Acta Med. Nagasaki 38:28–34

Nonvalvular atrial fibrillation as a prognostic factor in cerebral infarction

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Abstract: To evaluate the influence of nonvalvular atrial fibrillation (NVAF) on mortality, functional prognosis and recurrent stroke after first cerebral infarction, 141 cerebral infarction patients without valvular heart disease, which comprised 37 patients with atrial fibrillation, that is NVAF, and 104 patients without atrial fibrillation, were followed without anticoagulant therapy throughout hospitalization. Patients with NVAF were more likely than patients without AF to; have large size of cortical infarction ($p < 0.01$), present with a depressed mental status ($p < 0.01$), and develop early recurrence of stroke ($p < 0.05$). These led to significantly greater rates of mortality ($p < 0.001$) and some types of serious morbidity ($p < 0.01$). Age was the primary predictor of mortality in patients without AF, but had no impact on survival in patients with NVAF. Infarct size exerted the greatest influence on mortality and functional status of survivors in patient with NVAF.

Key Words: Nonvalvular atrial fibrillation, Cerebral infarction, Prognosis, Recurrence

Introduction

Approximately 15 to 20% of ischemic strokes have been thought to be caused by embolic infarctions of cardiac origin (1).

According to The Cerebral Embolism Task Force (1), 45% of these strokes are caused by nonvalvular atrial fibrillation (NVAF), which occurred in patients without valvular heart disease.

The risk of ischemic stroke caused by NVAF is said to be 3.0-8.8% per year (2, 3, 5). Patients with NVAF have previously been reported to have a 2.3-7.5 fold increase in relative risk of stroke (1, 5, 7, 8,). Also, the incidence of stroke rises sharply with age (3). Wolf et al have reported that age-specific incidence rates steadily increase from 0.2 per 1,000 for ages 30 to 39 years to 39.0 per 1,000 for ages 80 to 89 years (4). Prophylactic therapy trials to prevent initial ischemic stroke caused by NVAF (primary prophylaxis) as well as trials to prevent recurrence of stroke (secondary prevention) have been reported (8-11). Niemi et al (26) have stated that an important factor influencing the quality of life (QOL) after strokes is age.

However, there have been very few systematic studies concerning the influence of NVAF on prognosis after ischemic strokes (12, 13). Examining NVAF as an isolated risk factor is important because NVAF has been implicated in causing cerebral infarction, and the incidence of NVAF increases with age as noted above. The aim of our study was to investigate the influence of NVAF on survival, functional prognosis and recurrent stroke after initial cerebral infarction.

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Methods

The subjects in this study consisted of 141 consecutive cerebral infarction (CI) patients without valvular heart disease and other organic heart disease who admitted to the Sasebo Central Hospital from January, 1988 to January, 1991. These 141 cases were divided into two groups, atrial fibrillation (AF), that is nonvalvular atrial fibrillation (NVAF), and non-AF groups. Nonvalvular atrial fibrillation (NVAF) was defined as atrial fibrillation which occurred in patients without valvular heart disease.

Valvular heart disease was excluded by history, physical findings, electrocardiogram, echocardiogram, and chest roentgenogram. Patients did not receive anticoagulant therapy during time periods prior to or during hospitalization.

Diagnostic criteria were as follows: 1) AF: Chronic atrial fibrillation and paroxysmal atrial fibrillation in which more than one episode had been detected on previous twelve lead electrocardiogram or the monitor electrocardiogram. 2) Cerebral infarction: Acute onset of neurologic signs corresponding to serial computed tomography (CT) scan findings. Even when obvious low density areas were not detected on brain CT scan, definite focal neurologic signs sustaining for more than 3 days were diagnosed as cerebral infarction as well.

The CT scans were performed using a CT-W400 (Hitachi Co., Ltd.). A scanning time of 6.0 seconds was used

with images recorded at 10 mm intervals.

Consciousness level of the CI patients within 24 hours of cerebral infarction was classified using the Japan Coma Scale (JCS) (27); 0: clear, I: Patient awake without any stimuli, II: Patient able to be aroused with stimulation, but falls into previous state by cessation of stimulation, III: Patient unable to be aroused with any noxious stimulus (28).

