovery rate from morning hypertension was significantly higher following evening or bedtime dosing of medications compared with the morning dosing regimen. Recovery from morning hypertension was defined as the satisfaction of both of the following criteria: average morning and evening systolic blood pressure was <135 mm Hg and average difference between the morning and evening systolic blood pressure (morning systolic blood pressure–evening systolic blood pressure) was <15 mm Hg.

medications is more effective than morning administration at facilitating recovery from morning hypertension. However, there were no significant differences between the dosing schedules in the level of UACR reduction. Among the medication arms, amlodipine significantly reduced the morning and evening systolic blood pressure more than the other arms. However, there was no significant difference in the difference between morning and evening blood pressures among the medication arms.

Hypertension is known to be a major risk factor for cardiovascular events. In addition, it has been reported that antihypertensive medications strongly protect against cardiovascular diseases.[12] Therefore, antihypertensive treatment is commonly used in the clinic. The next logical step is to increase the quality of blood pressure control in hypertensive patients. It has been reported that morning hypertension is a strong risk factor for stroke.[6,13] The difference between the morning and evening self-measured blood pressures is an independent determinant of cardiac dysfunction.[14] The potential cardiovascular advantages of controlling morning hypertension have not been fully demonstrated. On the other hand, there are several reports that showed the reduced cardiovascular risks with the bedtime antihypertensive medications compared with the morning medications.[15–17] From this study, the bedtime antihypertensive medication was the most effective medication schedule reducing the morning systolic blood pressure and the difference between the morning and evening systolic blood pressure. Therefore, the bedtime antihypertensive medications could be the most effective timing to reduced cardiovascular risks controlling morning hypertension.

In this study, we evaluated the timing of the administration of antihypertensive medicine to control morning hypertension. We found that both evening and bedtime dosing of antihypertensive medication could effectively treat morning hypertension. Several studies support our results.[7,8] However, those studies either compared morning medication schedules with evening schedules or morning schedules with bedtime schedules but did not compare all three schedules to evaluate their effectiveness at lowering morning hypertension. Therefore, this study is the first to compare the effectiveness of antihypertensive medication at lowering blood pressure in patients with morning hypertension, who adhered to dosing schedules that included morning, evening and bedtime administrations of medication.

Patients are usually instructed to take medication in the morning to increase their adherence to the regimen, unless a medication specifically should be taken at another time. For this study, we selected subjects who had exhibited high adherence ($\geqslant$95%) to a medication regimen. Therefore, there was high adherence (more than 90%) to the dosing schedule, even among the patients who had been assigned to the evening or bedtime medication groups. However, there is a certain proportion of patients who show a low adherence to medication in general.[18] Therefore, when it is necessary to treat a patient with morning hypertension who does not comply well with medication regimens, prioritizing adherence is important because evening or bedtime dosing schedules may decrease compliance.

We also evaluated differences in the levels of reduction of the UACR between the morning, evening and bedtime medication schedules. Our results show that there were no significant differences in the UACR reduction level between the medication schedules. In the Japan Morning Surge-Target Organ Protection (J-TOP) study, the UACR was reduced more with bedtime administration than with morning administration of the angiotensin II receptor blocker candesartan.[8] However, in the J-TOP study, UACR reduction was evaluated over 6 months. In this study, we examined the effects of morning hypertension

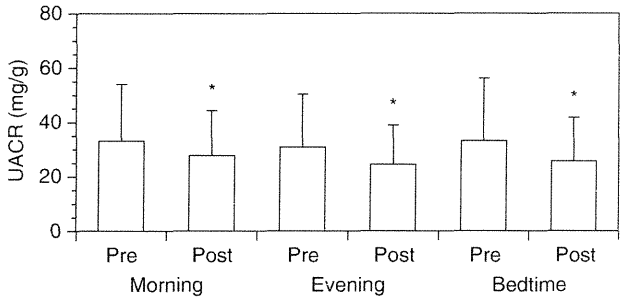

Figure 3 Effects of different dosing schedules on the urinary albumin/creatinine ratio (UACR). Although there were significant reductions in the UACR with all the dosing schedules ($P<0.001$, for all comparisons), there were no significant differences in the levels of reduction of UACR between the timings of medication administration (analyzed with repeated measure ANOVA). *$P<0.001$ compared with preintervention.

treatment for 2 months. The effects of treating morning hypertension on organ protection remain controversial. More than 6 months may be necessary to acquire sufficient statistical power to observe a significant difference between evening and bedtime administration of antihypertensive medications in terms of organ protection. In addition, the effects of the appropriate treatment of morning hypertension on cardiovascular disease prevention have not yet been determined.

This study has several limitations. First, all of the patients had experienced both an ischemic stroke (or strokes) and morning hypertension. Therefore, the study population may not represent the general population of patients with morning hypertension. Second, as described above, this study was designed to find the best medication dosing schedule to treat morning hypertension over a 2-month period. This time frame may be too short to observe differences in organ protection, for example, UACR reduction, between the different dosing schedules. Third, we evaluated self-measured home blood pressures. To more accurately assess blood pressure control, it may be better to evaluate ambulatory blood pressure measurements in the same time, as both self-measured home blood pressures and ambulatory blood pressure measurements are known to have some complementary strong and weak points each other. Fourth, as the dosing schedule, we have only got the information of medication schedule as morning, evening or bedtime. To understand more detailed performances of each medication schedule, it may be better to know the exact timing at which the patients took medicine.

