International Journal of Cardiology 174 (2014) 541–544

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Short stature and ischemic stroke in nonvalvular atrial fibrillation: New insight into the old observation ☆

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ARTICLE INFO

Article history:
Received 11 April 2014
Accepted 12 April 2014
Available online 21 April 2014

Keywords:
Stroke
Atrial fibrillation
Height
Diastolic function
Echocardiography

ABSTRACT

Background: For decades, repeated epidemiologic observations have been made regarding the inverse relationship between stature and cardiovascular disease, including stroke. However, the concept has not been fully evaluated in patients with atrial fibrillation (AF). We investigated whether patient's height is associated with ischemic stroke in patients with nonvalvular AF and attempted to ascertain a potential mechanism.

Methods: All 558 AF patients were enrolled: 211 patients with ischemic stroke (144 men, 68 ± 10 years) and 347 no-stroke patients (275 men, 56 ± 11 years) as a control group. Clinical characteristics and echocardiographic parameters were compared between the two groups.

Results: (1) Stroke patients were shorter than those in the control group (164 ± 8, vs. 169 ± 8 cm, $p < 0.001$). However, body mass index failed to predict ischemic stroke; (2) Short stature (OR 0.93, 95% CI 0.91–0.95, $p < 0.001$) along with left atrial (LA) anterior-posterior diameter and diastolic mitral inflow velocity (E) to diastolic mitral annuls velocity (E') (E/E') were independent predictor of stroke; (3) Height showed inverse correlation with E/E' independently, even after adjusting for other variables, including age, sex, and body weight, and comorbidities $\beta -0.20$, $p = 0.003$); (4) LA size showed no correlation with stature ($R = -0.06$, $p = 0.18$), whereas left ventricular size increases according to height of patients.

Conclusions: Short stature is associated with occurrence of ischemic stroke and diastolic dysfunction in patients with AF and preserved systolic function. Height is a non-modifiable risk factor of stroke and might be more important than obesity in Asian AF patients, who are relatively thinner than western populations.

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For decades, epidemiologic observations have been made regarding the inverse relationship between stature and cardiovascular (CV) disease including stroke [1]. However, it is unclear whether height is associated with stroke occurrence in nonvalvular atrial fibrillation (AF) (NV-AF) patients. We investigated whether height is associated with occurrence of ischemic stroke in NV-AF with preserved left ventricular (LV) ejection fraction (EF) (≥50%); and whether cardiac structure and function are influenced by stature.

All 558 NV-AF patients were enrolled. Ischemic stroke was defined as the presence of a focal neurologic deficit or a nonfocal encephalopathy lasting >24 h with evidence of cerebral infarction on brain magnetic resonance imaging. Echocardiography was performed and measurements were averaged for five cardiac cycles. LV EF was calculated using the modified Quinones method. Left atrial (LA) anterior–posterior (AP) diameter was measured and LA volume was calculated using the biplane area-length method. Mitral inflow velocity (E) was determined using the pulsed wave Doppler and diastolic mitral annulus velocity (E′) was measured using tissue Doppler imaging at the septal corner. E/E′ was calculated. Two-sample t-tests and chi-square tests with Fisher's exact tests were used for continuous and categorical variables, respectively. Binary logistic regression analysis was used to determine independent predictors for stroke. For inter-tertile comparison, we used the one-way ANOVA test and post hoc analyses were performed using the Bonferroni

☆ Funding Sources: This work was supported by research grants from the Gachon University Gil Medical Center, Republic of Korea (Grant number: 2013-10 and 2013-46, J.M.), Boryung Pharmaceutical Company (J.M.), the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2010-0021993, NRF-2012R1A2A2A02045367, B.J.), and a grant from the Korean Healthcare Technology R&D project funded by the Ministry of Health & Welfare (HI12C1552, B.J.).

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http://dx.doi.org/10.1016/j.ijcard.2014.04.154
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Table 1
Baseline characteristics and intergroup comparison of study patients.

	All (n = 558)	No stroke (n = 347)	Stroke (n = 211)	p-value
Clinical characteristics				
Age, years	60 ± 12	56 ± 11	68 ± 10	<0.001*
Male, n (%)	419 (75)	275 (79)	144 (68)	0.004*
Height, cm	167 ± 8	169 ± 8	164 ± 8	<0.001*
Body mass index (body weight [kg]/height^2 [m^2]), kg/m^2	25 ± 3	25 ± 3	24 ± 3	<0.001*
Paroxysmal AF, n (%)	349 (63)	242 (70)	107 (51)	<0.001*
Comorbidities, n (%)				
CHF	22 (4)	9 (3)	13 (6)	0.04*
Hypertension	305 (55)	153 (44)	152 (72)	<0.001*
Age >75 years	53 (10)	8 (2)	45 (21)	<0.001*
Diabetes mellitus	89 (16)	35 (10)	54 (26)	<0.001*
Dyslipidemia	100 (18)	57 (16)	43 (20)	0.26
CHADS2	0.8 ± 0.8	0.6 ± 0.7	1.3 ± 0.8	<0.001*
Antithrombotic medications	127 (23)	83 (25)	44 (21)	0.47
Anti-platelet agents, n (%)	72 (13)	37 (11)	35 (17)	0.51
Anticoagulants, n (%)	81 (15)	56 (16)	25 (12)	0.65
Echocardiography				
LV EF, %	63 ± 8	64 ± 7	63 ± 10	0.35
LA AP diameter, mm	43 ± 3	41 ± 6	46 ± 7	<0.001*
LA volume, mL	65 ± 25	58 ± 20	79 ± 30	<0.001*
LVEDD, mm	50 ± 4	50 ± 4	50 ± 5	0.52
E/E′	11 ± 5	10 ± 4	14 ± 6	<0.001*

