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Association between markers of arterial stiffness and atrial fibrillation in the Circulatory Risk in Communities Study (CIRCS)

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Highlights

- Limited evidence is available on the association between markers of arterial stiffness and atrial fibrillation amongst Asian populations.
- Augmentation index (AI), a marker of arterial stiffness, was measured by an automated tonometer the HEM-9000AI device.
- Atrial fibrillation was estimated by using resting electrocardiograph (ECG).
- AI values were positively associated with the prevalence of atrial fibrillation and total arrhythmia, independent of cardiovascular risk factors.

Background and aims: Limited evidence is available on the association between markers of arterial stiffness and the prevalence of atrial fibrillation among Asian populations. Therefore, we examined those associations amongst Japanese population.

Methods: We conducted a cross-sectional population-based study of 4,264 men and women aged 40-79 years. The augmentation index (AI), a marker of arterial stiffness, was calculated as the ratio of central pulse pressure/brachial pulse pressure, where the AI and central aortic pressure were measured by an automated tonometer the HEM-9000AI device (Omron Healthcare co., Kyoto, Japan). Atrial fibrillation was estimated by the Minnesota codes using resting electrocardiograph (ECG).

Results: The prevalence of atrial fibrillation and total arrhythmia were higher with larger AI values. These associations did not change after adjustment for known cardiovascular risk factors. The multivariable odd ratios (95% confidence intervals) in the highest versus lowest tertiles of AI were 3.4 (1.4-8.6, P for trend = 0.008) for atrial fibrillation and 1.8 (1.2-2.7, P for trend = 0.004) for total arrhythmia. There was no association of central or brachial pulse pressure levels with the prevalence of atrial fibrillation or total arrhythmia.

Conclusion: AI values, but not brachial or central pulse pressures, were positively associated with the prevalence of atrial fibrillation and total arrhythmia, independent of cardiovascular risk factors. (Words: 211)

Key words: Arterial stiffness, central pulse pressure; augmentation index; atrial fibrillation; epidemiology

1. Introduction

The speed of the left ventricular ejected pulse into the systemic arteries increases steadily in patients with aortic stiffness, and this makes the reflected pressure returns back early [1]. A meta-analysis of 11 prospective cohort studies has confirmed that markers of aortic stiffness such as central and brachial pulse pressures (PP) and augmentation index (AI) were associated with risk of cardiovascular and total mortalities and those associations were more evident for central PP than for brachial PP [2]. However, brachial PP was also associated with risk of new-onset atrial fibrillation [3]; which is a well-known risk factor for stroke and total death [4].

Few studies, however, have investigated the association between these markers of aortic stiffness and risk of atrial fibrillation [5-7]. AI values, but not brachial PP values, were positively associated with risk of atrial fibrillation in a Japanese case-control study; in which associations with central PP were not examined [5]. An Australian patients-based study showed that higher values of AI and central PP were more strongly associated with recurrence of atrial fibrillation than that brachial PP [6]. The association was stronger for AI than for central PP according to an American population-based cohort study [7]. On the light of the above limited evidence, we aimed to investigate the relationships of AI, central PP and brachial PP with risk of arrhythmia including atrial fibrillation and premature beats by using data from a large population-based cohort of Japanese population. Our hypothesis is that markers of arterial stiffness, especially AI, may be associated with risk of higher prevalence of atrial fibrillation and total arrhythmia.

2. Materials and methods

2.1. Subjects

Since 1963, the CIRCS has started annual cardiovascular risk surveys in a Japanese community-based cohort [8]. A total of 5,705 persons (2,253 men and 3,452 women) aged 40-79 years who attended the annual cardiovascular risk surveys between January 2010 and November 2012 in three communities of CIRCS: Yao City of Osaka Prefecture; Ikawa town of Akita Prefecture and Kyowa town of Ibaraki Prefecture. Out of them, 4,264 participates (1,593 men and 2,671 women) undertook AI measurement and thus eligible for this study (**Supplemental Figure 1)**. Participants were 549 men and 912 women in Yao (recruitment rate among the cardiovascular surveys participants =78% for men and 74% for women), 472 men and 763 women in Ikawa (recruitment rate =79% for men and 85% for women) and 572 men and 996 women in Kyowa (recruitment rate= 60% for men and 76% for women). The informed consent was obtained from all subjects. The study protocol was approved by the Ethics Committee of Osaka University, and was explained in detail by physicians, epidemiologists and trained staff members, for each participant.