The optimal timing of antihypertensive medication administration to treat morning hypertension was evaluated in this study. Our results indicate that antihypertensive medication taken in the evening or at bedtime is the most effective in treating morning hypertension when the patient adheres to the medication regimen. We did not observe a difference in organ protection, that is, UACR reduction, between the different antihypertensive medication dosing schedules during the 10-week intervention. Further studies are warranted to determine whether the appropriate treatment of morning hypertension could lead to organ protection or cardiovascular disease prevention.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Cancer-associated ischemic stroke is associated with elevated D-dimer and fibrin degradation product levels in acute ischemic stroke with advanced cancer

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Aim: Although several studies have reported various causes of ischemic stroke in patients with cancer, only a few have evaluated the clinical relevance of ischemic stroke pathogenesis to cancer. The aim of the present study was to elucidate the clinical characteristics of cancer-associated ischemic stroke.

Methods: We evaluated 154 ischemic stroke patients without cancer and 57 ischemic stroke patients with cancer who had either received continuous treatment for cancer within 5 years before to the onset of ischemic stroke, or who had been diagnosed with cancer within 1 year after the onset of ischemic stroke. Cancer patients were grouped into "cancer-associated ischemic stroke," the "conventional ischemic stroke," or "other."

Results: A total of 15 patients (26%) were classified into the cancer-associated ischemic stroke in cancer patients. In univariate analysis of the cancer-associated ischemic stroke and the others, there were significant differences in the prevalence of hypertension, hyperlipidemia and advanced cancer (clinical stage IV), and the levels of D-dimer, fibrin degradation product and hemoglobin. With multivariate regression analysis of those factors, the prevalence of hypertension, hyperlipidemia and advanced cancer (clinical stage IV), and the levels of D-dimer and fibrin degradation product remained as statistically independent factors, which were associated with cancer-associated ischemic stroke ($n = 111$, $\chi^2 = 67.21$, $P < 0.0001$).

Conclusion: In acute ischemic stroke, the cancer-associated ischemic stroke is associated with elevated D-dimer and fibrin degradation products, even after controlling hypertension, hyperlipidemia and advanced cancer (clinical stage IV). **Geriatr Gerontol Int 2012; ••: ••–••.**

Keywords: cancer, D-dimer, fibrin degradation product, ischemic stroke.

Introduction

Systemic thromboembolism associated with cancer was first described by Armand Trousseau and colleagues in 1865. In a more recent autopsy study of 3426 cancer cases, excluding primary brain tumors, 15% of the cases examined had experienced cerebrovascular events.[1] The

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causes of ischemic stroke in patients with cancer might differ from those in patients without cancer. Cancer can predispose patients to hypercoagulable states and might cause the development of deep vein thrombosis (DVT) and non-bacterial thrombotic endocarditis (NBTE).[2] NBTE is one of the most common causes of ischemic stroke in cancer patients,[3] and it has been found in 27% of cancer patients with ischemic stroke on post-mortem analysis.[1]

A number of previous studies have evaluated the characteristics of ischemic stroke patients with cancer. Cestari *et al.* classified the subtypes of ischemic stroke with cancer and found conventional ischemic stroke in just 35 of 96 patients (36%).[4] In addition, there were 36 of 52 patients (69%) with NBTE or embolism of an undetermined source in the subtype of embolic stroke.[4] In another study, embolic signals were detected with transcranial Doppler (TCD) in 45.9% of ischemic stroke patients with cancer.[5] In embolic stroke patients with cancer, a hypercoagulable state attributable to the cancer might have been one of the major causes of ischemic stroke.

However, these studies included a large number of elderly cancer patients, and it is possible that there was a certain proportion of these elderly patients in whom conventional ischemic stroke might have been attributable to atrial fibrillation (Af), atherosclerotic disease or other causes. This highlights the possibility that the causes of ischemic stroke in cancer patients are more complex than previously anticipated. To effectively detect and prevent ischemic stroke in cancer patients, it is necessary to define the causal relationship between ischemic stroke and cancer. However, the characteristics of ischemic stroke attributable to cancer that might allow its discrimination from conventional ischemic stroke remain undetermined.

The aim of the present study was to elucidate the clinical characteristics of cancer-associated ischemic stroke to differentiate it from the other type of ischemic stroke.

Methods

Design

This was a retrospective study of acute ischemic stroke patients admitted to Hiroshima University Hospital, Hiroshima, Japan, between January 2006 and August 2010. Ischemic stroke was confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI). We classified the patients as with cancer if they had active cancer or had been diagnosed with any cancer within 1 year after the onset of ischemic stroke, excluding primary intracranial tumors. Active cancer was defined by the presence of any continuous treatment for cancer within 5 years before the onset of ischemic stroke. The patients were classified as non-cancer patients if they had never been diagnosed with cancer, had undergone surgical removal of cancer more than 5 years before stroke onset and had shown no recurrence of cancer until their stroke onset, or had no clinical information regarding their cancer.

Data collection

Patients were classified as hypertensive when they had been diagnosed with hypertension before stroke onset, and/or were taking antihypertensive medication. Patients were classified as having diabetes mellitus (DM) if they had glycated hemoglobin (HbA_{1c}) ≥ 6.5% and fasting blood glucose ≥126 mg/dL, and/or were taking oral hypoglycemic agents or insulin. Patients were classified as hyperlipidemic if they had total cholesterol ≥220 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL and triglyceride level ≥150 mg/dL, and/or were taking antihyperlipidemic medication. Af was diagnosed with a standard electrocardiogram (ECG), 24-h ECG recording or 14-day ambulatory ECG monitoring.[6] The clinical stage of cancer was evaluated at the onset of ischemic stroke based on the tumor–node–metastasis (TNM) classification (for solid cancer) or the modified Ann Arbor (Cotswold's) staging (for malignant lymphoma).[7] In cases with an onset of ischemic stroke before cancer diagnosis, the clinical stage of cancer was evaluated at the time of cancer diagnosis. When a patient had multiple primary cancers, we evaluated the most advanced cancer.

