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Causes of Ischemic Stroke in Patients with Atrial Fibrillation

Atriyal Fibrilasyonlu Hastalarda İskemik İnme Sebepleri

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Abstract

Objective: Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting 1% of the adult population. However, ischemic strokes in patients with AF can be triggered by alternative mechanisms, especially in high-risk patients with additional vascular risk factors. In some patients, atherothrombotic mechanisms may cause stroke, and AF may be incidental or a symptom of atherosclerotic disease. In this case, it may be difficult to distinguish cardioembolic stroke from stroke due to large artery atherosclerosis. The aim of this study was to determine the causes of non-cardioembolic ischemic stroke in patients with non-valvular AF and to determine the risk factors for craniocervical atherosclerotic stenosis.

Materials and Methods: This study identified risk factors for craniocervical atherosclerotic stenosis in patients followed up at the Uludağ University Faculty of Medicine Department of Neurology with a diagnosis of ischemic stroke and non-valvular AF. In this study, 180 patients who were followed up with a diagnosis of non-valvular AF and acute ischemic stroke between January 1st, 2019 - March 1st 2020, in Uludağ University Faculty of Medicine Department of Neurology, were retrospectively included.

Results: In this study, the non-cardiac stroke rate was 20% in patients with non-valvular AF who had acute ischemic stroke. Ischemic stroke due to large vessel atherosclerosis was found in 14.4% of these patients, and 9.5% of all patients with AF were stented. When dermographic features, clinical features, and risk factors were analyzed for craniocervical atherosclerotic stenosis, a significant statistical result was obtained with male sex (p=0.020) and smoking (p<0.001).

Conclusion: Stroke is a heterogeneous group of diseases caused by many complex mechanisms. Prevention of stroke recurrence is possible by starting effective treatment early. The presence of critical artery stenosis in a patient with acute ischemic stroke with AF causes stroke recurrence and this relapse cannot be prevented by anticoagulant treatment. Angiographic evidence also revealed ethnic and racial differences in patients with acute ischemic stroke. Therefore, more precise information can be obtained through prospective studies in our population.

Keywords: Atrial fibrillation, ischemic cerebrovascular disease, craniocervical atherosclerotic stenosis

Öz

Amaç: Atriyal fibrilasyon (AF) yetişkin popülasyonun %1'ini etkileyen en yaygın kardiyak aritmidir. Bununla birlikte, AF'li hastalarda iskemik inmeler, özellikle ek vasküler risk faktörleri olan yüksek riskli hastalarda, alternatif mekanizmalarla tetiklenebilir. Bu hastaların bazılarında inmeye aterotrombotik mekanizmalar neden olabilir ve AF rastlantısal veya aterosklerotik hastalığın bir belirtisi olabilir. Bu durumda kardiyoembolik inmeyi büyük arter aterosklerozuna bağlı inmeden ayırt etmek zor olabilir. Bu çalışmanın amacı valvüler olmayan AF'li hastalarda non-kardioembolik iskemik inme sebeplerini saptamak ve kraniyoservikal aterosklerotik stenoz için risk faktörlerini belirlemektir.

Gereç ve Yöntem: Bu çalışma iskemik inme ve valvüler olmayan AF tanısıyla Uludağ Üniversitesi Nöroloji Kliniği'nde takip edilen hastalarda, non-kardiyak inme oranını saptamak ve inme geçiren valvüler olmayan AF'si olan hastalarda kraniyoservikal aterosklerotik stenoz için risk faktörlerini belirlemektedir. Bu çalışmaya, 1 Ocak 2019 - 1 Mart 2020 tarihleri arasında Uludağ Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı'nda valvüler olmayan AF ve akut iskemik inme tanısı ile takip edilen 180 hasta retrospektif olarak taranarak dahil edilmiştir.

Bulgular: Bu çalışmada akut iskemik inme geçiren valvüler olmayan AF'li hastalarda non-kardiyak inme oranı %20 olarak saptanmıştır. Bu hastalarda büyük damar aterosklerozuna bağlı iskemik inme %14,4 saptanmışken, AF'si olan tüm hastaların %9,5'ine stent takıldı. Kraniyoservikal aterosklerotik stenoz için dermografik özellikler, klinik özellikler ve risk faktörleri analiz edildiğinde erkek cinsiyet (p=0,020) ve sigara içiciliği (p<0,001) ile anlamlı istatistiksel sonuç elde edildi.