Localization of the cerebral infarction was classified into the following regions by CT scan findings; 1) Anterior cerebral artery region, 2) Middle cerebral artery, main trunk region, 3) Middle cerebral artery, cortical region, 4) Middle cerebral artery, perforating region, 5) Posterior cerebral artery region, 6) Multiple regions of the infarction, and 7) Undetectable infarction region. Size of the infarction was measured using the image with the largest area of low density on brain CT scan, and classified as 1) Undetectable infarction or less than 1 cm, 2) Small infarction of 1 to 3 cm, 3) Medium infarction of 3 to 5 cm, 4) Large infarction of more than 5 cm.

Activity of daily living (ADL) at a stable hospitalized state was categorized into five stages as in Table 1. Functional prognosis was classified into various degrees of recovery based on the patients ability to live and function independently.

Table 1. Classification of Activity of Daily Living

No impairment	: Free of any life restriction
Mildly impaired	: Mild life restriction
Moderately impaired	: Life restriction with gait disability
Markedly impaired	: Bedridden without impaired consciousness
Profoundly impaired	: Bedridden with impaired consciousness

Cerebral infarction was considered recurrent when a patient had an obvious history of cerebral infarction in the past and was hospitalized with new onset cerebral infarction, or when ischemic stroke recurred during the hospitalization.

All numerical measures are expressd as the mean ± the standard deviation in the figure and the table. Statistical analysis was performed using an unpaired t-test and hypothesis testing of proportions, and $p < 0.05$ was considered significant.

Results

Of the 141 patients, there were 77 males and 64 females, ages 44 to 93 (mean 73.2 ± 9.2). The AF-group consisted of 37 cases (26.2%) with 19 males and 18 females, ages 59 to 93 (mean 75.0 ± 8.2) and the non-AF group had 104 cases with 58 males and 46 females, ages 44 to 91 (mean 72.5 ± 10.8). The observation period during hospitalization was 4 to 706 days (mean 123.6 ± 160.3 days) in the AF group, and 3-1, 283 days (mean 90.6 ± 144.5 days) in the non-AF group. Only one patient under the age of 60 had atrial fibrillation, however, 23.1% to 36.1% of patients in the 70's, 80's or 90's had atrial fibrillation (Table 2). Fig. 1 shows infarct area (A) and size (B) in patients with and without atrial fibrillation. Prevalence of the infarct site was highest in the middle cerebral artery, cortical region in the AF group ($p < 0.001$), and in the middle cerebral artery, perforating region in the non-AF group ($p < 0.01$). In other infarct area, there were no significant differences in the prevalence between the two groups. Non-AF patients had many small infarctions ($p < 0.001$), but AF patients had medium ($p < 0.01$) and large ($p < 0.05$) infarctions, and 67.5% of cerebral infarctions associated with AF were larger in size than 3 cm (Fig. 1).

Table 2. Age Distribution of Patients with and without Atrial Fibrillation (AF)

		Age						Total
		< 50	50–59	60–69	70–79	80–89	90 ≦	
AF	+	0 (0)	1 (13)	10 (26)	12 (23)	13 (36)	1 (25)	37 (26)
	−	2	7	29	40	23	3	104
	Total	2	8	39	52	36	4	141

( ) : %

Most non-AF patients had a normal level of consciousness ($p < 0.01$) on admission comprising approximately 84% of all cases in JCS Class I. Of patients with AF, 37% were in JCS Class II ($p < 0.001$) and 20% in JCS Class III ($p < 0.05$). Thus, level of consciousness in AF patients tended to be lower than non-AF patients at the time of admission (Fig. 2A).

Thirty-four (24.1%) of the 141 patients died during their hospitalization. Mortality was 48.6% (18 of 37) in the AF group and 15.4% (16 of 104) in the non-AF group ($p < 0.001$) (Fig. 2B). As shown in Table 3, mortality increased with age in the non-AF group ($p < 0.01$), but not in the AF group. Incidence of death and sudden worsening are shown in Table 4. The number of deaths was 17 in the AF-group, and 16 in the non-AF group. In these 33 fatal cases, 12 (7 in the AF group and 5 in the non-AF group) experienced clinical deteriolation during their hospitalization. Among these patients with abrupt clinical decline, AF was a significant risk factor for the stroke with an occurrence rate of 18.9% (7 of 37 cases)($p < 0.01$). The causes of marked clinical decline were; recurrent infarction, ventricular arrhythmia (ventricular tachycardia and ventricular fibrillation), spontaneous pneumothorax, asphyxia, and acute pancreatitis (Table 5). In cases of initial infarct death, the interval from admission to death was approximately one week in both groups. In recurrent stroke cases, the second event occurred a few days after admission in the AF group, and the mean interval from recurrence to death was 47.8 days. In the non-AF group, there was only one patient with