Blood cell counts and blood coagulation factors (e.g. prothrombin time [PT; s], PT international normalized ratio [PT–INR], activated partial thromboplastin time [APTT; s], fibrinogen [mg/dL], D-dimer [μg/mL], fibrin degradation product [FDP; μg/mL], and antithrombin 3 [AT3; %]) were evaluated within 24 h of admission. D-dimer levels were measured by the latex agglutination method using a Sysmex XE7000 and the RIAS AUTO D-dimer NEO reagent (Kobe, Japan).

Ischemic stroke subtypes were classified by two stroke neurologists using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria and imaging examinations (e.g. brain MRI, carotid ultrasonography, transthoracic echocardiography [TTE]), which were carried out within 1 week after hospitalization.[8] In addition, patients with the cancer-associated ischemic stroke were further categorized in accordance with the patients for whom no causes of stroke other than cancer could be identified in the subtype of undetermined etiology, despite extensive evaluations including brain MRI, carotid ultrasonography and TTE. Patients were classified as conventional ischemic stroke if their ischemic stroke was a lacunar infarction or if they had Af, myocardial infarction, rheumatic valvular disease, valvular replacement, cardiomyopathy, severe stenosis

(>50%) of the infarct-related artery, arterial dissection or aortitis.

Statistical analysis

Medians (minimum to maximum) were used to describe continuous data, and frequency and percentage were used for categorical data. Univariate analyses were carried out to evaluate differences among the groups with regards to baseline characteristics, risk factors and laboratory data. Statistical analysis was carried out using JMP software version 9.0 for Windows (SAS Institute, Cary, NC, USA). Values were compared between patient groups using Fisher's exact test for categorical variables. Differences in continuous variables among the groups were examined using the Kruskal–Wallis test. When there was a statistically significant difference, the Wilcoxson signed rank test was applied to examine the difference between each group. Multivariate logistic regression was utilized to assess the relative importance of variables found to be related to the cancer-associated ischemic stroke, in initial univariate analyses. All analyses were two-tailed, and a value of $P < 0.05$ was considered statistically significant.

Results

A total of 211 consecutive acute ischemic stroke patients (79 women and 132 men) were identified between January 2006 and October 2010. The median age was 73 years (range 25–92). The patients' baseline characteristics are listed in Table 1. With our classifications, 15 patients (26%) were in the cancer-associated ischemic stroke group, 39 (68%) were in the conventional ischemic stroke group and three (6%) were not assigned to either classification among the cancer patients. No patient in the present study was assigned to both classifications. Of the three patients not assigned to either classification, one was classified as having a stroke of an undetermined etiology, because the general condition of the patient deteriorated before further evaluation. The two other patients in this group showed disseminated intravascular coagulation (DIC). There were no significant differences in prevalence of vascular risk factors in the cancer patients compared with that in the non-cancer patients. The most common vascular risk factor in the cancer patients was hypertension. It was similar to non-cancer patients. Ischemic stroke onset preceded cancer diagnosis in eight patients. The median duration from cancer diagnosis to stroke onset was 8 months (range –11 to 120) in the cancer patients. The patients in the cancer-associated ischemic stroke group had a lower rate of hypertension and hyperlipidemia than those in the conventional ischemic stroke group ($P < 0.05$).

Table 1 Baseline characteristics

		Non-cancer ($n = 154$)	Cancer ($n = 57$)	CAIS ($n = 15$)	CIS ($n = 39$)	Other ($n = 3$)
Age, years median (range)		73 (25, 92)	75 (50, 91)	74 (50, 87)	76 (56, 91)	67 (56, 86)
Sex	Female, *n* (%)	65 (42)	14 (25)	6 (40)	7 (20)	1 (33)
Risk factors	Hypertension, *n* (%)	100 (65)	33 (58)	5 (33)	26 (67)	2 (67)
	DM, *n* (%)	54 (35)	19 (33)	3 (20)	16 (41)	0 (0)
	Hyperlipidemia, *n* (%)	74 (48)	17 (30)	1 (7)	16 (41)	0 (0)
	Af, *n* (%)	55 (36)	19 (33)	0 (0)	19 (49)	0 (0)
Ischemic stroke subtypes	Small-vessel disease, *n* (%)	22 (14)	5 (9)	0 (0)	5 (13)	0 (0)
	Large artery atherosclerosis, *n* (%)	30 (20)	12 (21)	0 (0)	12 (31)	0 (0)
	Cardioembolism, *n* (%)	62 (40)	18 (32)	0 (0)	18 (46)	0 (0)
	Other determined etiology, *n* (%)	16 (10)	6 (10)	0 (0)	4 (10)	2 (67)
	Undetermined etiology, *n* (%)	24 (16)	16 (23)	15 (100)	0 (0)	1 (33)
Duration from cancer diagnosis to ischemic stroke onset, month median (range).		NA	8 (–11, 120)	13 (0, 69)	7 (–11, 120)	7 (0, 11)

Af, atrial fibrillation; CAIS, cancer-associated ischemic stroke; CIS, conventional ischemic stroke; DM, diabetes mellitus; NA, not assessed.

Table 2 Distributions of primary cancers

	Cancer ($n = 57$)	CAIS ($n = 15$)	CIS ($n = 39$)	Other ($n = 3$)
Lung	8	2	6	0
Stomach	7	1	6	0
Liver	6	2	4	0
Colon	5	0	5	0
Prostate	4	0	4	0
Malignant lymphoma	4	1	3	0
Pancreas	3	2	0	1
Gall bladder	3	2	1	0
Kidney	3	2	1	0
Esophagus	3	0	2	1
Pharynx	2	0	1	1
Breast	3	1	2	0
Others	6	2†	4‡	0

†These two patients had uterus cancer and malignant melanoma. ‡These four patients had thyroid cancer, gastrointestinal stromal tumor, bladder cancer or soft tissue tumor of the elbow. CAIS, cancer-associated ischemic stroke; CIS, conventional ischemic stroke.