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Öz

Sonuç: İnme birçok karmaşık mekanizmanın sebep olduğu heterojen bir hastalık grubudur. İnme rekürrensinin önlenmesi etkin tedaviye erken başlamakla mümkündür. AF'si olan bir akut iskemik inme hastasında kritik arter stenozunun olması inme rekürrensine sebep olur ve bu nüks antikoagülan tedavi ile önlenemez. Anjiyografik kanıtlar akut iskemik inmeli hastalarda etnik ve ırksal farklılıkları da ortaya koymuştur. Bu sebeple kendi popülasyonumuzda yapılacak prospektif çalışmalarla daha kesin bilgilere ulaşılabilir.

Anahtar Kelimeler: Atriyal fibrilasyon, iskemik serebrovasküler olay, kraniyoservikal aterosklerotik stenoz

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting 1% of the adult population (1). The prevalence of AF is <0.5% in the 4th and 5th decades, whereas it is 5-15% in the 8th decade, increasing with age (2,3,4,5). With aging, possibly age-related atrial myocardial loss and isolation of the atrial myocardium and associated conduction problems increase the risk of development of AF. AF causes thrombus formation in the left atrium, increasing the risk of ischemic stroke because this thrombus can move and block the cerebral arterial circulation and cause ischemic stroke (6).

Non-valvular AF is a common cause of cardioembolic ischemic stroke and accounts for approximately two-thirds of cardioembolic ischemic strokes. Pathophysiologically, the main stroke mechanism in patients with AF is considered to be cardioembolism. However, ischemic strokes in patients with AF can be triggered by alternative mechanisms, especially in the high-risk group with additional vascular risk factors. Atherothrombotic mechanisms may cause stroke in some patients, and AF may be a sign of incidental or atherosclerotic disease (7). In this situation, it is difficult to differentiate cardioembolic ischemic stroke from ischemic stroke due to large artery atherosclerosis. The aim of this study was to determine the causes of non-cardioembolic ischemic stroke in patients with nonvalvular AF and to determine risk factors for craniocervical atherosclerotic stenosis.

Materials and Methods

This study aimed to determine the rate of non-cardioembolic ischemic stroke and the risk factors for craniocervical atherosclerotic stenosis in patients with non-valvular AF who had a stroke in patients who were admitted to the Uludag University Emergency Department with the diagnosis of ischemic stroke and non-valvular AF and were hospitalized and followed up in the neurology clinic. In this study, 180 patients who were followed up with the diagnosis of non-valvular AF and acute ischemic stroke at Uludag University Faculty of Medicine, Department of Neurology between January 1st 2019 - March 1st 2020, were retrospectively included.

The inclusion criteria for the study were being admitted to the University Emergency Department with a diagnosis of acute ischemic stroke, the presence of AF, undergoing echocardiography (ECHO) or 24-hour rhythm Holter monitoring if necessary, absence of mitral stenosis, clarification of the etiology of the stroke, and being followed up regularly for 3 months after stroke by Uludag University Faculty of Medicine Department of Neurology.

The exclusion criteria were having valvular AF, not undergoing brain and neck computed tomography (CT) angiography, not having cerebral magnetic resonance imaging (MRI), leaving the neurology clinic, not coming to the follow-ups, and non-detection of the patient's clinical outcome [modified Rankin scale (mRS) at the end of the 3rd month].

Approval for the study was obtained from the Uludag University Faculty of Medicine Clinical Research Ethics Committee (dated: 30.03.2020, no: 2020-5/4). Patient approval was not required because it was a retrospective study.

Patients who were admitted to the Uludag University Emergency Department with focal neurologic deficits and diagnosed as having acute ischemic stroke after neuro-imaging were evaluated by neurology specialists; neurologic examinations of the patients were performed, and the patients whose cranial CT scan was evaluated at the time of admission were recommended to be hospitalized in the neurology ward and treatment was initiated. Afterwards, brain-neck CT angiography, second cranial CT, cranial MRI, electrocardiography, ECHO, 24-hour rhythm Holter examination, and digital cerebral angiography were performed to determine the etiology of stroke.