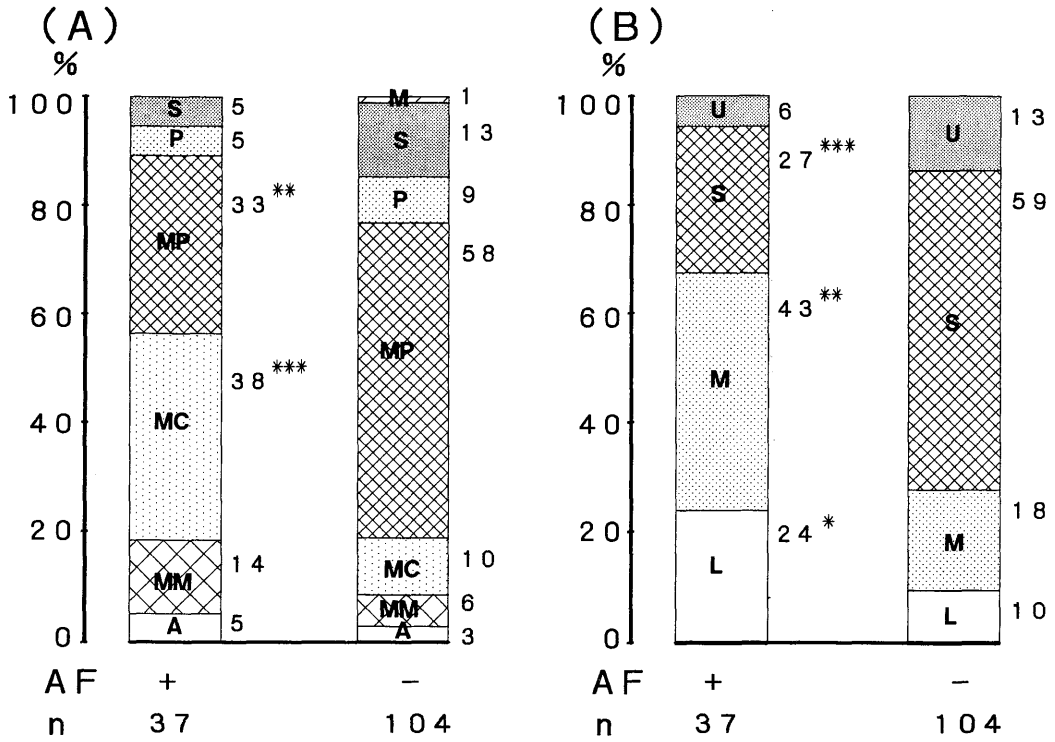

Fig. 1. Infarct area (A) and size (B) in patients with and without atrial fibrillation. A: anterior cerebral artery, MM: middle cerebral artery main trunk, MC: middle cerebral artery cortical branch, MP: middle cerebral artery perforating branch, P: posterior cerebral artery, S: small, M: multiple, and L: large infarction, M: medium infarction, S: small infarction, U: undetected.
*P < 0.05 VS non-AF, ** P < 0.01 VS non-AF, *** P < 0.001 VS non-AF