2.2. Measurement of AI and cardiovascular risk factors

Protocol-standardized measurements of radial AI and central aortic pressure [9,10] using the automated tonometer, HEM-9000AI (Omron, Healthcare co., Kyoto, Japan) by trained technicians were conducted for participants in a sitting position after 5 minutes of rest. The second systolic peaks of the radial artery systolic blood pressure (SBP2) were obtained by calibrating the radial waveforms with brachial systolic

pressure, and the SBP2 values were considered as the central aortic pressure levels [10]. The central PP was defined as the central aortic systolic pressure minus the brachial diastolic blood pressure, and the brachial PP was defined as the systolic minus the diastolic brachial blood pressures. The AI value was calculated as central PP/brachial PP × 100 (%) [10], and AI measurement was normalized by the heart rate of 75 bpm for the analysis [11].

The details for cardiovascular risk factors and other covariates' measurements and procedures of quality-control for the current study have been reported earlier [9,12]. In brief, body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Seated right arm brachial systolic and diastolic blood pressures were measured by trained technicians via standard mercury sphygmomanometers after giving 5 minutes rest for the participants [13]. Two trained physician-epidemiologists used the Minnesota code to classify the resting electrocardiograph (ECG) that was obtained in supine position [14]. Minnesota codes 8-3-1 and 8-3-2 were defined as atrial fibrillation; codes 8-1-1 and 8-1-2 were defined as premature beats including atrial and ventricular premature beats; and the codes 8-1-1, 8-1-2, 8-3-1, 8-3-2, and 8-9-1 were defined as total arrhythmia. A fasting glucose level of ≥7.8 mmol/L, a non-fasting glucose level of ≥11.1 mmol/L or the use of medication for diabetes mellitus defined participants with diabetes mellitus. A systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg or the use of medications to lower blood pressure defined hypertensive participants.

Serum was separated within 30 minutes from collecting non-fasting blood samples that were drawn from participants in sitting position and collected in plain

siliconised glass tube. An automatic analyser (Hitachi 7250, Hitachi Medical Corp., Ibaraki, Japan) provided readings for serum total and HDL-cholesterol and triglycerides levels using enzymatic method and serum glucose levels using hexokinase method at an international member of the US National Cholesterol Reference Method Laboratory Network (CRMLN); the Osaka Medical Centre for Health Science and Promotion [15].

Current smokers were participants who smoked ≥1 cigarette per day. Via an interview, the weekly alcohol intake in the traditional Japanese "go" units, that was then converted into daily grams ethanol intake (1 "go" unit =23 g of ethanol) was assessed.

2.3. Statistical analysis

We analysed the association of brachial PP, central PP and AI values with the prevalence of atrial fibrillation, premature beats and total arrhythmia in all subjects, because those association did not vary by sex; P for interaction >0.05. Differences in age- and sex-adjusted and multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for atrial fibrillation, premature beats and total arrhythmia were calculated by using logistic regression analysis across increasing tertiles of brachial PP levels (<42, 42-52, and >53 mmHg); central PP levels (<43, 43-55, and >56 mmHg) and AI values (<79, 79-87, and >88%) with the lowest tertile of each as reference.

The hypothesized confounders in the current study included age (years), communities, sex, BMI (kg/m^2), systolic blood pressure (mmHg), smoking status

(never, ex- and current), drinking status (never, ex- and current: <46 and excessive drinking of ≥46g/day), heart rate (beats/minute), history of diabetes mellitus (yes or no), the use of antihypertensive medication (yes or no) and cholesterol-lowering medication (yes or no) and serum total and HDL-cholesterol and triglycerides levels (mmol/L). All *p* values for statistical tests were two-tailed, and values of $p < 0.05$ were regarded as indicative of statistical significance, using the SAS statistical package version 9.4 (SAS Institute Inc., Cary, CA).

