

Aortic Knob Width as a Novel Indicator of Atherosclerosis and Obstructive Sleep Apnea

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Aim: Patients with obstructive sleep apnea (OSA) are likely to show increased arterial stiffness and progressive systemic atherosclerosis. Chest radiography reveals atherosclerotic changes in the aorta *via* measurement of aortic knob width. However, to our knowledge, aortic knob width in patients with OSA has never been evaluated.

Methods: We measured the aortic knob width in chest radiographs of 549 patients (age: 52.5 ± 13.2 years; 69 women) who underwent overnight polysomnography. Moreover, we evaluated the association between aortic knob width and other clinical characteristics, including cardio-ankle vascular index (CAVI) and apnea-hypopnea index (AHI). Multivariate linear regression analysis was conducted to identify factors associated with aortic knob width.

Results: A significant direct correlation between aortic knob width and CAVI and between aortic knob width and AHI was observed. In multivariate linear regression analysis, either CAVI or AHI was independently associated with aortic knob width ($p=0.004$ and $p<0.001$, respectively) in addition to age, male gender, body mass index, and systolic blood pressure.

Conclusion: A significant independent correlation between aortic knob width and OSA severity was observed. Our findings suggest that an increase in the aortic knob width suggests atherosclerotic changes in the aorta and may be associated with OSA and increased arterial stiffness.

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Key words: Obstructive sleep apnea, Aortic knob, Atherosclerosis, Arterial stiffness, Cardio-ankle vascular index

Introduction

Obstructive sleep apnea (OSA) is a common disease and has been considered a critical issue due to its cardiovascular consequences. Patients with OSA experience repetitive episodes of blood pressure (BP) elevation in response to each apneic event, which prevents the physiological nighttime BP dip (i.e., non-dipping). In addition, OSA is associated with daytime hypertension^{1, 2)}. Daytime and nighttime BP elevation may stiffen the arteries in combination with increased oxi-

dative stress³⁾, which is caused by repetitive episodes of intermittent hypoxia and reoxygenation associated with apneas and hypopneas. Moreover, increased oxidative stress may facilitate atherosclerosis by impairing endothelial function and enhancing the inflammatory cascade, which further stiffens the arteries⁴⁾. Indeed, arterial stiffness parameters, such as pulse wave velocity and cardio-ankle vascular index (CAVI), are elevated in patients with OSA^{5, 6)}. Additionally, repetitive respiratory efforts during obstructive apneas increase negative intrathoracic pressure⁷⁾. This negative intra-

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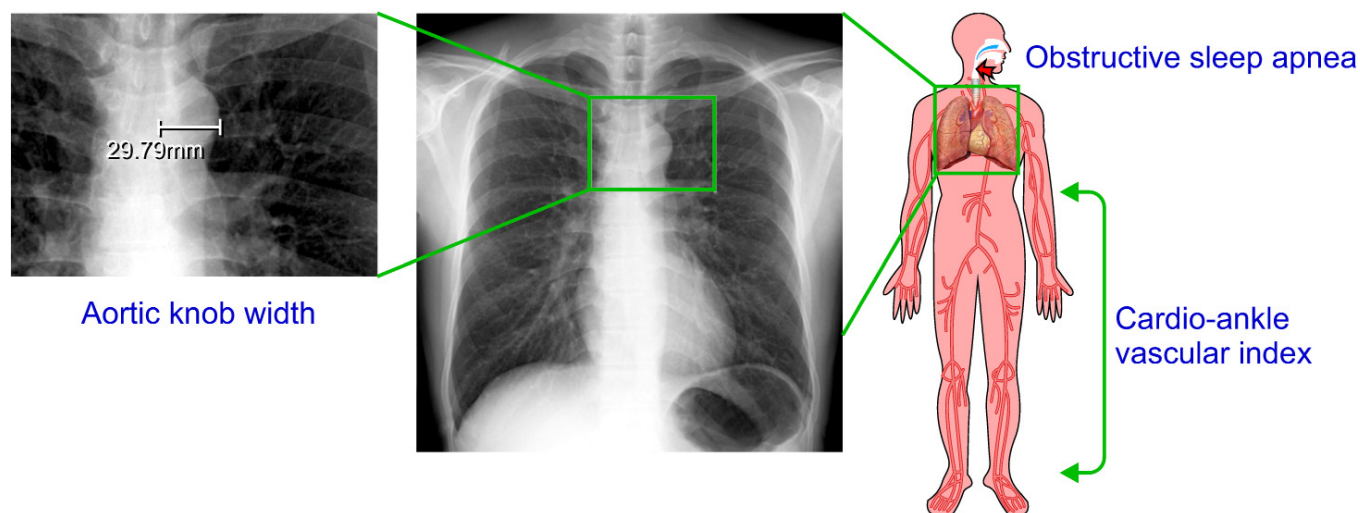


Fig. 1. Aortic knob width was measured along the horizontal line from the point of the lateral edge of the trachea to the left lateral wall of the descending aorta.

thoracic pressure in combination with increased arterial stiffness and atherosclerosis can lead to aortic dilatation and possibly aortic diseases, including aortic aneurysm and aortic dissection^{8,9}).