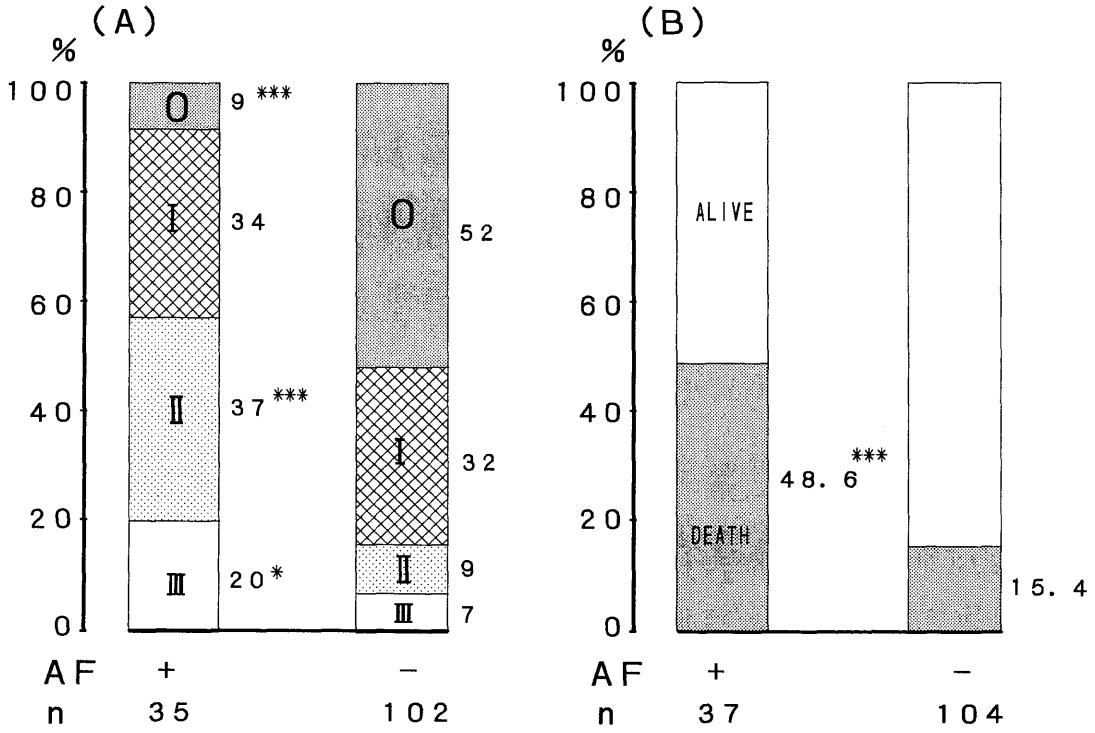

Fig. 2. (A) Level of consciousness on admission based on Japan Coma Scale (JCS) ;O: clear, I: patient awake spontaneously, II: patient able to be aroused, but then falls into previous state with cessation of stimulation, III:patient is unable to be aroused with any noxious stimulus, (B) Mortality rate in patients with and without atrial fibrillation.
*** P < 0.001 VS non-AF

Table 3. Age of Survivors and Non-survivors

			Average Age	Age						Total
				< 50	50–59	60–69	70–79	80–89	90 ≦	
AF	+	Alive	73.5 ± 6.6 NS	0	1	4	10	4	0	19
		Expired	76.6 ± 9.5 NS	0	0	6	2	9	1	18
	−	Alive	71.0 ± 9.0 **	2	7	27	36	15	1	88
		Expired	80.6 ± 8.1 **	0	0	2	4	8	2	16
			Total	2	8	39	52	36	4	141

** p < 0.01 VS other group AF: Atrial Fibrillation

Table 4. Incidence of death and sudden worsening in Patients with and without Atrial Fibrillation (AF)

	AF	
	+ (n = 37)	− (n = 104)
Expired (Sudden worsening)	17 (7)	16 (5)
Sudden worsening (%)	7/37 (18.9)**	5/104 (4.8)

** P < 0.01 VS other group

Table 5. Major Complications and Causes of death in Patients with and without Atrial Fibrillation (AF)

	AF					
	+ (n = 37)			− (n = 104)		
Complication & Causes of Death	No.	Age	Days after admission to death	No.	Age	Days after admission to death
Infarction	3	72.3 ± 8.5	5.3 ± 1.2	2	77.0 ± 11.3	7.5 ± 6.4
Recurrent stroke	5**	77.4 ± 7.9	47.8 ± 30.2	1	60	3
Pneumonia	4	72.0 ± 9.7	222.8 ± 322.4	1		400
Prostration	3	86.7 ± 6.5	212.3 ± 158.9	8**	85.6 ± 4.1	283.0 ± 426.2
Ventricular Arrhythmia	1	85	92	2	81.5 ± 3.5	33.0 ± 42.4
Pneumothorax				1	77	7
Asphyxia				1	75	30
Hepatic failure	1	81	77			
Acute pancreatitis	1	61	72			

** P < 0.01 VS other group

a recurrence on the third day of hospitalization. This patients died on that day.

Additional complication of pneumonia and severe exhaustion (prostration) which eventually led to patient demise occurred an average of 222.8 and 212.3 days after admission in the AF group and 400 and 283.0 days in the non-AF group, respectively. Thus, extensive, prolonged debilitation occurred in both groups. In the non-AF group, death due to extreme exhaustion (prostration) was recognized with high incidence (8 cases, 50.8%)($p < 0.01$).

Approximately 70% of patients in the non-AF group had no or only mild impairment of ADL ($p < 0.05$). On the other hand, in the AF group, markedly impaired ADL ratings were significantly higher with approximately half of the patient in this group becoming bedridden (Fig. 3).

