

## Atrial fibrillation among patients with stroke

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Stroke is the most common cause of death after cardiovascular disease and malignant disease. Stroke is defined as acute nonconvulsive damage of the CNS, and it presents itself as infarction or hemorrhage.<sup>1</sup> The causes of stroke are ischemia in approximately 85% of cases and hemorrhage in the remaining 15%. Risk factors for development of stroke are hypertension, high lipid profile, and smoking. Ischemic events of the brain are categorized into 2 groups: thrombotic (in situ thrombosis formation) and embolic (migration of preformed thromboses or plaque). Embolic strokes are the most common causes of ischemic infarction in the brain.<sup>2</sup> The heart itself, is the most common source of emboli to the brain. In approximately 40% of cases, the exact source of emboli remains unknown even after evaluation of heart and extracranial vessels. Without considering underlying cardiac pathology, persistent and paroxysmal atrial fibrillation (AF) are the most important causes and sources of emboli to the brain. Nonvalvular AF, acute or chronic ischemic heart disease, ventricular aneurysm, rheumatic valvular disease, mechanical prosthetic valve, cardiomyopathy, infective endocarditis, myxomatoid mitral valve, paradoxical embolism, left atrial myxoma are all important causes of cardiac source cerebral emboli.<sup>3</sup> Nonvalvular AF, which itself accounts for approximately 80% of this rhythm disturbance is the most important and common cause of cardiac source of emboli to the brain, and accounts for approximately 50% of cases of cerebral emboli. In one study, 2000 old patients were followed over 42 months. Forty-six percent of patients with AF had embolic infarction, while only 17% of patients with normal sinus rhythm had embolic infarction. In another study, 43% of patients who had AF also had a history of brain infarction in their past medical history. In another study, on old patients with stroke admitted to the hospital during a period of 50 months, 38% of patients had AF rhythm. Further evaluation of the Framingham study revealed 5.6% times increase in risk of stroke among patients with nonvalvular AF, and 17.5% times increase in risk of stroke among the valvular AF group.<sup>3</sup> As there was no previous survey on the prevalence of AF and its relation to stroke in Iran, therefore, we decided to carry out a randomized clinical study in Golestan Hospital, Ahwaz, Iran as the only referral center of stroke in Khozestan Province.

Between March 2005 and April 2006, patients with stroke from the Neurology Department of Golestan Hospital, Ahwaz, Iran were included in this study. The inclusion criteria includes patients who had a clinical diagnosis of stroke for the first time confirmed

by axial computed tomography (ACT) compatible with thromboembolic or hemorrhagic stroke either at presentation or during admission. The exclusion criteria includes patients with transient ischemic attack, clinical diagnosis without ACT findings compatible with stroke, patients with chronic or recurrent ischemic or hemorrhagic stroke, brain tumors, and other systemic and infectious encephalopathy. All of the patients underwent a survey of age, gender, and atherosclerotic and stroke risk factors (blood pressure measurement at and during admission every 2-6 hours, analysis of lipid profile, regular fasting blood sugar control) and other routine biochemical tests. In addition to 12-lead serial electrocardiogram at and during admission, serial Doppler and 2-dimensional echocardiography were obtained during admission. Blood pressure level less than 130/80 mm Hg, triglyceride, and cholesterol level less than 200 mg/dl, fasting blood sugar less than 126 mg/dl, were considered normal levels in this study. A patient was considered diabetic if he or she had one of the following criteria: 1) reliable past medical history of diabetes, 2) drug history of oral hypoglycemic agent or insulin injection, 3) fasting blood sugar level more than 126 mg/dl on 2 separate occasions. Cardiac murmur (grade 3/6 or greater) at examination or moderate to severe valvular stenosis or regurgitation on echocardiography, were criteria for consideration as valvular heart diseases. The Framingham criteria for clinical diagnosis of heart failure were used: major criteria - paroxysmal nocturnal dyspnea, neck vein distension, rales, cardiomegaly, acute pulmonary edema, S3 gallop, increased venous pressure ( $>16$  cm H<sub>2</sub>O), positive hepatojugular reflux, and minor criteria - extremity edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, vital capacity reduced by one-third from normal, tachycardia (120 bpm) and major or minor - weight loss  $>4.5$  kg over 5 days' treatment). To establish a clinical diagnosis of congestive heart failure by these criteria at least one major and 2 minor criteria are required. An ejection fraction (EF) less than 40% was considered as other criteria for inclusion as congestive heart failure. In addition all of the electrocardiographs and echocardiographic data at admission and during the hospital stay were interpreted by a cardiologist. This study was approved by the ethics committee of the cardiovascular research center of the university hospital and written informed consent were obtained from all patients. The data were collected and analyzed by SPSS software, chi-square test was used for comparison between groups and *p* value less than or equal to 0.05 was considered statistically significant. Four hundred and twelve patients with a male female ratio of 1.2/1 and mean age of  $52 \pm 12$  were studied. Sixty-two point nine percent (259 patients) had thromboembolic stroke and 37.1% (153 patients) had hemorrhagic stroke.