3. Results

Table 1 shows the age- and sex- adjusted population characteristics of selected cardiovascular risk factors according to tertiles of brachial and central PP and AI levels. When compared with participants in the lowest tertiles of brachial and central PP and AI levels, those in the highest tertiles were older, with higher levels of AI, central aortic and brachial systolic blood pressures and were more likely to be hypertensives. Mean values of alcohol consumption, triglyceride levels, prevalence of diabetes and medication use for hypertension were positively associated with brachial and central PP levels. Whereas, the prevalence of diabetes and use of cholesterol-lowering medications were lower across increasing AI levels. There were no statistical differences for total and HDL-cholesterol levels and smoking status among tertiles of brachial and central PP and AI levels.

The ORs (95% CI) of ECG-confirmed arrhythmias according to tertiles and 1-SD increment of central and brachial PP and AI levels were shown in Table 2. The 1-SD increment of AI was associated with1.6, 1.3 and 1.3-fold increased odds for risks of atrial fibrillation, premature beats and total arrhythmia, respectively. Compared with participants in the lowest tertile of AI levels, age- and sex- adjusted prevalence of atrial fibrillation and total arrhythmia, but not of premature beats were higher for those in the highest tertile of AI levels. These associations did not change substantially after adjustment for known cardiovascular risk factors; the multivariable ORs (95% CI) were 3.4 (1.4-8.6, P for trend = 0.008) for atrial fibrillation, 1.4 (0.7-2.6, P for trend = 0.30) for premature beats and 1.8 (1.2-2.7, P for trend = 0.004) for total arrhythmia.

There were no association of brachial or central PP levels with prevalence of atrial fibrillation, premature beats or total arrhythmia.

4. **Discussion**

In the present community population-based study of 4,264 Japanese men and women aged 40-79 years, participants in the highest AI tertile displayed approximately two- to three-fold higher prevalence of atrial fibrillation and total arrhythmia than those in the lowest tertile. There were no associations of brachial or central PP with the prevalence of arrhythmia including atrial fibrillation.

Our finding of association between AI values and arrhythmia is consistent with the results from previous studies [5-7]. A 7-year follow-up study of 5,797 Americans aged ≥45 years has shown that hazard ratio (95%CI) of atrial fibrillation was 1.16 (1.02-1.32) per 1-SD (12.4%) increment of AI values [7]. A 3-year follow-up study of 68 atrial fibrillation patients, after initial catheter ablation procedure, indicated that patients in the highest quartile of AI values versus those in the lowest quartile had 1.6-fold increased recurrent rates of atrial fibrillation [6]. A case-reference study of 244 outpatients with atrial fibrillation showed that atrial fibrillation patients had higher mean of AI values than control subjects: mean ± SD = 88.9 ±1.0 versus 81.8 ±1.0, respectively, $p<0.001$ [5].

Values of AI [6,7], central PP [6,7] and brachial PP [3] were associated with risk of new-onset atrial fibrillation. Increased levels of AI values and central and brachial PP levels are markers for increased left ventricular load and left ventricular hypertrophy [16], which can elevate the pressure in the left atrium causing left atrial dilatation and atrial fibrillation [17]. However, after atrial fibrillation occurs, central and brachial blood pressures and their PPs decline [18-20]; while AI, the ratio of central and brachial PPs, remains a significant covariate for atrial fibrillation. This

implies that high AI may be the better surrogate marker for atrial fibrillation as well as aortic stiffness. Moreover, AI values but not brachial systolic pressure levels were positively associated with higher prevalence of left ventricular mass index [21]. In Australian patients-based study showed that higher values of AI and central PP were associated with higher risk of atrial fibrillation [6]. A population-based cohort study followed 5,797 American men and women aged ≥45 years for 7.1 years indicated that AI values rather than central PP levels were associated with risk of atrial fibrillation. The multivariable HR per 1-SD increment of AI values and central PP levels in that study were 1.16 (1.02-1.32, P=0.02) and 1.11(0.98-1.25, P=0.09), respectively [7]. Elevated AI might be a marker of concentric left ventricular hypertrophy, which may explain the association with incident atrial fibrillation [7].

On the other hand, the correlation of central PP with the intima media thickness of carotid arteries was stronger than that of brachial PP among 3,520 Americans aged 18 to 88 years (r=0.293 vs. 0.249, respectively, $p < 0.002$) [22]. A meta-analysis of 5,648 subjects with a mean of 45 months follow-up revealed that central PP was associated more strongly with mortality from cardiovascular disease and all causes than brachial PP: the relative risk (95%CI) was 1.32(1.22-1.42) versus 1.19(1.10-1.28), p=0.057 [2].