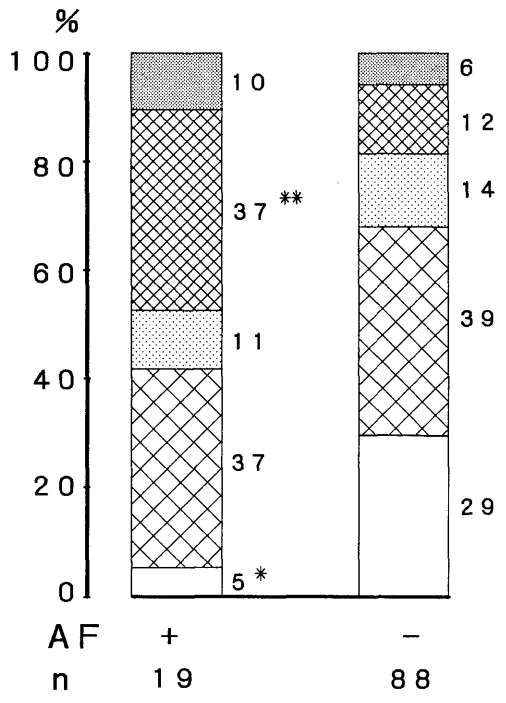

Fig. 3. Final outcome in Activity of Dairy Living after rehabilitating following cerebral infarction.
□ = No impairment, ▨ = Mildly impaired
▩ = Moderately impaired, ▩ = Markedly impaired
■ = Profoundly impaired.
* P < 0.05 VS non-AF, ** P < 0.01 VS non-AF

Thirty-one recurrent cerebral infarctions were observed in both groups (Table 6). The recurrence rate was 38% (14 of 37) in the AF group and 16% (17 of 104) in the non-AF group ($p < 0.01$). Mortality rate in patients with stroke was shown in Table 7. In the AF group, ten (44%) patients died of the initial stroke, and this mortality was significantly higher than that in the non-AF group ($p < 0.001$). In the non-AF group, the recurrent infarction cases had a much higher mortality than first infarction cases group ($p < 0.05$). There were no statistically significant differences between the mortality of initial and recurrent strokes in the AF group, nor difference in mortality of recurrent cases between in patients with and without AF.

Table 6. Incidence of initial and recurrent strokes in 141 patients with and without Nonvalvular atrial fibrillation (NVAF)

	AF	Non-AF	Total
Initial stroke	23	87	110
		**	
Recurrent stroke	14 (38%)	17 (16%)	31
Total	37	104	

** P < 0.01 VS non-AF

Table 7. Mortality rate in Patients with stroke

	Initial stroke		Recurrent stroke	
	AF	Non-AF	AF	Non-AF
Mortality rate (%)	44 (10/23)	13 (11/87)	57 (8/14)	29 (5/17)
	***		*	
	NS		NS	

* P < 0.05 VS non-AF, *** P < 0.001 VS non-AF

The interval from previous stroke to recurrence was studied in 29 of 31 recurrences (13 of 14 in AF and 16/17 in the non-AF group)(Table 8), where the interval from initial stroke to recurrence was definite known. Five cases (38.5%) of the AF group recurred within two months of a previous stroke, particularly 4 cases (30.8%) recurred within one month. Thus in the AF group, early recurrence was more frequent than in the non-AF group ($p < 0.05$). Recurrences more than one year after a previous stroke occurred with equal frequency in both groups. However, in the AF group there were no recurrences more than 6 years after the previous stroke, whereas there were 5 cases (31.3%) of recurrent stroke more than 10 years after a previous event (3 more than 20 years after previous stroke) in the non-AF group.

Table 8. Interval to Recurrence of Stroke in Patients with Recurrent Stroke

	AF (n = 13)	Non-AF (n = 16)
< 2W	2	1
< 1M	4	1
< 2M	5*	1
< 1Y	6	6
< 2Y	8	6
< 3Y	10	7
< 4Y	10	8
< 5Y	11	11
< 6Y	13	11
> 10Y	13	13
> 20Y	13	16

* P < 0.05 VS non-AF

Discussion

Nonvalvular atrial fibrillation (NVAF) which occurred in patients without valvular heart disease is the most common cardiac condition associated with presumed embolic stroke, accounting for approximately 45% of all embolic strokes (14.25). Aproximately 35% of patients with AF is said to experience an ischemic stroke during their life time (5. 6. 15). Aberg et al (7) reported in an autopsy study that among 504 AF patients without valvular of congenital heart diseases, systemic embolism was evident in 42%, half of which were found in brain.

