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ORIGINAL RESEARCH

Low Carotid Flow Pulsatility Index Correlates With the Presence of Unruptured Intracranial Aneurysms

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BACKGROUND: We assessed cases of incidental unruptured intracranial aneurysm (UIA) discovered on screening magnetic resonance angiography to identify hemodynamic and atherosclerotic risk factors.

METHODS AND RESULTS: The data of 1376 healthy older subjects (age range, 31–91 years) without cerebro- or cardiovascular diseases who underwent brain magnetic resonance angiography as part of a medical checkup program at a health screening center were examined retrospectively. We looked for an increase in classical risk factors for UIAs (age, sex, hypertension, and smoking) and laboratory data related to lifestyle diseases among subjects with UIAs. Brachial-ankle pulse wave velocity, central systolic blood pressure, radial augmentation index, and carotid flow pulsatility index were also compared between those with and without UIAs. We found UIAs in 79 (5.7%) of the subjects. Mean age was 67.1±9.0 years, and 55 (70%) were women. Of the 79 aneurysms, 75 (95%) were in the anterior circulation, with a mean diameter of 3.1 mm (range, 2.0–8.0 mm). Subjects with UIAs were significantly older and had more severe hypertension. The carotid flow pulsatility index was significantly lower in subjects with UIAs and negatively and independently correlated with UIAs. Tertile analysis stratified by carotid flow pulsatility index revealed that subjects with lower indices had higher levels of low-density lipoprotein cholesterol.

CONCLUSIONS: The presence of UIAs correlated with lower carotid flow pulsatility index and elevated low-density lipoprotein cholesterol in the data from a population of healthy older volunteers. A reduced carotid flow pulsatility index may affect low-density lipoprotein cholesterol elevation by some molecular pathways and influence the development of cerebral aneurysms. This may guide aneurysm screening indications for institutions where magnetic resonance angiography is not routine.

Key Words: carotid flow pulsatility index ■ cerebrovascular hemodynamics ■ incidental findings ■ magnetic resonance angiography ■ unruptured intracranial aneurysms

Technical advances in magnetic resonance angiography have increased the likelihood of detecting unruptured intracranial aneurysms (UIAs),[1] and aneurysm rupture prophylaxis is now a major focus of efforts to reduce the overall mortality and morbidity from subarachnoid hemorrhage due to UIA rupture.[2]

In Japan, most UIAs are incidentally found on a complete medical checkup, and although they may carry a low risk of rupture, when rupture does occur, it usually results in severe morbidity and high mortality. In order to manage UIAs optimally, it is important to identify factors involved in their incidence. Risk factors such as older age, female sex, current smoking, and hypertension are already well established.[3] However, little information is available with regard to whether hemodynamic and atherosclerotic factors affect the incidence of aneurysms, including whether carotid flow pulsatility reflects the transmission of pulsatile energy into the cerebral microcirculation and whether lipoprotein levels are involved with aneurysm rupture.[4,5]

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CLINICAL PERSPECTIVE

What Is New?

- This clinical study investigated carotid flow pulsatile index as the arteriosclerotic biomarker, besides classical risk factors of incidental unruptured intracranial aneurysms (age, sex, hypertension, smoking, etc.).
- A reduced carotid flow pulsatility index may affect low-density lipoprotein cholesterol elevation by some molecular pathways and influence the development of cerebral aneurysms.

What Are the Clinical Implications?

- This study concluded that the presence of unruptured intracranial aneurysms might be closely correlated with lower carotid flow pulsatile index in a population of healthy subjects through cerebrovascular and molecular changes.
- Changes in cerebrovascular and molecular environment are likely involved in the initiation of unruptured intracranial aneurysms, albeit that further validation studies necessary.

Nonstandard Abbreviations and Acronyms

AI	augmentation index
UIA	unruptured intracranial aneurysm

In this study, we aimed to assess UIAs incidentally found on magnetic resonance angiography and to identify associated biomarkers for their occurrence, focusing on cerebrovascular hemodynamics.