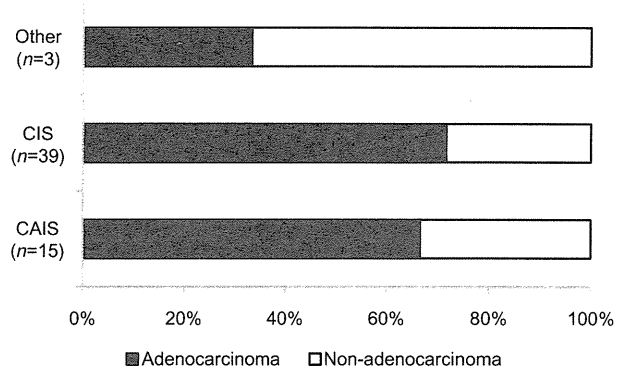

Figure 1 Histological types of primary cancer in the ischemic stroke classification in association with cancer. The difference in the distribution of adenocarcinoma between the cancer-associated ischemic stroke (CAIS) group and the conventional ischemic stroke (CIS) group was not significant.

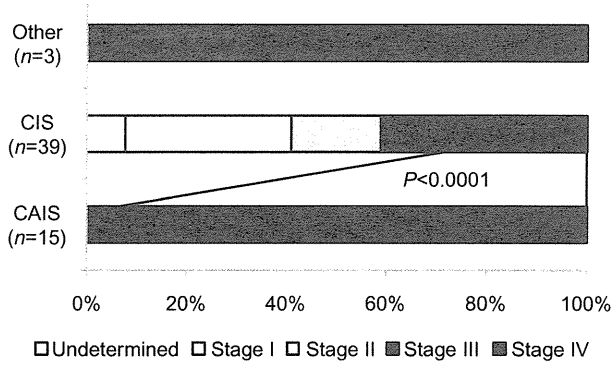

Figure 2 Clinical stage of primary cancer in the cancer-associated ischemic stroke group. There was a higher prevalence of advanced cancer (clinical stage IV) in patients with cancer-associated ischemic stroke (CAIS) compared with patients with conventional ischemic stroke (CIS).

The distributions of the primary cancers are shown in Table 2. Primary cancers were located in the lung in eight patients (14%) and in the stomach in seven patients (12.2%). Through histological classification, it was determined that 39 patients (68%) had adenocarcinoma. There was no significant difference in the distribution of adenocarcinoma between the cancer-associated ischemic stroke and the conventional ischemic stroke groups (Fig. 1). There was a higher prevalence of advanced cancer (clinical stage IV) in the cancer-associated ischemic stroke group than in the conventional ischemic stroke group ($P < 0.0001$; Fig. 2).

Blood cell counts, including hemoglobin and platelet counts, were evaluated in all patients. D-dimer and FDP levels were evaluated in 177 (84%) and 118 patients (56%), respectively. There was no significant difference in platelet counts among the groups. Hemoglobin was low in both cancer groups compared with that of the non-cancer group. D-dimer and FDP levels were significantly higher in the cancer-associated ischemic stroke group than in the non-cancer group and conventional ischemic stroke group ($P < 0.05$; Fig. 3). To assess the association between blood coagulation and clinical stage of primary cancer, differences between D-dimer and FDP levels were evaluated in the different clinical stages. Levels of D-dimer and FDP in the patients with cancer of clinical stage IV were significantly higher than those in patients of clinical stages I–III (D-dimer: 1.3 μg/mL [0.1–29.0] in stages I–III and 8.3 μg/mL [0.4–81.5] in stage IV and FDP: 3.1 μg/mL [0.8–50.5] in stages I–III and 15.1 μg/mL [1.2–100.2] in stage IV, $P < 0.05$, respectively).

In univariate analysis on the cancer-associated ischemic stroke and the other groups, there were significant differences in the prevalence of hypertension, hyperlipidemia, and advanced cancer (clinical stage IV) and the levels of D-dimer, FDP and hemoglobin. Then, we carried out multivariate logistic regression analysis on the cancer-associated ischemic stroke and the others with those factors. As a result, the prevalence of hypertension, hyperlipidemia, and advanced cancer (clinical stage IV), and the levels of D-dimer and fibrin degradation product remained as statistically independent factors, which associated with cancer-associated ischemic stroke ($n = 111$, $\chi^2 = 67.21$, $P < 0.0001$; Table 3).

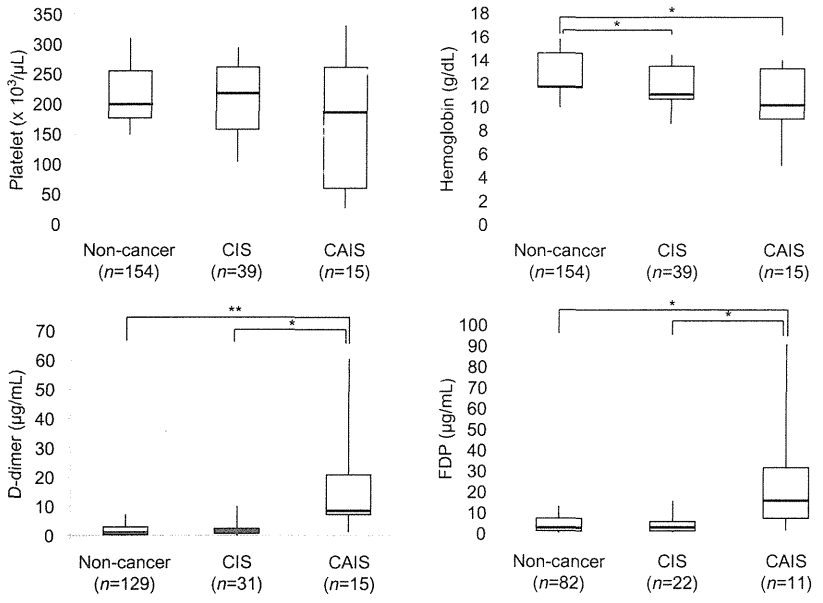

Figure 3 Blood cell counts and coagulation factors in the cancer-associated ischemic stroke group. There was no significant difference in platelet counts between the cancer-associated ischemic stroke (CAIS) and the conventional ischemic stroke (CIS) groups. Although hemoglobin level was low in both cancer patient groups compared with that of the non-cancer patients, there was no significant difference between the patients with CAIS and those with CIS. D-dimer and fibrin degradation product (FDP) levels were significantly higher in the CAIS group than the other groups. Boxplot graph was made with median, 10th, 25th, 75th and 90th values. Significant differences among groups: $*P < 0.05$, $**P < 0.0001$.