The strengths of the present study include the validated population-based assessment of cardiovascular risk factors [8,12] and measuring central aortic pressure and AI values via a non-invasive technique. We used the automated tonometer HEM-9000AI to assess central aortic pressure and AI values rather than the invasive standard direct cardiac catheterisation measurements; however, the correlation of

central aortic pressure levels was high between the two measurement systems ($r= 0.95$, $p < 0.001$) among 18 hypertension patients aged 47-78 years [23]. Second, the cross-sectional design of the current study disabled us from drawing a causal relationship. Third, the ECGs were examined only once; however, the internal quality control for data collection and ECG reading in CIRCS [8] made the misclassification for evaluated arrhythmias small.

In conclusion, high AI values were associated with increased prevalence of atrial fibrillation and total arrhythmia independent of cardiovascular risk factors among general population.

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

Renzhe Cui, Kazumasa Yamagishi, Isao Muraki, Mina Hayama-Terada, Mitsumasa Umesawa, Hironori Imano, Yuanying Li, Ehab S Eshak, Tetsuya Ohira, Masahiko Kiyama, Takeo Okada, Akihiko Kitamura, Takeshi Tanigawa, Hiroyasu Iso participated in the study design and data collection; Renzhe Cui, Hiroyasu Iso and Ehab S. Eshak analyzed the data; Renzhe Cui, Hiroyasu Iso and Ehab S. Eshak participated in interpretation of data and drafting of the manuscript; Renzhe Cui and Ehab S. Eshak provided statistical expertise. Kazumasa Yamagishi, Isao Muraki, Mina Hayama-Terada, Mitsumasa Umesawa, Hironori Imano, Yuanying Li, Ehab S Eshak, Tetsuya Ohira, Masahiko Kiyama, Takeo Okada, Akihiko Kitamura, Takeshi Tanigawa, Hiroyasu Iso participated in the study concept and design, acquisition of data and interpretation of data, and critical revision of the manuscript.

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Appendix

CIRCS collaborators

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Table 1 Age-and sex-adjusted population characteristics according to tertiles of brachial and central pulse pressure levels and augmentation index values

	Brachial pulse pressure, mmHg			Central pulse pressure, mmHg			Augmentation index, %		
Tertile	Low	Middle	High	Low	Middle	High	Low	Middle	High
Total number	1,388	1,511	1,365	1,404	1,443	1,417	1,467	1,311	1,486
Men, %	39	37	36	41	37*	34‡	38	38	36
Age, year	58.4	61.8‡	66.2‡	58.5	61.8‡	65.8‡	59.6	62.8‡	63.9‡
Brachial pulse pressure, mmHg	36.2	47.7‡	63.1‡	42.3	47.8‡	56.6‡	48.2	48.8	49.7‡
Systolic blood pressure, mmHg	111.6	123.6‡	137.9‡	118.3	123.1‡	131.5‡	121.4	124.5‡	127.0‡
Diastolic blood pressure, mmHg	75.4	75.9	74.8	76.0	75.3	74.9†	73.2	75.7‡	77.3‡
Central aortic pressure, mmHg	118.1	125.6‡	136.6‡	111.0	124.6‡	144.2‡	116.7	127.1‡	136.1‡
Augmentation index, %	83.0	83.2	84. 5‡	78.6	83.1‡	88.8‡	72.9	83.4‡	94.1‡
Body mass index, kg/m^2	23.1	23.4†	23.6‡	23.2	23.4	23.6†	23.5	23.5	23.1†
Total cholesterol, mmol/L	5.48	5.52	5.48	5.46	5.48	5.54*	5.49	5.49	5.50
HDL-cholesterol, mmol/L	1.67	1.66	1.64	1.66	1.66	1.66	1.67	1.66	1.65
Triglycerides, mmol/L	1.18	1.22	1.32‡	1.21	1.22	1.29*	1.22	1.23	1.28
Alcohol intake, g/day	15.6	17.8	20.1†	16.2	17.8	19.7*	17.8	17.5	18.1
Current smoker, %	37	37	38	37	38	36	35	38	38
Hypertension, %	23	29‡	59‡	27	33†	51‡	33	36	41‡
Antihypertensive medication, %	10	14†	18‡	10	13*	18‡	14	14	13
Cholesterol-lowering medication, %	10	10	12	10	11	10	12	10	9†
Diabetes mellitus, %	8	11†	17‡	10	13*	13*	13	13	10*

*p<0.05, †p<0.01, ‡p<0.001 compared with the lowest tertile.