METHODS

The authors declare that all supporting data are available within the article. Subjects were participants in a complete medical checkup program at the Ehime University Hospital Anti-aging Center, which is specifically designed to evaluate for atherosclerosis, including cerebrovascular disease.[6] All clinical data were obtained through the checkup program for retrospective analysis. In this cross-sectional observational study, several clinical parameters were measured. Even though information about the prevalence of adult polycystic kidney disease and other diseases associated with an increased risk of intracranial aneurysms was not available, we expected the influence to be minimal in our cohort of almost healthy people. All subjects in this study were of Japanese descent and signed written informed consent approved by the institutional ethical committees of Ehime University Graduate School of Medicine. Enrollment was between March 2006 and December 2013. The data of a total of 1489 subjects were available and assessed for the finding of incidental intracranial aneurysm. Of the study subjects, 113 subjects had missing carotid flow (mL/min) information; we therefore did not incorporate these cases. Thus, a total of 1376 cases constituted the study population.

Risk Factor Evaluation

Lifestyle, medical history, and prescribed drugs were evaluated by questionnaire. Anthropometric measurements were performed by a trained nurse. Venous blood for measurement of serum lipids and plasma glucose was collected in the morning after fasting for at least 12 hour. Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg, diastolic BP ≥90 mm Hg, or the use of an antihypertensive drug. Type 2 diabetes mellitus was defined as a fasting plasma glucose ≥126 mg/dL, HbA1c ≥6.5%, or use of antihyperglycemics. Dyslipidemia was defined as any or all of the following: low-density lipoprotein cholesterol (LDL-C) ≥140 md/dL, triglycerides ≥150 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL, or use of medication to lower lipid levels. Serum creatinine and hsCRP (high-sensitivity C-reactive protein) were also measured.

Diagnosis of UIAs

Time-of-flight magnetic resonance angiography was performed with a 3T magnetic resonance imaging (MRI) scanner (Signa EXCITE: GE Healthcare, London, UK) using the following sequence parameters: repetition time/echo time = 25.0/3.1 ms, scan time 239 s, section thickness 1.0 mm, field of view 190×170, matrix 512×224, and voxel volume 0.39 mm^3. All images were evaluated by 2 trained physicians (neuroradiologist and neurosurgeon), who were blinded to the clinical data. All scans included reformatted maximum intensity projection images and original time-of-flight images. For some suspected cases of exceedingly small aneurysms, volume-rendered images were created to improve the accuracy of diagnosis. Cases of infundibular dilatation were differentiated from aneurysms by altering volume-rendered opacity. Measurement of UIAs' maximal diameter was calculated on volume-rendered images, and several analyses for detecting the association between UIA size and some biomarkers were also provided.

Assessment of Brachial-Ankle Pulse Wave Velocity

Brachial-ankle pulse wave velocity was measured with a volume plethysmographic apparatus (FORM/

ABI; Omron Colin Co. Ltd., Komaki, Japan) as previously described.[7] Briefly, the subject was examined after resting in the supine position for 5 minutes. Electrocardiographic electrodes were placed on both wrists, and BP cuffs were wrapped on both arms and ankles. Pulse volume waveforms at the arms and ankles were recorded using a semiconductor pressure sensor. Measurements were reported as the means of bilateral measurements.

Radial Waveform Analysis and BP Measurement

The radial augmentation index (RAI) was measured in the left radial artery using automated tonometry (HEM-9000AI; Omron Healthcare, Kyoto, Japan), with subjects in the sitting position after at least 5 min of rest. Brachial BP was measured simultaneously in the right arm with an oscillometric device incorporated into the HEM-9000AI. The HEM-9000AI device is programmed to automatically determine the pressure against the radial artery to obtain the optimal arterial waveform. Central BP was calculated by calibration with the brachial BP. Central pulse pressure was calculated by the formula:

$$\text{Central pulse pressure} = (\text{Central systolic BP} - \text{Central diastolic BP}) \quad (1)$$

Central pulse pressure was also obtained as Central systolic BP2−Central diastolic BP2. Radial AI was calculated as follows: Central pulse pressure/pulse pressure × 100 (%).[8] In addition, given that radial AI is influenced by heart rate, the index was corrected for a heart rate of 75 bpm as radial AI75. Measurements were repeated twice, and the values were obtained.[9,10]

Echo- Doppler Examination of the Carotid Arteries

The carotid arteries were evaluated using an SSD-3500SV (Aloka, Tokyo, Japan) with a 7.5-MHz probe equipped with a continuous flow doppler and phase-locked echo-tracking system. The assessments were performed with the subjects in the supine position, with the head turned and the neck immobile. All ultrasonic readings were evaluated and appraised by a technician who had no knowledge of the subjects' profiles. Intima-media thickness of the far wall of the common carotid artery was measured as previously described.[11] Three measurements on each side were averaged.