The demographic characteristics of the patients and their medical histories (previous stroke, previous transient ischemic attack, diabetes, hypertension, coronary artery disease, heart failure, valvular heart disease, AF, liver or kidney failure, drug use) were questioned and mRS and CHA_2DS_2-VASC scores calculated at the time of admission to the emergency room were recorded in the epicrisis in each patient. One hundred eighty patients who met the inclusion and exclusion criteria of the study were included in the study. Stroke etiology and clinical outcome (mRS at the end of the 3rd month) were determined from the hospital records in the outpatient clinic controls.

Stroke etiology of the patients was classified by a neurologist according to the Causative Classification of Stroke System (CCS) stroke classification. The brain and neck CT angiographies of the patients were evaluated by a radiologist and the degree of stenosis was classified according to the North American Symptomatic Carotid Endarterectomy Trial method. In patients with craniocervical atherosclerotic stenosis, whether the stenosis was symptomatic was evaluated in terms of clinical and radiologic correlation and categorized. Non-cardioembolic stroke rate was determined and risk factors for craniocervical atherosclerotic stenosis in patients with AF were identified.

Statistical Analysis

Clinical, demographic, and radiologic data of patients with AF with acute ischemic stroke were compared. All data analyses were performed using the IBM SPSS Statistic 23 package program. For continuous variables with normal distribution; number, mean and standard deviation were used, and independent samples were

analyzed using a t-test. The median, 25th and 75th percentiles were used for variables without normal distribution and were analyzed using the Mann-Whitney U test. Percentages are given for categorical variables. Categorical variables were analyzed using the chi-square test. Variables with $p<0.05$ were considered statistically significant.

Results

A total of 180 patients, 85 (47%) males and 95 (53%) females, with non-valvular AF were included in this study. The mean age was 72.14±0.78 years. The mean age of the women was 73.6±1.1 years and the mean age of the men was 70.5±1.0 (p=0.038). In our study, 34 (19%) patients had paroxysmal AF and 146 (81%) had chronic AF. The mean CHA_2DS_2-VASC score of patients with non-valvular AF was 5.25±1.53. Of 46 (25.5%) patients with craniocervical atherosclerotic stenosis, 32 had symptomatic internal carotid artery stenosis, 27 had asymptomatic internal carotid artery stenosis, 10 had right vertebral artery stenosis, 12 had left vertebral artery stenosis, and four had basilar artery stenosis. Stenosis degrees are shown in Table 1.

The stroke etiology of the patients was categorized according to the CCS. Accordingly, the etiology was large vessel atherosclerosis in 26 (14.4%) patients, cardioembolism in 144 (80%) patients, small vessel occlusion in seven (3.9%) patients, and other causes in three (1.7%) patients. The non-cardiac stroke rate was found as 20% in the patients. Carotid artery stenting was performed on 17 (9.5%) patients. Stenting was performed to the symptomatic internal carotid artery in nine patients and the asymptomatic internal carotid artery in eight patients.

There was a statistically significant relationship between patients with stroke who had non-valvular AF with and without craniocervical atherosclerotic stenosis in terms of male sex (p=0.020) and smoking (p<0.001), whereas there was no relationship between the groups in terms of age, hypertension, diabetes mellitus, heart failure, coronary artery disease, CHA_2DS_2-VASC score, low-density lipoprotein-cholesterol level, mRS at

Table 1. Degrees of atherosclerotic stenosis in craniocervical arteries in patients with non-valvular atrial fibrillation

Degree of stenosis	Symptomatic internal carotid artery	Asymptomatic internal carotid artery	Right vertebral artery	Left vertebral artery	Basilar artery
No stenosis	148	153	170	168	176
<50%	4	5	-	1	1
50-70%	7	10	1	3	1
70-99%	14	10	4	7	2
Occluded	7	1	6	1	-