Table 3 Multivariate logistic regression analysis on the cancer-associated ischemic stroke and the others

Factors	χ^2	*P*-value
Hypertension	11.13	0.0008
Hyperlipidemia	4.16	0.0414
Advanced cancer	48.47	<0.0001
D-dimer	12.60	0.0004
FDP	9.24	0.0024
Hemoglobin	2.15	0.9988

$n = 111$, $\chi^2 = 67.21$, $P < 0.0001$. FDP, fibrin degradation product.

Discussion

In the present study, we evaluated the clinical characteristics of ischemic stroke patients with cancer. Of the 58 patients examined, 16 (28%) were classified as having cancer-associated ischemic stroke. The characteristics of cancer-associated ischemic stroke were evaluated by comparison with the non-cancer group and conventional ischemic stroke group. There was no significant difference in the prevalence of adenocarcinoma between the cancer-associated ischemic stroke and the conventional ischemic stroke groups. However, there was a higher prevalence of advanced cancer (clinical stage IV) in patients with cancer-associated ischemic stroke than in patients with conventional ischemic stroke. There was a lower prevalence of hypertension and hyperlipidemia in patients with the cancer-associated ischemic stroke than in patients with the conventional ischemic stroke. There were no significant differences between the two groups in hemoglobin and platelet counts. FDP and D-dimer levels were significantly higher in patients with the cancer-associated ischemic stroke than in the non-cancer group and the conventional ischemic stroke group. In acute ischemic stroke, cancer-associated ischemic stroke was associated with elevated D-dimer and fibrin degradation products, even after controlling hypertension, hyperlipidemia and advanced cancer (clinical stage IV).

In the present study, we attempted to select the patients with cancer-associated ischemic stroke using the TOAST criteria. Kim *et al.* have also tried to classify ischemic stroke patients with cancer using conventional and cryptogenic stroke mechanisms.[9] In their classification, ischemic stroke patients with undetermined etiologies according to the TOAST criteria were categorized solely with reference to cryptogenic stroke mechanisms. Although their classification method is almost equal to our method, they classified five NBTE patients as a conventional ischemic stroke mechanism. NBTE is widely recognized as a unique cause of cardioembolism frequently observed in cancer patients, as has been reported in a post-mortem series.[1] Although transesophageal echocardiography (TEE) is the most appropriate method to diagnose cardiac sources of embolism, such as NBTE,[10] it is difficult to carry out TEE in all cancer patients, as TEE is an invasive examination. In the present study, we carried out TEE in just 37% of the patients who were suspected to have had a cardioembolic stroke from the results of imaging analysis and who could tolerate esophageal intubation. Although our execution rate of TEE was higher than that in previous reports,[4,11] it is quite likely that there is a selection bias. Therefore, we tried to classify cancer-associated ischemic stroke without using the finding of TEE. As a

result, three patients with NBTE in the cancer-associated ischemic stroke group were included, because there were not embolic sources, despite extensive examination without TEE. From this result, this classification method could be adequate in a clinical site.

D-dimer is a plasmin-derived degradation product of cross-linked fibrin that is elevated in patients with hypercoagulability. D-dimer levels were elevated in a wide variety of conditions with intravascular clotting, including ischemic stroke itself. Previous studies have reported that D-dimer is higher in stroke patients with cancer than in stroke patients without cancer.[4] In the present study, we have shown that, among ischemic stroke patients, D-dimer levels were more elevated in patients with cancer-associated ischemic stroke than non-cancer and conventional ischemic stroke. The patients with NBTE showed high D-dimer levels. There were three patients with NBTE found with TEE in the cancer-associated ischemic stroke group. Their D-dimer levels were 8.7 μg/mL, 23.1 μg/mL and 55.5 μg/mL; these values were markedly higher than those of the other patients in this group. It might be because NBTE can result from a hypercoagulable stage. Furthermore, we investigated the possibility that patients with advanced cancer show high levels of D-dimer. Interestingly, the levels of D-dimer were higher in the patients with stage IV cancer than in those with clinical stages I–III. From the present results, D-dimer and FDP remained as independently significant, even after controlling the prevalence of hypertension, hyperlipidemia and advanced cancer (clinical stage IV). Therefore, although the elevation of blood coagulation factors in the patients with the cancer-associated ischemic stroke might be attributable to a higher clinical stage of primary cancer, it was independently associated with the cancer-associated ischemic stroke.

Uemura *et al.* reported that hemoglobin levels were reduced in cancer patients compared with patients with no malignancy.[12] Their explanation for the reduced hemoglobin levels in cancer patients was the general condition of these patients as a result of cancer cachexia or gastrointestinal bleeding in gastrointestinal cancer patients. The present results support those of Uemura *et al.*; hemoglobin levels in the cancer groups were lower than the non-cancer group in the present study. However, there was no significant difference in hemoglobin levels between the patients with cancer-associated ischemic stroke and those with conventional ischemic stroke. The present results suggested that hemoglobin levels cannot be a marker used to distinguish between cancer-associated ischemic stroke and conventional ischemic stroke in cancer patients.