The aortic knob is composed of the descending thoracic aorta, as visualized in chest radiography. Dilatation and calcification of the aortic knob are considered to be atherosclerotic changes. Previous studies have revealed the correlation between aortic knob width and the severity of arterial stiffness or atherosclerotic diseases in patients with hypertension and coronary artery disease (CAD)¹⁰⁻¹², as well as several markers of target organ damage¹³. However, to our knowledge, there have been no studies focusing on aortic knob width in patients with OSA or on the association between aortic knob width and OSA severity. Therefore, this study has been conducted to test our three hypotheses: (1) that aortic knob width increases as OSA severity increases; (2) that there is a dose-response relationship among apnea-hypopnea index (AHI), OSA severity, and aortic knob width; and (3) that this relationship is independent of arterial stiffness parameters and other factors associated with atherosclerosis.

Methods

Study Population

This study was a *post hoc* analysis of a prospectively collected dataset¹⁴. In this analysis, we collected data of participants who underwent overnight polysomnography and CAVI measurements the day after the procedure. Consecutive adults from July 2006 to December 2007 who underwent chest radiography on the same day as that of overnight polysomnography

were included. The exclusion criteria were as follows: (1) chest radiograph not properly centered; (2) heart failure; (3) cerebrovascular disease with a neurologic deficit; (4) known aortic disease; (5) peripheral vascular disease or ankle-brachial index ≤ 0.9 at the time of CAVI measurement; (6) open chest surgery, and (7) receiving dialysis. The ethics committee of Toranomon Hospital approved this study (No. 787).

Data Collection

Medical history and anthropometric data were collected from patient records. After fasting overnight, all participants underwent blood tests, including glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and hemoglobin A1c. The presence of hypertension was defined based on the prescription of antihypertensive agents or when systolic/diastolic BP was $\geq 140/90$ mmHg. The presence of diabetes mellitus was defined based on the prescription of anti-diabetic medication or when fasting glucose level was ≥ 126 mg/dL.

Aortic Knob Width

All patients underwent chest radiography in the posteroanterior view. An examiner who was blinded to the results of the patient's arterial stiffness measurements or OSA severity reviewed the chest radiographs. The widest point of the ascending aortic knob was measured along the horizontal line from the point of the lateral edge of the trachea to the left lateral wall of the aortic knob (**Fig. 1**). Intra-examiner reproducibility was determined by measuring the aortic knob width two times at least 1 month apart for ten randomly selected patients. Similarly, inter-examiner repro-

Table 1. Baseline and clinical characteristics of patients

OSA severity	No (n=45)	Mild (n=68)	Moderate (n=153)	Severe (n=283)	p for trend
Age, years	43.1 ± 15.1	52.5 ± 11.7	54.5 ± 12.4	52.9 ± 13.1	< 0.001
Male, n (%)	29 (64)	57 (84)	131 (86)	263 (96)	< 0.001
BMI, kg/m ²	23.5 ± 3.8	25.5 ± 4.0	25.9 ± 3.5	27.1 ± 4.2	< 0.001
Smoker, n (%)	27 (60)	33 (49)	82 (54)	141 (50)	0.352
Known CAD, n (%)	0 (0)	1 (1)	5 (3)	10 (4)	0.155
Hypertension, n (%)	7 (16)	31 (46)	83 (54)	149 (53)	< 0.001
Diabetes mellitus, n (%)	0 (0)	3 (4)	8 (5)	29 (10)	0.004
Glucose, mg/dL	96.8 ± 12.2	102.1 ± 22.3	107.7 ± 30.4	104.1 ± 21.0	0.069
Hemoglobin A1c, %	5.3 ± 1.3	5.3 ± 0.7	5.4 ± 0.6	5.5 ± 0.7	0.163
Total cholesterol, mg/dL	187.3 ± 35.4	201.0 ± 30.3	199.8 ± 33.4	198.8 ± 35.0	0.047
Triglycerides, mg/dL	132.4 ± 77.9	154.9 ± 83.0	151.8 ± 91.3	178.0 ± 153.7	0.032
HDL cholesterol, mg/dL	51.2 ± 11.3	49.6 ± 12.6	48.2 ± 12.5	46.4 ± 12.1	0.020
Systolic BP, mmHg	124.9 ± 15.1	130.8 ± 18.1	131.4 ± 17.0	133.2 ± 15.7	0.002
Diastolic BP, mmHg	78.0 ± 11.6	83.2 ± 10.5	84.0 ± 10.7	84.6 ± 10.7	< 0.001
CAVI	7.0 ± 1.5	7.5 ± 1.2	7.7 ± 1.4	7.6 ± 1.4	0.011
Antihypertensive drug	1 (2)	26 (38)	68 (44)	121 (43)	< 0.001
Antidiabetic drug	0 (0)	1 (1)	1 (1)	2 (1)	0.963
Aortic knob width, mm	32.9 ± 5.4	35.9 ± 5.0	37.5 ± 5.0	38.1 ± 4.9	< 0.001
AHI, /h	2.2 ± 1.6	10.2 ± 3.0	23.1 ± 4.2	51.3 ± 15.8	< 0.001
Arousal index, /h	18.2 ± 10.5	22.9 ± 9.4	28.9 ± 10.9	50.0 ± 18.6	< 0.001
ODI (3%), /h	0.5 ± 1.0	4.7 ± 3.7	14.6 ± 6.6	42.2 ± 19.4	< 0.001
Lowest SpO ₂ , %	90.5 ± 3.9	80.8 ± 15.2	76.6 ± 14.9	73.3 ± 10.7	< 0.001