Carotid Flow Pulsatility Index

Color Doppler evaluation was performed on the common carotid arteries 10 mm proximal to the bifurcation. Blood flow velocity was detected with the sample volume reduced to the smallest possible size (1 mm) and placed at the center of the vessel. The angle between the ultrasound beam and the long axis of the vessel was kept between 45° and 55°. For Doppler spectral analysis, peak systolic velocity and end-diastolic velocity were measured by continuous-wave Doppler examination in the internal carotid artery proximity as well as in the common carotid artery 10 mm proximal to the bifurcation. For all participants, the scan transducer was applied longitudinally for at least 3 cardiac cycles for blood flow velocity measurements. Because of the consequences of initial forward flow, the highest velocity during systole was identified as the peak systolic velocity, and the lowest velocity during diastole was used as the end-diastolic velocity. The highest value of the minimum of 3 measurements was recorded and measurements were reported as the mean of the bilateral measurements. The carotid flow pulsatility index was the difference between peak systolic velocity and end-diastolic velocity divided by the mean flow velocity.

Statistical Analysis

All continuous variables are expressed as the mean±SD, unless otherwise indicated. The normal distribution (Kolmogorov-Smirnov test) and the homoscedasticity (Levene test) of data were verified. Comparisons between the 2 groups were assessed using the unpaired *t* test for parametric variables and the Mann-Whitney *U* test for nonparametric variables. The chi-square test was used to assess frequency differences between the number of UIA cases and number of subjects of male sex, the number(s) with hypertension, diabetes mellitus, and/or dyslipidemia; and the number of current smokers. Descriptive analysis of the UIA-associated variables was performed according to tertiles of the carotid flow pulsatility index using the chi-square test. Mean values for each variable were compared using ANOVA followed by Bonferroni's post hoc and Student's *t* test. Factors independently associated with UIAs were assessed via logistic regression analysis. In all comparisons, $P<0.05$ was considered statistically significant. Correlations between variables were evaluated using Pearson's correlation coefficient. Analyses were performed using commercial software (SPSS software package for Windows version 17, SPSS, Chicago, IL, USA).

RESULTS

The clinical characteristics of cases with and without UIAs are summarized in Table 1. Among 1376 cases, 85 aneurysms were detected in 79 cases (6%), with 6

Table 1. Clinical Profile of All Study Subjects, and Comparison Between Subjects With and Without Unruptured Intracranial Aneurysm

	Total	UIA (–)	UIA (+)
Number	1376	1297	79
Location (anterior/posterior)		…	75/4
Age, y	65.2±9.4	65.0±9.4	67.1±9.0‡
Female sex, n (%)	816 (59.3)	761 (58.7)	55 (69.6)‡
Body mass index, kg/m^2	23.3±3.0	23.3±3.0	23.4±3.1
Serum creatinine, mg/dL	0.73±0.18	0.73±0.18	0.70±0.17
Fasting glucose, mg/dL	103±19	104±19	101±12
Hba1c, %*	5.5±0.6	5.5±0.6	5.4±0.4
Total cholesterol, mg/dL	218±37	217±37	221±40
High-density lipoprotein cholesterol, mg/dL	67±18	66±18	69±18
Low-density lipoprotein cholesterol, mg/dL	129±33	129±33	132±38
Triglycerides, mg/dl	109±61	109±62	105±52
High-sensitivity C-reactive protein, mg/L	0.12±0.27	0.12±0.27	0.09±0.10
Hypertension, n (%)	593(43)	544 (42)	49 (62)§
Diabetes mellitus, n (%)	87 (6)	83 (6)	4 (5)
Dyslipidemia, n (%)	333 (24)	315 (24)	18 (22)
Smoking, n (%)	96 (7)	0 (7)	6 (8)
Intima-media thickness, mm	0.79±0.15	0.79±0.15	0.78±0.16
Brachial–ankle pulse wave velocity, cm/s	1581±333	1578±332	1617±345
Systolic blood pressure, mm Hg	134±19	134±19	136±19
Diastolic blood pressure, mm Hg	77±11	77±11	77±11
Pulse pressure, mm Hg	57±14	57±14	59±14
Pulse rate, beats/min	66±10	66±10	67±11
Central systolic blood pressure, mm Hg	127±20	127±19	129±19
Central pulse pressure, mm Hg	50±15	50±15	52±14
Radial augmentation index, %	89±11	89±11	91±11
Radial augmentation index 75, %†	86±10	85±10	88±11‡
Peak systolic velocity, cm/s	74.5±17.0	74.7±17.0	71.9±15.7
End diastolic velocity, cm/s	21.0±6.1	21.0±6.1	21.5±6.0
Carotid flow pulsatility index	1.39±0.24	1.39±0.24	1.32±0.21§