Atrial fibrillation was seen in 13.5% (56 patients) of all of the stroke patients. In the thromboembolic group, 51 patients (19.7%) had AF while the number in the hemorrhagic group was 5 (3.2%) ( $p < 0.001$ ). Ninety-one percent of patients with AF and stroke had thromboembolic stroke, and only 9% had hemorrhagic stroke ( $p < 0.05$ ), 58.4% of patients with sinus rhythm and stroke had thromboembolic stroke, and 41.6% had hemorrhagic stroke ( $p > 0.05$ ). Although 3 quarters of the patients in the thromboembolic group were above 60 years, there was no significant difference in prevalence of AF between age groups of above 60 years or below 60 in thromboembolic stroke patients (21% versus 15.8%),  $p > 0.05$ . Although the number of male patients was outnumbered in all groups of patients with stroke (thromboembolic or hemorrhagic) comparison of male to female ratio in these groups (AF groups and other groups) did not reveal any significant statistical difference ( $p > 0.05$ ). According to initial definition, 6.7% of patients were in the valvular disease group (28 patients). Prevalence of AF among stroke patients with valvular heart disease was higher than the prevalence of AF in stroke without valvular heart disease (53.5% versus 10.7%)  $p < 0.001$ . The overall prevalence of CHF was 4.3% (18 patients). The prevalence of AF among stroke patients with congestive heart failure (based on previous definition) was 33.3% in contrast to 12.6% in the stroke group without CHF. The difference between the 2 groups was statistically significant  $p < 0.01$ . The most common risk factors in all patients with stroke were hypertension (67%), smoking (26.6%), diabetes (18.2%), and hyperlipidemia (13.3%). The prevalence of risk factors for atherosclerosis are compared between all of the stroke patients as a group and patients with AF and stroke as another group, and there was no significant statistical differences between these groups (Table 1).

Atrial fibrillation is one of the most common arrhythmias in the older age group (approximately 1% of people above age of 60, and 5% of people above age 69 years) and stroke is the most dreadful complication of it. Occurrence of AF is more probable in males than in females. Atrial fibrillation may be paroxysmal or

persistent and both conditions may be a precipitating factors for stroke.<sup>3</sup> Recent studies revealed no significant differences in major events between chronic AF with rate control than rhythm control.<sup>3</sup> Atrial fibrillation in the older age group is usually associated with chronic heart disease such as hypertension, ischemic heart disease, congestive heart failure, or valvular heart disease. In addition, some acute illnesses such as pneumonia, acute infection of other organs, surgery, and acute ischemic heart attack may be a precipitating factor for AF.<sup>4</sup> Mitral stenosis and prosthetic heart valve complicated by AF have been known as high risk conditions for peripheral artery embolism for a long time, but even in patients with AF and without valvular heart disease there is a high risk of embolic events and brain infarction. The incidence of cerebral ischemic infarction in the older age group with AF is 5% (per year), which is approximately 6 times more than the incidence in patients of this age group without AF.<sup>4</sup> This study revealed a significantly higher prevalence of AF in the thromboembolic group compared to the hemorrhagic group (19.7% versus 3.2%). However, a comparison of prevalence of brain infarction among stroke patients with AF and normal sinus rhythm revealed a higher prevalence of infarction in the AF group (91% versus 58.4%). The significant role of AF in the occurrence of brain infarction is clearly seen in this study. Even in the patients with AF other etiologies of brain infarction should not be ignored. Other etiologies of stroke such as atheroma of ascending aorta or aortic arch, cerebral vessels disease, and cardiac causes other than AF have been found in approximately 25% of cases of AF and stroke.<sup>5</sup> Higher occurrences of AF among older aged patients and male groups have been reported in previous investigations, however, in this study we did not find any significant difference between prevalence of AF in age groups above and below 60 years, and/or the male to female ratio among patients who had stroke and AF versus other groups of stroke. As indicated in past similar studies, hypertension, diabetes, hyperlipidemia, and cigarette smoking were the most important risk factors for stroke in this study.

Another important finding in this study is that in stroke patients with underlying cardiac problems (valvular or congestive disease), AF is more common (53.5% and 33.3%) than in groups of stroke patients without these 2 underlying problems (10.7% and 12.6%). So there is strong evidence that proves a close association between valvular heart disease, congestive heart failure, and AF and high probability of embolic stroke in this condition (AF). Although the results of our study are compatible with previous studies in other parts of the world, the results may not reflect real numbers on stroke in the Khozestan province as our study was carried out only on admitted patients and most of the stroke patients were managed in outpatient

**Table 1** - Prevalence of risk factors and gender among patients with stroke.

Risk factors	Male	Female	%			
			HTN	HLP	DM	Smoking
All stroke patients	54.8	45.2	67	13.3	18.2	26.6
Stroke without AF	54.4	45.5	69	14.6	19	27.4
Stroke with AF	57	43	53.5	5	12.5	21.4

HTN - hypertension, HLP - hyperlipidemia, DM - diabetes mellitus, AF - atrial fibrillation

services and were not included in the study. This fact reveals the necessity for more extensive study in the future. We suggest every patient with AF who has risk factor for cerebral embolism such as history of stroke, transient ischemic attack, hypertension, diabetes, age >75, left atrial enlargement significant valvular heart disease, coronary artery disease, congestive heart failure should receive oral anticoagulant drugs (warfarin). The goal of therapy is INR (international normalization ratio) between 2-3. If anticoagulation is impossible or impractical (due to low socioeconomic state) the patient will be treated with aspirin (75-375 mg daily).<sup>5</sup> As the low risk of stroke (2% per year) in patients who have AF and lack of risk factors for embolism they can be treated by aspirin alone, although some new studies show that aspirin does not provide complete prevention.<sup>5</sup> This study revealed a significantly higher prevalence of AF in patients with ischemic stroke, especially those with congestive heart failure or valvular heart disease and it further emphasizes the importance of treatment with anticoagulant drugs for prevention of embolic brain disease in an older aged group who suffer from the above mentioned cardiac problems.

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