Table 2. Evaluation of demographic features, risk factors, and clinical features for craniocervical atherosclerotic stenosis in patients with non-valvular atrial fibrillation

Variables	Patients with cerebrocervical atherosclerotic stenosis (n=46)	Patients without cerebrocervical atherosclerotic stenosis (n=134)	p value
Age* mean ± SD	71.77±0.96	73.22±1.29	0.524
Sex** (male)	17 (37%)	29 (21.6%)	0.020
Hypertension**	37 (80.6%)	100 (74.6%)	0.551
Diabetes mellitus**	16 (34.7%)	44 (32.8%)	0.857
Smoking**	18 (39.1%)	17 (12.6%)	<0.001
Heart failure**	16 (34.7%)	33 (24.6%)	0.253
Coronary artery disease**	14 (30.4%)	29 (21.6%)	0.314
CHADS VASC score* mean ± SD	5.32±1.51	5.2±1.55	0.726
LDL* mean ± SD	120.20±38.55	112.25±31.24	0.222
mRs* mean ± SD	3.04±1.67	3.23±1.70	0.594
Stroke recurrence**	11 (24%)	16 (12%)	0.085
Clinical outcome** (good outcome)	31 (67.3%)	85 (63.4%)	0.760
Stroke etiology**			
Large vessel atherosclerosis (n=16)	26 (56.6%)	0 (0%)	
Cardioembolism (n=154)	21 (45.6%)	123 (91.7%)	
Small vessel disease (n=7)	2 (4%)	5 (4%)	<0.001
Other causes (n=3)	0 (0%)	3 (2%)	
Cryptogenic stroke (n=0)	0 (0%)	0 (0%)	

*Mann-Witney U test, **Pearson chi-square/continuity correction/Fisher exact test, SD: Standard deviation, LDL: Low-density lipoprotein

admission, stroke recurrence, and clinical outcome (mRS at the end of the 3rd month) (Table 2).

Discussion

In this study, the rate of non-cardiac stroke was found as 20% in patients with non-valvular AF who had acute ischemic stroke. The rate of ischemic stroke due to large vessel atherosclerosis was found as 14.4% in these patients, and 9.5% of all patients with non-valvular AF underwent carotid artery stenting.

Stroke is the second most common cause of death and the main cause of disability (4). AF is the most common cardiac arrhythmia and is a global problem (8). Compared with age-matched control groups, AF increases the risk of ischemic stroke 4-5 times (2,3), and the risk of ischemic stroke associated with AF is greater in older patients. Ischemic stroke risk is independent of AF being paroxysmal or chronic (9,10,11,12).

In patients with AF, ischemic stroke causes atrial fibrosis and decreased contractility of the myocardium, resulting in cessation of blood flow, particularly in the left atrial appendage. Approximately 90% of thrombi in patients with non-valvular AF originate from the left atrial appendage. Left atrial appendix enlargement and decreases in left atrial appendix flow rates are associated with an increased risk of thrombus formation and ischemic stroke (13,14,15). In addition, the incidence of carotid artery stenosis is high in patients with AF with acute ischemic stroke (16), and ischemic stroke due to small vessel occlusion can be seen in 9% to 16% of patients with AF with ischemic stroke (17,18). Anticoagulation may not prevent ischemic stroke recurrence, especially in these patients (19,20,21,22). Craniocervical atherosclerotic stenosis can be seen in 50% of patients with AF with acute ischemic stroke, and high-grade (70% and above) stenosis or occlusion is observed in 11% to 24% (7,16,17,23,24). In 14% of patients, there is high-grade (70% and above) stenosis in the symptomatic ipsilateral internal carotid artery, and it is thought that the etiology of ischemic stroke in these patients is ischemic stroke due to large artery atherosclerosis (7).

Studies have indicated that the coexistence of AF and carotid artery stenosis in patients with cerebral ischemic stroke worsens the clinical outcome (mRS at the end of the 3rd month) (7,16). In our study, there was no difference in terms of clinical outcome (mRS at the end of the 3rd month) between patients with and without craniocervical atherosclerotic stenosis. The probable reason for this may be the early detection of craniocervical atherosclerotic stenosis with routine brain-neck CT angiography in each patient and early treatment with the detection of a pathology.