AF = atrial fibrillation; CHF = congestive heart failure; BMI = body mass index; LV EF = left ventricular ejection fraction; LA = left atrium/atrial; AP = anterior–posterior; LVEDD = left ventricular end-diastolic dimension; E/E′ = mitral inflow velocity/diastolic mitral annulus velocity.
* Indicates $p < 0.05$.

procedure. Pearson's bivariate correlation was used to determine correlation between variables. Multiple linear regression analysis was performed to test the association of variables with E/E′.

Baseline characteristics are shown in Table 1. Patients with stroke were older, more likely to be female, and particularly, shorter than subjects without stroke; body mass index (BMI) was smaller in the stroke group. On echocardiography, longer LA AP diameter, larger LA volume and higher E/E′ were observed in the stroke group. In a binary logistic regression analysis (Table 2), height showed an independent association with stroke, even after adjusting for age, sex, hypertension and diabetes. Meanwhile, BMI showed inverse correlation with stroke and failed to predict the adverse event independently after adjusting for demography and presence of other co-morbidities. LA AP diameter, LA volume and E/E′ also independently predicted stroke. We divided study patients into tertiles according to height (Fig. 1): LV size increases with height and it is intuitive: "the larger the body, the larger the heart" (Fig. 1-A). However, the LA volume rather showed an inverse trend, failed to reach statistical significance though (Fig. 1-B). Strikingly, E/E′ was highest in the first tertile and lowest in the third tertile (Fig. 1-C). LV size showed positive linear correlation with height (Fig. 2-A), whereas LA volume did not (Fig. 2-B); notably E/E′ was associated with height (Fig. 2-C). In multiple linear regression analysis, height independently determined E/E′ ($\beta = -0.20$, $t = -2.95$, $p = 0.003$) after adjusting for age, sex, body weight, hypertension and diabetes.

Main findings are as follows: 1) NV-AF patients with ischemic stroke are shorter than those without stroke; 2) LA volumes are not entirely dependent on stature, whereas LV size increases with height; and 3) stature and E/E′ showed inverse correlation. This study revealed the relationship between stature and diastolic dysfunction in NV-AF and we suggest that height is an unmodifiable risk factor; hence, more impaired diastolic function in shorter patients with NV-AF might play a pathophysiological role in stroke occurrence.

Copious hypotheses have been suggested to explain the inverse relationship between short stature and stroke. Short stature is related to vessel diameter [2]. Socioeconomic status affects height and CV outcomes [3]. Inadequate nutrition during childhood results in short stature in adulthood and increases CV risk including stroke [4]. Height decreases during the aging process and short stature represents the old age of stroke patients [5]. Simultaneously, stature is influenced by prognostic factors of stroke, such as hypertension and diabetes mellitus [5]. In this study, we revealed the association between stature and diastolic dysfunction in NV-AF and this finding suggests a new hypothesis for an old observation. Height is negatively correlated with central arterial pressure augmentation because of shorter distance to sites of peripheral pulse wave reflection [6]. Greater central pressure augmentation in shorter subjects induces cardiac overloading [7] and diastolic dysfunction [8]; thus it might explain the higher prevalence of stroke in short patients.

Although LV systolic dysfunction is a well-known risk factor for stroke in AF patients [9], it is still unclear whether diastolic function also plays a prognostic role regarding stroke. E/E′ reflects LV filling pressure not only in sinus rhythm but also in AF [10], and it serves as a robust prognosticator in CV diseases including AF [11]. Lee et al. [12] reported that E/E′ was a predictor of stroke in NV-AF patients. In this study, we observed an inverse association of E/E′ with stature; this novel finding can, at least partially, explain the correlation between stature and stroke.

Table 2
Predictors of stroke in AF patients.

	Crude OR (95% CI)	p-value	Adjusted[a] OR (95% CI)*	p-value
Clinical characteristics				
Age	1.11 (1.10–1.14)	<0.001*	–	–
Male	0.56 (0.38–0.83)	0.004*	–	–
CHADS2 score	32 (15–66)	<0.001*	–	–
Height	0.93 (0.91–0.95)	<0.001*	0.96 (0.92–0.99)	0.02*
Body mass index	0.87 (0.82–0.93)	<0.001*	0.94 (0.87–1.02)	0.12
Echocardiography				
LA AP diameter	1.13 (1.09–1.16)	<0.001*	1.10 (1.06–1.14)	<0.001*
LA volume	1.04 (1.03–1.05)	<0.001*	1.03 (1.02–1.04)	<0.001*
E/E′	1.20 (1.14–1.26)	<0.0018	1.10 (1.04–1.16)	<0.001*

* Indicates $p < 0.05$.
[a] Adjusted for age, sex, hypertension and diabetes

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