Circulating mucinous material has been reported in embolic stroke patients with mucin-producing adenocarcinomas.[13–15] Seok *et al.* reported that embolic signal was observed in patients with metastasis or adenocarcinoma.[5] Of the patients in the present study, 68% were adenocarcinoma patients. However, there was no significant difference in histological types between the cancer-associated ischemic stroke and the conventional ischemic stroke patients. These results require confirmation in a larger number of patients.

In the present results, there was a significant difference in the clinical stage of cancer, but not the histological type between the patients with cancer-associated ischemic stroke and those with conventional ischemic stroke. A few previous reports have evaluated the relationship between cancer-associated ischemic stroke and its clinical stage. Kim *et al.* showed a high prevalence of distant metastasis in cryptogenic stroke mechanisms.[9] This report supports the present results in that there was a high prevalence of advanced cancer in the patients with cancer-associated ischemic stroke.

The present study has some limitations. First, this was a single-center retrospective study. Our hospital functions as both a regional cancer center and an advanced emergency center. The proportion of ischemic stroke patients with cancer might differ between our hospital and the general population. Therefore, there might be a selection bias for ischemic stroke patients with cancer. Second, the method of classifying cancer-associated ischemic stroke is not generalized. With our classification system, all of the ischemic stroke patients with Af were classified as having cardioembolism in conventional ischemic stroke. However, there is a possibility that some of these stroke cases might have been attributable to a hypercoagulable state as a result of cancer rather than to Af. Further selection criteria are necessary to select the Af patients in whom the ischemic stroke was a result of hypercoagulability as a result of cancer. Therefore, further research investigating the association between ischemic stroke and cancer is needed. Finally, although TEE is necessary to diagnose NBTE, TEE cannot be carried out in all cases because of patients' general conditions, anatomical reasons (e.g. esophageal or gastric cancer and esophageal varix) and/or lack of patient cooperation.

In conclusion, 26% of the patients studied were classified as having cancer-associated ischemic stroke. Based on our results, elevated D-dimer and FDP levels can be associated with cancer-associated ischemic stroke, even after controlling hypertension, hyperlipidemia and advanced cancer (clinical stage IV).

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Disclosure statement

None.

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－「血漿と間質液の膠質浸透圧差」）なる式であらわした（スターリングの法則）．これに従い，浮腫は毛細血管の静水圧の上昇，血漿膠質浸透圧の低下，毛細血管透過性亢進により生じることが理解される．

毛細血管圧と体液の移動との関係を図3-11に示した．正味（ネット）の毛細血管圧は毛細血管静水圧，組織圧，膠質浸透圧によって規定される．ネット毛細血管圧すなわち有効毛細血管圧は，動脈側で大きく，(37 － 1) － 25 = 11 mmHg であるが，静脈側に進むにつれて毛細管静水圧の低下とともに低下し，静脈側では (17 － 1) － 25 = － 9 mmHg になる．毛細血管内静水圧の上昇，膠質浸透圧の低下によりネット毛細血管圧が上昇すると，水やナトリウムが間質に移動する．組織圧はもともと小さい値なので，変動因子としてはあまり重要ではない．

b　全身因子

全身因子としては，抗利尿ホルモンの分泌促進，レニン・アンギオテンシン・アルドステロン系の活性化，交感神経活動の亢進などが考えられており，浮腫を維持するうえで重要な役割を果たすと考えられている．

5　その他の症状

心疾患，徐脈性不整脈，起立性低血圧などでめまい，失神が生じることがある．また右→左短絡血流をもつ先天性心疾患などで指端末節が肥大するばち指がみられることがある．また，還元ヘモグロビン濃度が5 g/dL 以上になるとチアノーゼが生じ，口唇などが紫色になる．先天性心疾患で右→左短絡がある場合や肺での酸素摂取障害，末梢循環不全などでもチアノーゼがみられる．

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3　診断と検査

診察を行う前に，その患者の様子をいち早くとらえることは重要である．循環器疾患は，ときにより緊急対応を要求されるからである．

a　救急性があるのはどのようなときか

①顔面に苦悶様の様子をみてとれるとき

苦しい，息苦しい，胸苦しい，ひどく痛む，胸が押さえられるように痛む．

②意識不明であるとき

気が遠くなると訴えるとき，意識がない，など．

b　緊急状態かどうか調べる

脈は規則正しいか，触れ方ははっきりしているか，意識はどうかなど救急蘇生法をいつ開始するか考えながら行動する．以上のような救急性がない場合であれば問診から開始する．

1　医療面接（問診）

1　主訴（患者が最も訴えたいこと）

なぜ，病院に来ようと思ったのか．

息苦しい

息苦しいという症状は最も心臓疾患を疑う症状である．胸が痛い，息苦しいときは患者にとってこのうえもなく不安となるものである．

胸が痛い（胸痛）

胸が痛いという症状は，心臓の筋肉が虚血により障害を受けた場合，心筋周囲の炎症，大動脈などが裂けた場合，胸膜の炎症，肋間神経の痛み，食道や胆嚢の炎症などいろいろな原因で胸痛は出現する．心臓の疾患を疑う場合の特徴は，胸骨下1／3あたりに耐えがたい痛みが生じた場合である．最も注意しなくてはならない虚血性心疾患の特徴的症状である．

現病歴（起始および経過）

症状の時間経過を聴くことは重要である．

労作にともなうもの

労作にともなう症状は，体が多くの酸素を要求するにもかかわらず，十分な酸素を体の必要な部位に送ることができないことが原因で出現する．歩いていると苦しい，階段を上ると苦しい，荷物をもって歩くと苦しいなどと訴える場合に労作性狭心症や心不全を疑う．労作により心臓に負荷がかかると不整脈が出現することがあり，動悸を感じる場合と，苦しいと訴える場合がある．