The differentiation between embolic and thrombotic infarction is often difficult (15). In general, however, in patients with a cardiac condition associated with sudden onset ischemic stroke, an embolic etiology of cerebral infarction must be entertained (22, 23). Recently, there have been many reports demonstrating a lack of efficacy of aspirin to prevent cerebral embolism (9-11). In our study, anticoagulant was not administered around the time of cerebral infarction, and thus anticoagulant therapy could not be evaluated as a preventive measure to avoid reinfarction.

According to Framingham study, the incidence of AF rises sharply with age (3), and the incidence of ischemic stroke of NVAF patients over 24-year follow-up was 5.6 times higher than in patients without AF (2). NVAF confers little added risk for cerebral infarction in patients under the age of 60 (16), but risk increases with age (4). In our study, the incidence of NVAF increased with age.

Kuramoto et al (17) reported that among 405 AF patients in 2,340 consecutive autopsies, large cerebral infarction

was observed in 22%, and medium sizes cortical infarction in about 15%. Similarly, our study shows an association of NVAF with medium or large sized cortical infarction. It is likely that this fact accounts for our finding that patients with NVAF presented more often with a decreased level of consciousness and accordingly a high mortality rate ensued. Thus, these findings suggest that NVAF is a very important cause of fatal massive cerebral infarction (12). Marquardsen (18) indicated by the use of life-table analysis of cerebral hemorrhage and infarction, that "early death" is an appropriate categorization of patients who die within 3 weeks of their stroke. According to this standard, 7 cases in our series were early deaths, and 4 of these were patients with NVAF. In fatal cases, sudden worsening during hospitalization was frequently observed in patients with NVAF, many of whom developed recurrent strokes. Mortality after ischemic stroke was significantly affected by age in non-AF patients, but there was no affect of age on survival in patients with AF. In patients with NVAF, mortality was primarily determined by size of the cortical infarction rather than age despite the sharply increased incidence of NVAF in the elderly. In non-AF patients, age itself appears to play a central role leading to prostration and debilitation in the elderly, and finally death after an extended period of hospitalization. But in NVAF patients, mortality was determined during a short period of hospitalization due to importance of infarct size in determining survival.

In surviving patients, approximately 70% of non-AF patients returned to an independent lifestyle, however, in NVAF patients almost half fell into a bedridden state, with a total of 60% never recovering to an independent life. Therefore, NVAF plays an important role in determining functional prognosis as well as survival. Again this is likely related to initial infarct size.

Yamanouchi (19) reported that 41.4% of patients with cerebral infarction and AF had more than two recurrent strokes in their life. In our study, 37.8% of NVAF patients developed recurrent stroke and the mortality rate of initial stroke in NVAF patients was 43.5%. Sage et al (20) has reported a 38% death rate in initial stroke. They followed up the surviving patients with stroke up to 9 years without anticoagulant therapy and demonstrated that the risk of recurrent cerebral infarction remained at approximately 20% per year through out the 9 year observation period. In embolic infarction with organic heart disease, the risk of early recurrence, especially within 2 weeks, must be emphasized (21-23). Stroke recurrence within the first 6 months following initial stroke is more than twice as common in the group of patients with NVAF as compared with that in the group of patients without AF (25). However, in NVAF patients early recurrent stroke has not often been reported and recurrences tends to be scattered over subsequent years (1, 20, 24). In our study, 5 of 14 recurrent cerebral infarctions occurred within 2 months after initial stroke in patients with NVAF (4 of these 5 occurred within 1 month), and the remaining 9 were scattered over more than 1 year of follow-up including 2 cases who with recurrence after 6 years. There was no difference in the incidence of recurrence more than 1 year after initial infarction between the NVAF and non-AF groups.

Summary

In this series, infarcts associated with NVAF tends to occur as large cortical infarctions as previously reported (17, 21). Many patients with cerebral infarction and NVAF presented with a depressed level of consciousness and a high mortality rate ensued. Infarct size rather than age itself, was the primary factor influencing mortality in patients with NVAF. Majority of surviving patients remained functionally impaired. Finally, patients with NVAF and stroke are at high risk for recurrent infarction in the early post-infarct stage, but continue to be at risk for recurrence even years after the initial stroke.

Acknowledgement

The author would like to thank Prof. Katsusuke Yano, the Third Department of Internal Medicine, Nagasaki University School of Medicine for his revision.

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