Hba1c indicates glycosylated hemoglobin; UIA, unruptured intracranial aneurysm.

*Hba1c: equivalent to the internationally used HbA1c defined by the National Glycohemoglobin Standardization Program.

†Radial augmentation index 75: radial augmentation index (RAI) corrected for a heart rate of 75 bpm.

‡P<0.05 compared with UIAs (–) group.

§P<0.01 compared with UIA (–) group.

cases of 2 aneurysms. Of the 85 aneurysms, 79 (93%) UIAs were in the anterior circulation with a median maximum diameter of 3.1 mm (range, 2.0–8.0). The group with UIAs had a significantly higher age (67.1±9.0 year) compared with the group without UIAs (65.0±9.4 year; P<0.05). Although there was no significant difference in BP measurements between the 2 groups, a past history of hypertension was significantly higher in the group with UIAs (49 cases; 62%) compared with the group without UIAs (544 cases; 42%; P<0.01). Other known risk factors for UIAs, including smoking, did not significantly differ between cases with and without UIAs, whereas there was a significant difference between cases with and without UIAs regarding values of radial AI75 and carotid flow pulsatility index.

Factors Associated With the Presence of UIAs

To further investigate which parameters—radial AI75, carotid flow pulsatility index, or both—were independently associated with cerebral UIAs, logistic regression analysis was performed. Five variables (age, female sex, presence of hypertension, radial AI75, and carotid flow pulsatility index), identified by univariate analysis, were entered into a multivariate logistic regression model. The results showed that hypertension and lower carotid flow pulsatility index were independently associated with the presence of UIAs. (Table 2).

Characteristics of Subjects Stratified by Carotid Flow Pulsatility Index

Because a lower value of the carotid flow pulsatility index had been shown to be an independent factor correlating with the presence of UIAs, all subjects were classified into tertile groups by the value of the carotid flow pulsatility index, where the lower tertile (455 subjects) was <1.29, the middle tertile (456 subjects) was 1.29–1.47, and the upper tertile (455 subjects) was >1.47. The lowest tertile carotid flow pulsatility index

Table 2. Factors Associated With the Prevalence of Unruptured Intracranial Aneurysm

	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age	1.03 (1.00–1.05)	0.05		
Sex (female)	1.61 (0.99–2.64)	0.06		
Hypertension	1.53 (1.15–2.03)	<0.01	2.24 (1.37–3.65)	<0.01
Radial AI75	1.02 (1.01–1.04)	0.03		
Carotid flow pulsatility index	0.37 (0.16–0.85)	0.02	0.26 (0.11–0.64)	<0.01

Variables with *P*<0.1 by univariate analysis were entered into the multivariate analysis model.
OR indicates odds ratio; and Radial AI75, radial artery augmentation index corrected for a heart rate of 75 beats/min.

group was revealed to have the largest number of UIAs (Figure 1).

Atherosclerotic biomarkers stratified by the carotid flow pulsatility index are shown in Table 3, where serum creatinine and LDL-C had significant differences between the lower tertile carotid flow pulsatility index group and the other 2 groups, but not in fasting glucose, HbA1c, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and hsCRP.

Individual data analyses of all subjects revealed the carotid flow pulsatility index value had a significant negative correlation with the crude LDL-C level (Figure 2) and also a negative correlation with the maximal dimension of individual UIAs when defined as size zero in subjects without UIAs (Figure 3).