安静時に出現するもの

安静時に出現するものには，冠攣縮性狭心症や不整脈などがある．意図しないときに胸がざわざわすると訴えることがある．

突然起こるもの

虚血性心疾患や不整脈は突然出現することが多い．心筋梗塞は冠動脈の動脈硬化部位に，血栓ができて急速に詰まってしまうことから発症する．そのために症状は突然出現することが多い．不整脈は虚血性心疾患に合併することがある．致死的不整脈が出現すると，左心室の収縮が不完全になるために，十分な血液を体に送りだせなくなり死に至ることがある．

徐々に出現したもの

各種疾患による心不全などは，徐々に原因となる疾患が悪化して生じる．

既往歴

冠動脈疾患の原因になるもの，または悪化させるものとしての危険因子（リスクファクター）とされるものがある．

糖尿病，高血圧，脂質異常症，タバコ，ストレス，タイプAの性格，肥満，高尿酸血症，年齢が40歳以上の男性などがあげられる．リスクファクターの有無，または治療歴の聴取は重要である．

冠動脈疾患では，さらに川崎病の既往の有無について聴くことも必要である．

弁膜症ではリウマチ熱との関連もあるので，6～15歳ごろに咽頭の感染症であるA群 β 溶血性連鎖球菌感染の後2週間ほどで関節痛が出現したか，発熱はあったかなどを聴く必要がある．

個人歴

何かもとになっているものはないのか

喫煙の原因になっていることがないか，心臓疾患ではリスクファクターの有無をよく聴きだす必要がある．ストレスが多いと狭心症や心筋梗塞を起こしやすい．不安，不眠や食欲不振などがストレスの症状としてあらわれることがある．

〈タイプA〉

患者の中には，診察を長く待つことに対して強く不満を訴える人がいる．長く待たせることはもちろん避けなくてはならないが，いつもいらいらしている場合や，1つのことをとことんすませないと気がすまない性格の人は，虚血性心疾患を起こしやすい．このような患者は椅子の背もたれに深く腰かけることはなく，いつでも立てるように椅子の前縁に座っている場合が多い．このような性格をタイプAと表現している．一方で社長のように，どっしりと深く腰かけてゆったりした性格をタイプBとしている．

b　嗜好品

喫煙歴は冠動脈疾患との関連が高い．

飲酒は動脈硬化のリスクファクターや使用する薬剤の代謝に関係する場合がある．

c　薬物使用

治療中の疾患を知るために，現在継続して内服している薬の有無を聞きだす．

d　生活環境

一人暮らしの男性は虚血性心疾患のリスクであるともいわれる．外食が多い場合は塩分やカロリー摂取に偏りが生じる場合がある．

(5) 家族歴

虚血性心疾患や肥大型心筋症や不整脈（QT延長症候群ほか）などの診断の際に，両親や兄弟で同じような症状の人がいないかを聞くことは診断の助けになる．

<症　例>

(1) 症例1

①68歳の男性．

②主訴：右腕の痛み．

③起始および経過：糖尿病の血糖コントロールのために運動を行っていた．3カ月前から夕食後に散歩に出かけると途中で右腕が痛くなるようになった．散歩にでかけると5分程で右腕が捕まれるように痛くなり，少し歩く速さを遅くし様子をみていると徐々に軽快するのでそのまま散歩を持続することができた．出現する頻度や程度は増悪する様子はなかった．食後に運動しないときは症状の出現はなく，てんぷらなどの油ものを食べる機会は少ないが，食べて腕が痛んだことはなかった．便の色が白っぽくなったことはない．

④職業および嗜好品：無職，喫煙や飲酒はない．温厚な性格．

⑤来院時所見：身長 168 cm，体重 70 kg．脈拍 70／分．整．血圧 140/90 mmHg．眼球結膜に黄疸を認めない．頸部に変形はなく，血管雑音を聴取しない．心音と呼吸音に異常はない．腹部に圧痛はない．上腕と母指丘の筋肉は保たれていて左右差を認めない．足背動脈は左右とも良好に触知する．アキレス腱反射の低下と振動覚の減弱は認めない．

⑥検査所見：尿糖（－）．食後2時間血糖 148 mg/dL，LDL-C 180 mg/dL，HDL-C 38 mg/dL．腹部エコーで胆石や胆管の拡張は認めない．

⑦安静時心電図は正常範囲である．

⑧診断と検査の進め方

1　右腕の痛みから胆石症を疑う．しかし痛みは食後ではあるが，散歩にでかけないと出現せず食事の内容とは関連がない．

表 3-2 痛みに対する病歴聴取の 8 項目（SIQORAAA）

	痛みに対する病歴の聴き方	症例 1	症例 2	症例 3
S	site（痛みの場所）	右腕	胸の上の方	前胸部
I	intensity（痛みの強さ．10 段階のペインスケール［pain scale］で痛みの強さを表現してもらう．痛みなしを「0」，最悪を「10」とする）	推定 4（歩く速さを遅くする程の痛み）	推定 6（我慢できる程の痛み）	推定 9（目が覚める程の痛みで，救急車を呼ぼうと思った）
Q	quality（痛みの性状）	腕を捕まれるような痛み	圧迫感は 20 分ほどで消失	圧迫感が持続する
O	onset（発症時間，発症の仕方，症状の変化）	3 カ月前から	3 日前の朝に初めて出現した	9 時間前の深夜 2 時から持続している
R	radiation（放散痛）	右肩まで痛む	両肩，両手の先まで痛む	左鎖骨から左肩が痛い
A	aggravating factors（増悪因子）	夕食後の歩行で出現する	出勤時に出現する	痛みは継続している
A	alleviating factors（緩解因子）	歩く速度を遅くすると軽減する	朝以外には胸痛はない	寛解することはない
A	associated factors（随伴症状）	食後に出現するが，腹痛はともなわない		