Table 2. Odds ratios (95%CIs) of arrhythmia according to tertiles of brachial and central pulse pressure levels and augmentation index values

	Branchial pulse pressure, mmHg			P for trend	Central pulse pressure, mmHg			P for trend	Augmentation index, %			P for trend
Tertiles	Low	Middle	High		Low	Middle	High		Low	Middle	High	
Total number	1,388	1,511	1,365		1,404	1,443	1,417		1,467	1,311	1,486	
Atrial fibrillation[1], n	13	12	12		15	10	12		8	10	19	
Age- and sex- adjusted OR	1.0	0.7 (0.3-1.6)	0.5 (0.2-1.2)	0.13	1.0	0.6 (0.3-1.4)	0.7 (0.3-1.7)	0.51	1.0	1.3 (0.5-3.4)	2.4 (1.0-5.8)	0.03
Multivariable adjusted OR	1.0	0.7 (0.3-1.7)	0.5 (0.2-1.2)	0.53	1.0	0.7 (0.3-1.8)	1.1 (0.5-2.9)	0.75	1.0	1.5 (0.6-4.2)	3.4 (1.4-8.6)†	0.008
1-SD increment OR**		1.0 (0.6-1.7)				0.9 (0.6-1.4)				1.6 (1.1-2.3)†		
Premature beats[2], n	18	28	24		27	20	23		18	26	26	
Age- and sex- adjusted OR	1.0	1.3 (0.7-2.4)	1.1 (0.6-2.4)	0.88	1.0	0.6 (0.4-1.2)	0.7 (0.4-1.2)	0.22	1.0	1.5 (0.8-2.8)	1.3 (0.7-2.4)	0.40
Multivariable adjusted OR	1.0	1.3 (0.7-2.3)	1.1 (0.6-2.1)	0.16	1.0	0.7 (0.4-1.3)	0.8 (0.4-1.5)	0.54	1.0	1.6 (0.8-2.9)	1.4 (0.7-2.6)	0.30
1-SD increment OR**		1.2 (0.8-1.7)				0.9 (0.6-1.1)				1.3 (1.0-1.7)*		
Total arrhythmia[3], n	57	70	66		71	58	64		46	70	77	
Age- and sex- adjusted OR	1.0	1.0 (0.7-1.4)	0.9 (0.6-1.2)	0.39	1.0	0.7 (0.5-1.0)	0.7 (0.5-1.1)	0.14	1.0	1.6 (1.1-2.4)*	1.6 (1.1-2.3)*	0.02
Multivariable adjusted OR	1.0	1.0 (0.7-1.4)	0.8 (0.6-1.2)	0.66	1.0	0.8 (0.5-1.1)	0.9 (0.6-1.3)	0.53	1.0	1.7 (1.2-2.5)†	1.8 (1.2-2.7)†	0.004
1-SD increment OR**		0.8 (0.7-1.1)				0.9 (0.8-1.1)				1.3 (1.1-1.6)‡		

[1] Minnesota codes 8-3-1 and 8-3-2. [2] Minnesota codes 8-1-1 and 8-1-2. [3] Minnesota codes 8-1-1, 8-1-2, 8-3-1, 8-3-2, and 8-9-1.

*p<0.05, †p<0.01, ‡p<0.001, compared with the lowest tertile.

** Multivariable OR. 1-SD of brachial PP, central PP and augmentation index were respective 16.5, 12.9 and 11.0.

OR: odds ratio. Multivariable adjustment for age, sex, BMI, heart rate, systolic blood pressure, smoking and drinking status, serum total and HDL-cholesterol, triglycerides, diabetes mellitus, antihypertensive medication and cholesterol-lowering medication use and communities.

Supplemental Figure legend

Supplemental Figure 1.
Recruitment of study participants aged 40 to 79 years in annual cardiovascular risk survey from January, 2010 to November, 2012

Participant's flow chart