DISCUSSION

Prevalence of UIAs

In this cross-sectional study, the prevalence of UIAs was shown to be 6% in all 1376 subjects, which seems to be slightly higher than previous reports, where only 1.8%–2.8% were detected with 1.5T MRI.[12–14] In the detection of UIAs 3T MRI has demonstrated superior ability to 1.5T MRI.[15] We previously reported a higher detection rate of 8.4% using 3T MRI in outpatients who had neurological disorders.[1] Given that the current data were obtained from asymptomatic subjects, a lower rate of UIAs than that in symptomatic patients is understandable.

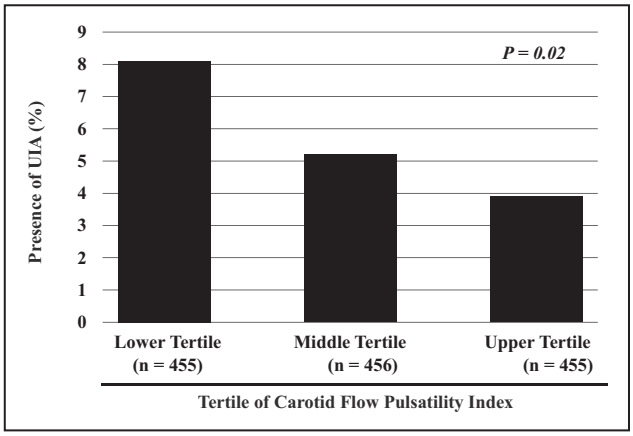

Figure 1. Percentage of unruptured intracranial aneurysms (UIAs) in tertile groups stratified by carotid flow pulsatility index, where the lowest tertile of carotid flow pulsatility index was <1.29 (n=455), the middle tertile range was 1.29 to 1.47 (n=456), and the upper tertile was >1.47 (n=455)
The lowest tertile had a significantly higher prevalence of UIAs than the other 2 tertiles.

Clinical Characteristics of UIAs

Older age and the presence of hypertension were significantly associated with UIAs, consistent with former reports that UIAs are more common in individuals >50 years[16,17] and with hypertension.[18] In contrast, there was no significant difference in the history of current smoking between the groups with and without UIAs. It is well known that smoking induces an inflammatory response and proinflammatory phenotypic modulation of vascular smooth muscle cells, increases degradation of the extracellular matrix, and consequently affects subsequent aneurysm formation;[19,20] however, our data did not suggest involvement of smoking in the prevalence of UIAs, which may be attributable to the extremely low rate of smoking (6%) in our population compared with the general population. Female sex is also a well-known nonmodifiable risk factor associated with the presence of UIAs, especially after menopause. Kang et al. reported that UIA prevalence increases sharply after age 50 years and is significantly higher in women than in men.[18] This phenomenon can be explained by the estrogen depletion, which enhances inflammatory reactions,[21] and given that the median age of menopause in this study was 52 years, it would be comprehensible. In our analysis among people ≥62 years, there was a significant difference in the percentage of women between the UIA and non-UIA groups (crude odds ratio [OR], 1.845; 95% CI, 1.051–3.237; *P*=0.03).

As risk factors for cerebro- and cardiovascular events we added radial AI and carotid flow pulsatility index for the analysis of the prevalence of UIAs. Radial AI can be easily and noninvasively recorded by radial applanation tonometry and is well known as an important predictor of cardiovascular events and all-cause mortality over brachial BP parameter,[22] in addition,

Table 3. Atherosclerotic Biomarkers, Stratified by Carotid Flow Pulsatility Index

	Lowest Tertile	Middle Tertile	Upper Tertile	
	<1.29 (n=455)	1.29–1.47 (n=456)	>1.47 (n=455)	*P* value
Serum creatinine, mg/dL	0.69±0.14	0.73 0.19‡	0.78±0.18†,‡	<0.0001
Fasting glucose, mg/dL	100.2±16.4	101.9±14.3	107.9±24.4†,‡	<0.0001
Hb_{a1c}, %*	5.4±0.6	5.5±0.6	5.7±0.7†,‡	<0.0001
Total cholesterol, mg/dL	222.6±36.1	219.7±38.2	210.7±35.5†,‡	<0.0001
High-density lipoprotein cholesterol, mg/dL	69.1±17.3	67.0±18.1	63.5±17.6†,‡	<0.0001
Low-density lipoprotein cholesterol, mg/dL	132.9±33.2	130.6±33.2†	124.3±32.0†,‡	<0.0001
Triglycerides, mg/dL	102.8±61.9	110.2±59.8	114.8±62.1‡	0.011
High-sensitivity C-reactive protein, mg/dL	0.11±0.28	0.12±0.29	0.13±0.24	0.455