＊SIQORAAA：シック オア スリーエー，SICK OR Abdominal Aortic Aneurysm（病気か腹部大動脈瘤）という覚え方もある．

（ローレンス・ティアニー，松村正巳（2010）ティアニー先生の臨床入門，pp.26-27，医学書院より作成）

2) 頸椎の変形や手掌の筋肉の萎縮がないので，頸腕症候群は否定的である．
3) 心筋虚血に特有な前胸部痛はない．軽度の耐糖能障害はあるが，糖尿病性の神経障害はないことから，糖尿病による無痛性の心筋虚血を起こしているとは考えにくい．
4) 冠動脈リスクファクターとして，(1) 45 歳以上の男性，(2) 高血圧，(3) 耐糖能異常，(4) 高 LDL 血症，(5) 低 HDL 血症，がある．
5) 24 時間心電図を施行したところ，食後の右腕の痛みとともに心電図に虚血を認めた．
6) 冠動脈造影で，右冠動脈の狭窄を認めた．
7) 診断は，右冠動脈狭窄による労作性狭心症で，誘因は食後の高血糖であると考えた．

(2) 症例 2

1) 56 歳の男性．
2) 主訴：肩と胸の痛み．
3) 発症経過：金曜日の朝 6 時 45 分ごろに出勤する途中で両肩が痛くなった．同時に胸の上の方が痛み，20 分ほどで自然に消失した．土曜の朝は少し変であったが，日曜の朝は何ともなかった．月曜の朝に金曜と同じ肩と胸の痛みがあり，両手の先の方に痛みが移動したのちに軽減した．持続は 20 分ほどであった．先週の火曜日にテニスをしたがそのときに胸痛はなかった．朝以外では症状の出現がなく，日曜日に庭仕事を少ししたが何ともなかった．来院時に胸痛はなかった．
4) 職業および嗜好品：会社員で喫煙歴はない．
5) 来院時所見：身長 170 cm，体重 67 kg．脈拍 66／分，整．血圧 150/98 mmHg．顔貌は正常．

眼瞼結膜に貧血はない．心音と呼吸音に異常はない．
⑥検査所見：尿糖（－），尿たんぱく（－）．白血球 4,600．空腹時血糖 106 mg/dL（基準 60-110），心筋トロポニン T 擬陽性，UN 15 mg/dL（基準 8-20），Cr 1.0 mg/dL（基準 0.5-1.3），AST 1[illegible] IU/L（基準 0-40），ALT 12 IU/L（基準 0-40），LDH 159 IU/L（基準 106-211），CK 84 IU/L（[illegible]準 56-244）．
⑦安静時心電図では，V_3 から V_5 で二相性 T 波を認めるが，異常 Q 波と ST の上昇は認めない．
⑧診断と検査の進め方
1）3 日前から出現した胸痛で，心電図で T 波の異常があり，心筋トロポニン T が異常を示し[illegible]ため，急性冠症候群と診断した．
2）救急車で搬送し，冠動脈造影施行したところ，左冠動脈前下降枝＃ 6 に 75%狭窄を認めた．
3）一般的に冠攣縮性狭心症であると，冠動脈に狭窄病変を認めないこともある．本例の胸痛[illegible]テニスを行っても出現しないので，冠動脈狭窄だけでは労作時に心筋虚血が生じていなか[illegible]たと考える．胸痛は朝しか出現しないことから，冠攣縮性狭心症で発症から 3 週間未満の[illegible]安定狭心症であったものが，急性心筋梗塞（心内膜下梗塞）になったと考える．

(3) 症例 3
① 60 歳の男性．
②主訴：胸痛．
③起始経過：日曜日の夜の食事を 23 時に摂り，就寝したが，深夜 1 時 30 分ごろに前胸部痛で[illegible]醒した．左鎖骨下から第 2 肋間あたりが痛く，左肩も張っていたので，救急車を要請しようと思[illegible]た．しかし，当日の朝に社長として訓示する予定であったので，朝まで我慢して出社した．1 週[illegible]の朝の出勤時に左肩と左上胸部が苦しかった．新入社員に訓示を述べたあとに診療所に来院した[illegible]来院時に胸痛は持続している．
④既往歴：高血圧でアムロジピンを内服している．
⑤職業および嗜好品：会社社長，たばこは数本／日
⑥来院時所見：身長 167 cm，体重 72 kg．脈拍 104／分，整．血圧 186/94 mmHg．顔貌はやや[illegible]悶様である．心音はギャロップリズムでⅣ音を聴取する．呼吸音は清である．
⑦検査所見：白血球 11,500．空腹時血糖 120 mg/dL．HbA1c（JDS）5.2%，心筋トロポニン T[illegible]性．Cr 0.88 mg/dL．TC 260 mg/dL，TG 52 mg/dL．HDL 65 mg/dL，LDL 170 mg/dL．AS[illegible]114 IU/L，ALT 34 IU/L，LDH 430 IU/L（基準 106-211），CK 1230 IU/L（基準 56-244），[illegible]MB 106.5 U/L（基準 25 以下）．
⑧心電図：V_1 から V_4 で ST 上昇をともなう QS パターンがあり，典型的な急性前壁心筋梗塞[illegible]を認める．
⑨診断と検査の進め方
1）胸痛が持続していることと，心音でⅣ音を聴取したので高血圧と左心不全をともなう急性心[illegible]筋梗塞と考えた．
2）心電図所見で心筋梗塞と心筋トロポニン T が陽性であることを確認した時点で，救急車を要[illegible]請しカテーテル治療の可能な病院へ搬送した．搬送先で行った心エコーで前壁中隔から心[illegible]部にかけて心筋収縮能の低下を認めた．
3　心臓カテーテル施行し，左冠動脈前下降枝＃ 7 に 100%の閉塞，右冠動脈＃ 4AV に 90%[illegible]を認め，ステントを留置した．