AHI, apnea-hypopnea index; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CAVI, cardio-ankle vascular index; HDL, high-density lipoprotein; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; SpO₂, peripheral oxygen saturation.

ducibility was determined by measuring the same samples by another examiner.

CAVI Measurement

CAVI was measured (VaSera VS-1000; Fukuda Denshi; Tokyo, Japan) using previously described methods¹⁵. Participants rested in the supine position for 5 min before measurement was performed. Electrocardiography, phonocardiography, and pressures and waveforms of the brachial and ankle arteries were obtained. CAVI was automatically calculated. Moreover, BP records used in the study were obtained through CAVI measurements.

Polysomnography

All participants underwent overnight polysomnography using a digital polygraph (SomnoStar Alpha Sleep System, SensorMedics Corp., Yorba Linda, CA, USA) equipped with electroencephalogram, electrooculogram, electromyogram, finger pulse oximeter, respiratory effort sensors, and airflow sensors. Accepted definitions and scoring methods were used to diagnose OSA¹⁶. OSA severity was classified according to AHI as follows: AHI < 5 events/h indicated no OSA; 5 ≤

AHI < 15 events/h indicated mild OSA; 15 ≤ AHI < 30 events/h indicated moderate OSA; and ≥ 30 events/h indicated severe OSA.

Statistical Analysis

Patients were assigned to four groups based on OSA severity. Continuous variables were expressed as mean and standard deviation or median and interquartile range, and categorical variables were expressed as numbers and percentages. Williams' test and Cochran-Armitage test were used to analyze the trend for continuous variables and percentages for categorical variables, respectively. Inter- and intra-examiner reproducibility were analyzed using the intraclass correlation coefficient (ICC). Univariate correlation analyses between aortic knob width and the following clinical variables were conducted: age, gender, body mass index (BMI), systolic BP, smoking history, presence of known CAD, CAVI measurement, AHI, total cholesterol triglycerides, high-density lipoprotein cholesterol, and hemoglobin A1c. Variables associated with aortic knob width in the univariate correlation analysis ($p < 0.1$) were used in the multivariate regression analysis. The final multivariate regression model used to identify the cor-