According to the Trial of Org 10172 in Acute Atroke (TOAST) stroke classification, patients with AF and ipsilateral high-grade stenosis are classified as "stroke of unknown cause" (25). The TOAST classification is insufficient when classifying the etiology of stroke of patients with acute ischemic stroke. We categorized the ischemic stroke etiology of our patients according to the CCS stroke classification. In the presence of ipsilateral high-grade (70% and above) atherosclerotic stenosis and AF, it would be difficult for a thrombus to pass through the narrowed lumen, so this stroke was recommended to be classified as ischemic stroke due to large artery occlusion (19). However, lesion localization in cranial MRI is important. According to the CCS stroke classification, if there are multiple ipsilateral and unilateral "borderzone" infarctions in the area of the affected artery, it is probably ischemic stroke due to large artery occlusion. The patient's clinical picture is also important. If there is a history of transient monocular blindness, transient ischemic attack, or stroke in the artery area affected by atherosclerosis in the past month, it is probably ischemic stroke due to large artery occlusion (26). The CCS stroke classification should be used routinely for each patient because the TOAST stroke classification is insufficient when classifying the etiology of stroke of these patients. Some authors consider the development of AF in individuals without atherosclerosis as an unexpected event (27). However, in a study on young patients without risk factors and heart disease, the presence of AF was significantly associated with high carotid intima-media thickness and carotid-femoral pulse wave velocity and low aortic flexibility indexes (28). In particular, experimental and imaging studies revealed strong biologic evidence for a causal relationship between atherosclerosis and AF. On the one hand, carotid artery atherosclerosis and wall thickening are closely related to coronary atherosclerosis and microvascular damage, which can cause hypoperfusion and ischemia of the atrium, and later fibrosis and AF (28,29,30,31,32,33,34).

Conclusion

Stroke is a heterogeneous group of diseases caused by many complex mechanisms. Prevention of stroke recurrence is possible by starting effective treatment early. High-grade (70% and above) craniocervical atherosclerotic stenosis in a patient with acute ischemic stroke with AF causes stroke recurrence and this recurrence cannot be prevented by anticoagulants. The patient needs to use antiaggregant treatment and revascularization of the stenotic vessel may even be needed in some patients. We wanted to draw attention to craniocervical atherosclerotic stenosis, which was seen in patients with AF who had ischemic stroke. The rates of non-cardiac stroke in patients with AF were previously determined, but we found this again in our population at our referral center. According to our data, the rate of non-cardiac stroke in patients with non-valvular AF was 20%. The craniocervical atherosclerotic stenosis rate was 25.5%. Carotid artery stenting was performed on 9.5% of our patients. The most important risk factor for craniocervical atherosclerotic stenosis is smoking. Angiographic evidence has also revealed ethnic and racial differences in patients with acute ischemic stroke. For this reason, more precise information can be obtained with prospective studies to be conducted in our population.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Uludag University Faculty of Medicine Clinical Research Ethics Committee (dated: 30.03.2020, no.: 2020-5/4).

Informed Consent: Patient approval was not required because it was a retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.D., M.B., B.H., Concept: Y.D., M.B., B.H., Design: Y.D., M.B., B.H., Data Collection or Processing: Y.D., M.B., B.H., Analysis or Interpretation: Y.D., M.B., B.H., Literature Search: Y.D., M.B., B.H., Writing: Y.D.