*Hb_{a1c} indicates glycosylated hemoglobin: c, equivalent to the internationally used Hb_{A1c} defined by the National Glycohemoglobin Standardization Program.
†$P<0.05$ when compared with the lower pulsatility index of carotid pulsatility index.
‡$P<0.05$ when compared with the middle pulsatility index of carotid velocity.

carotid flow pulsatility index may be assessed using by carotid artery ultrasound and reflects stroke development.[23] In our study radial AI itself was not significantly different between the groups with and without UIAs, whereas radial AI75 of the group with UIAs was higher than that of the group without UIAs and carotid flow pulsatility index showed a significant difference between the 2 groups. Thus, we used a multivariate logistic regression model that adjusted for the 5 factors of age, female sex, presence of hypertension, radial AI75, and carotid flow pulsatility index. Predictably, the presence of hypertension was an independent correlate of the presence of UIAs; further, a lower carotid flow pulsatility index had a strong independent association with the presence of UIAs.

Presence of UIAs Versus Carotid Flow Pulsatility Index

Tertile analysis revealed that the lowest tertile of the carotid flow pulsatility index had greatest number of UIAs among all groups, implying that low carotid flow

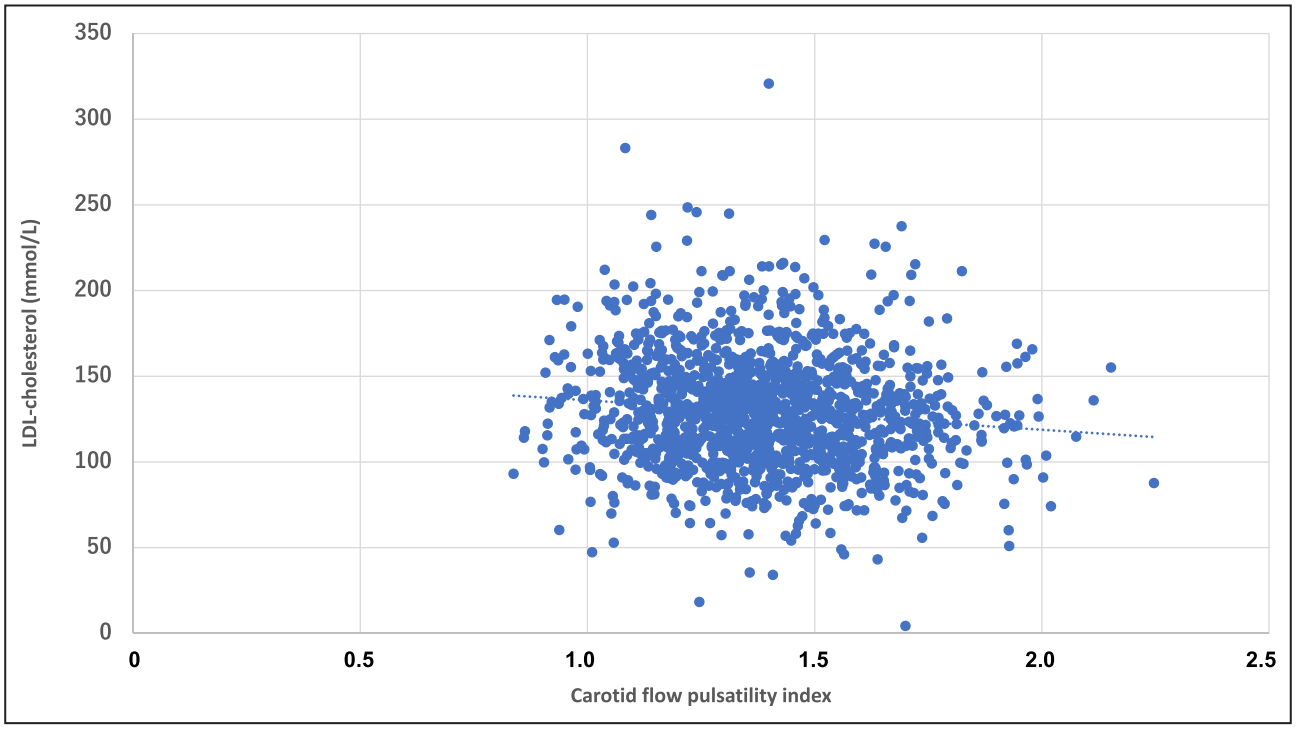

Figure 2. The association between carotid flow pulsatility index and LDL level (mg/dl) reveals a significant negative correlation (*P*<0.001).
LDL indicates low-density lipoprotein.

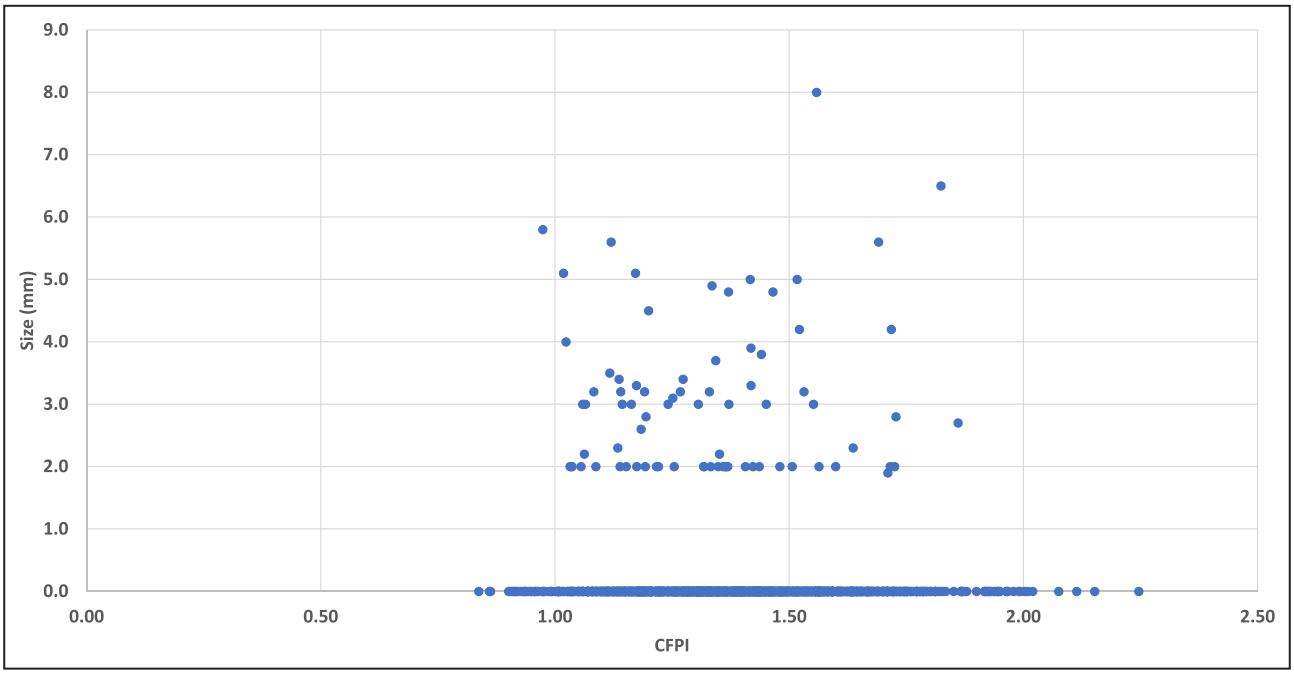

Figure 3. Carotid flow pulsatility index and maximal aneurysm size (subjects without aneurysm as size zero) are plotted, where significant negative correlation is observed between the 2 factors (*P*<0.05).
CFPI indicates carotid flow pulsatility index.