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References

1. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart 2001;86:516-521.
2. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119-125.
3. Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006;27:949-953.
4. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. Am J Cardiol 2009;104:1534-1539.
5. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042-1046.
6. Kim YH, Roh SY. The mechanism of and preventive therapy for stroke in patients with atrial fibrillation. J Stroke 2016;18:129-137.
7. Kim YD, Cha MJ, Kim J, et al. Increases in cerebral atherosclerosis according to CHADS2 scores in patients with stroke with nonvalvular atrial fibrillation. Stroke 2011;42:930-934.
8. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837-847.
9. Phillips SJ. Is atrial fibrillation an independent risk factor for stroke? Can J Neurol Sci 1990;17:163-168.
10. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-2375.
11. Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke 2005;36:1115-1119.
12. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. Ann Neurol 1989;25:382-390.
13. Yamamoto M, Seo Y, Kawamatsu N, et al. Complex left atrial appendage morphology and left atrial appendage thrombus formation in patients with atrial fibrillation. Circ Cardiovasc Imaging 2014;7:337-343.
14. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. J Am Coll Cardiol 1994;23:961-969.
15. Beinart R, Heist EK, Newell JB, et al. Left atrial appendage dimensions predict the risk ofstroke/TIA in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2011;22:10-15.
16. Chang YJ, Ryu SJ, Lin SK. Carotid artery stenosis in ischemic stroke patients with nonvalvular atrial fibrillation. Cerebrovasc Dis 2002;13:16-20.
17. Benbir G, Uluduz D, Ince B, Bozluolcay M. Atherothrombotic ischemic stroke in patients with atrial fibrillation. Clin Neurol Neurosurg 2007;109:485-490.
18. Park YS, Chung PW, Kim YB, et al. Small deep infarction in patients with atrial fibrillation: evidence of lacunar pathogenesis. Cerebrovasc Dis 2013;36:205-210.
19. Hart RG, Pearce LA, Miller VT, et al. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. Cerebrovasc Dis 2000;10:39-43.
20. Miller VT, Rothrock JF, Pearce LA, et al. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. Stroke prevention in atrial fibrillation investigators. Neurology 1993;43:32-36.
21. Evans A, Perez I, Yu G, Kalra L. Secondary stroke prevention in atrial fibrillation: lessons from clinical practice. Stroke 2000; 31:2106-2111.
22. Evans A, Perez I, Yu G, Kalra L. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? Stroke 2001;32:2828-2832.
23. Bogousslavsky J, Van Melle G, Regli F, Kappenberger L. Pathogenesis of anterior circulation stroke in patients with nonvalvular atrial fibrillation: the Lausanne Stroke Registry. Neurology 1990;40:1046-1050.
24. Miller VT, Pearce LA, Feinberg WM, et al. Differential effect of aspirin versus warfarin on clinical stroke types in patients with atrial fibrillation. Stroke prevention in atrial fibrillation investigators. Neurology 1996;46:238-240.
25. Adams HP Jr, Bendixen BH, Kappelle JL, et al. Classification ofsubtype of acute ischemic stroke: definitions for use in amulticenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
26. Ay H, Benner T, Arsava EM, et al. A computerized algorithm foretiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke 2007;38:2979-2984.
27. Chen LY, Foo DC, Wong RC, et al. Increased carotid intima-media thickness and arterial stiffness are associated with lone atrial fibrillation. Int J Cardiol 2013;168:3132-3134.
28. Sillesen H, Muntendam P, Adourian A, et al. Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study. JACC Cardiovasc Imaging 2012;5:681-689.
29. Davies MJ, Pomerance A. Pathology of atrial fibrillation in man. Br Heart J 1972;34:520-525.
30. Nucifora G, Schuijf JD, Tops LF, et al. Prevalence of coronary artery disease assessed by multislice computed tomography coronary angiography in patients with paroxysmal or persistent atrial fibrillation. Circ Cardiovasc Imaging 2009;2:100-106.
31. Sinno H, Derakhchan K, Libersan D, et al. Atrial ischemia promotes atrial fibrillation in dogs. Circulation 2003;107:1930-1936.
32. Weijs B, Pisters R, Haest RJ, et al. Patients originally diagnosed with idiopathic atrial fibrillation more often suffer from insidious coronary artery disease compared to healthy sinus rhythm controls. Heart Rhythm 2012;9:1923-1929.
33. Iwakiri T, Yano Y, Sato Y, et al. Usefulness of carotid intima-media thickness measurement as an indicator of generalized atherosclerosis: findings from autopsy analysis. Atherosclerosis 2012;225:359-362.
34. Sorop O, Merkus D, de Beer VJ, et al. Functional and structural adaptations of coronary microvessels distal to a chronic coronary artery stenosis. Circ Res 2008;102:795-803.