pulsatility index may affect the initiation of UIAs through hemodynamic change between carotid and cerebral artery. In clinical settings pulsatility index can be used as a diagnostic parameter of wall shear stress (WSS),[24] and changes in the carotid flow pulsatility index could therefore express the level of WSS. With regard to aneurysm formation, WSS seems to be involved and has been reported by many,[25–28] with both high and low WSS suggested to be involved in UIA formation. Low WSS is likely associated with the development of inflammatory-cell-mediated destructive remodeling and development of thick-walled aneurysms. In contrast, high WSS seems to play a crucial role in the development of thin-walled, rapidly developing aneurysms.[28] If these 2 notions are correct, we might further speculate that the UIAs identified in our healthy subjects might have developed over a certain longer period, given their consistency with former aneurysm type; that is, low WSS may play a significant role in the development of thick-walled aneurysms. An in vivo study revealed that blood flow reduction induces the apoptosis of endothelial cells,[29] implying that UIAs may be formed by reduced WSS[25] through the attenuation of vascular endothelial structures made by molecular changes. Therefore, a low carotid flow pulsatility index would induce the alteration of vascular environment, presumably resulting in the initiation of UIAs.

It is well known that aneurysms share risk factors with atherosclerosis development;[30] thus, we scrutinized the association of main atherosclerotic biomarkers in tertile groups stratified by carotid flow pulsatility index, where LDL-C had significant differences between the lower tertile carotid flow pulsatility index group and the other 2 groups. Dyslipidemia increases the risk of aortic aneurysm in Takayasu arteritis. Higher LDL-C levels appear correlate with aneurysm formation[31] and higher LDL-C infiltration is observed in ruptured aneurysms.[5] Subsequent individual analyses of all cases revealed that carotid flow pulsatility index had a significantly negative correlation with LDL-C levels, suggesting that a reduced carotid flow pulsatility index may affect LDL-C elevation by some molecular pathways and influence the development of cerebral aneurysms. In addition, carotid flow pulsatility index also was found to have a weak negative correlation with aneurysm size, in which subjects without UIAs were defined as size zero. Considered together, we speculate that the combination of the cerebrovascular hemodynamic changes could be affected by lower carotid flow pulsatility indices and the molecular changes in endothelial cells of intracranial arteries that could be induced by higher levels of LDL-C might stimulate aneurysm formation.

LIMITATIONS

There are some noteworthy limitations to this study.

1. In most countries, including the United States, magnetic resonance angiography of the brain

is not considered part of any routine screening program. In Japan, a brain health checkup program is widely provided to the general public. Our health checkup program is an extensive screening program for volunteers in Japan. Because this difference exists between the United States and Japan, caution is required when generalizing our findings.
2. Our analyses were retrospective, and a degree of selection bias may have been introduced. Study participants were recruited from antiaging checkup examinees, and accordingly the participants may not necessarily have represented the general population. Because the Japanese population tends to develop both enlargement and rupture of brain aneurysms more often compared with Whites,[32] it is unclear how applicable our findings are to other racial and ethnic groups. In addition, because our program participants were fitness conscious, heavy smokers and/or heavy alcohol drinkers may have been underrepresented.
3. The cross-sectional nature of the study prevents any assignation of causality in the association between carotid flow pulsatility index and UIA. For example, we could not know when UIA was initiated.
4. We were unable to assess the relationship of carotid flow pulsatility index to ruptured UIAs as no program participants had experienced subarachnoid hemorrhage.
5. The study population exclusively comprised Japanese subjects. Because the body size of Asians is smaller than that of Europeans[33] and high-density lipoprotein cholesterol is extremely high, our findings may not be entirely generalizable to other populations.

CONCLUSIONS

In summary, we detected UIAs in 79 (5.7%) of total 1376 healthy subjects. Scrutinizing clinical characteristics, subjects with UIAs were significantly older ($P<0.05$) and had higher BP ($P<0.01$). The carotid flow pulsatility indices of subjects with UIAs were significantly lower than those without UIAs ($P<0.01$). The carotid flow pulsatility index correlated negatively with the presence of UIAs even after correction of confounding factors. Though a tertile analysis lower carotid flow pulsatility index group revealed higher value of LDL-C than the other 2 tertiles, taken together, changes in cerebrovascular and molecular environment are likely involved in the initiation of UIAs, albeit that further validation studies necessary.

ARTICLE INFORMATION

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Disclosures

None.

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