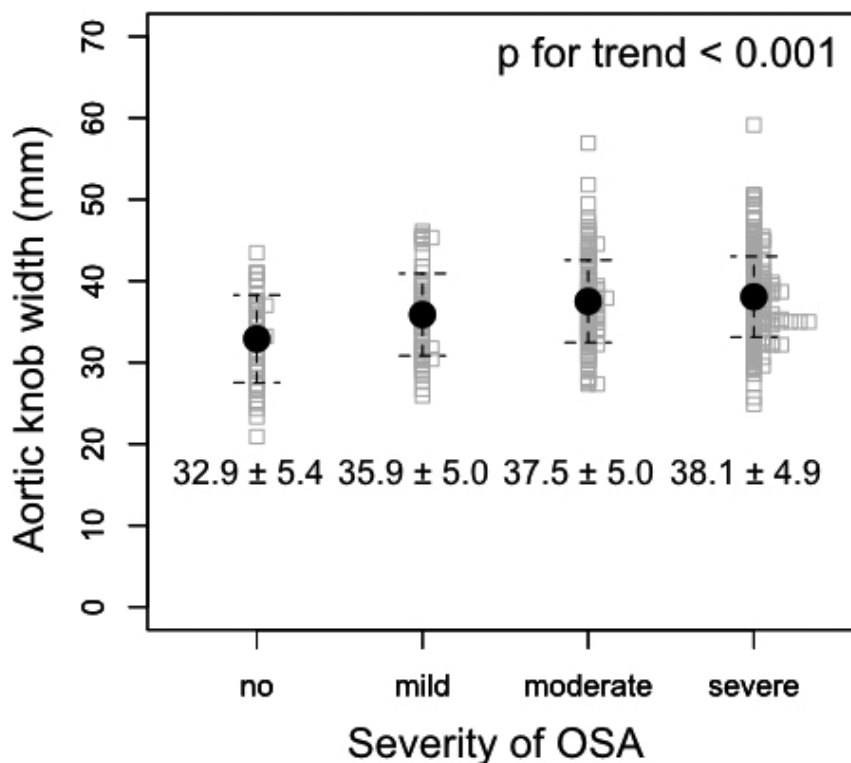


Fig. 2. Box plots of aortic knob width according to the severity of obstructive sleep apnea (OSA).

relates of aortic knob width was determined by stepwise selection and forward/backward elimination with maximized Akaike information criterion. In addition, variance inflation factor (VIF) was calculated to identify possible multicollinearity between variables. Statistical analyses were performed using R software, version 3.4.3 (R Core Team, Austria). Two-sided p values < 0.05 were considered statistically significant.

Results

Patient characteristics are summarized in [Table 1](#). A total of 549 patients were included in this study, with 45 (8.2%) showing no OSA; 68 (12.4%), mild OSA; 153 (27.9%), moderate OSA; and 283 (51.5%), severe OSA. The mean patient age was 52.5 ± 13.2 years, and 480 (87.4%) of the patients were men. An increasing trend in age and BMI was observed, which corresponded to an increase in OSA severity (p for trend < 0.001). The prevalence of hypertension and diabetes mellitus increased with an increase in OSA severity ($p < 0.001$ and $p = 0.004$, respectively).

ICC of intra- and inter-examiner reproducibility was 0.96 and 0.92, respectively, in ten randomly selected patients (age: 51.9 ± 14.0 years; 9 men; aortic knob width 37.9 ± 4.2 mm).

The mean aortic knob width was 37.2 ± 5.2 mm. An increase in aortic knob width and CAVI corresponded to an increase in OSA severity ($p < 0.001$ and $p = 0.011$, respectively) ([Fig. 2](#), [Table 1](#)). In univariate analyses ([Table 2](#)), aortic knob width was positively and significantly correlated with CAVI ($r = 0.37$, $p < 0.001$, [Supplemental Fig. 1](#)). Similarly, aortic knob width was significantly correlated with AHI ($r = 0.25$, $p < 0.001$), arousal index ($r = 0.26$, $p < 0.01$), and 3% ODI ($r = 0.24$, $p < 0.01$), as well as several clinical variables. In multivariate linear regression analysis, the known CAD, hemoglobin A1c, antihypertensive drug, arousal index, and 3% oxygen desaturation index were omitted from the final model ([Table 3](#)) after stepwise selection. Model analysis revealed that age, BMI, systolic BP, CAVI, AHI, and male gender were independent correlates of aortic knob width. VIF of these variables were 1.9, 1.5, 1.2, 2.1, 1.2, and 1.1, respectively.

Discussion

To the best of our knowledge, this is the first study to examine the association between aortic knob width and OSA severity. The findings of this study provide several important insights that may help explain the associations between OSA and arterial stiffness/

Table 2. Correlations between aortic knob width and clinical variables

Variables	Correlation coefficient	<i>p</i> value
Age	0.46	<0.001
Male	0.08	0.064
BMI	0.21	<0.001
Systolic BP	0.31	<0.001
Smoker	0.01	0.865
Known CAD	0.09	0.027
Hemoglobin A1c	0.21	<0.001
Total cholesterol	-0.02	0.669
Triglycerides	-0.01	0.906
CAVI	0.37	<0.001
Antihypertensive drug	0.20	<0.001
Antidiabetic drug	0.04	0.308
AHI	0.25	<0.001
Arousal index	0.26	<0.001
ODI (3%)	0.24	<0.001
Lowest SpO ₂	-0.14	0.001

AHI, apnea-hypopnea index; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CAVI, cardio-ankle vascular index; ODI, oxygen desaturation index; SpO₂, peripheral oxygen saturation.

atherosclerosis or aortic diseases. First, aortic knob width increased as OSA severity increased. A significant dose-response relationship between aortic knob width and AHI was observed. Second, there was a significant correlation between aortic knob width and the arterial stiffness parameter, CAVI, which is consistent with the report of another study including 374 patients with hypertension¹⁰. Third, multivariate regression analysis revealed that in patients with OSA, AHI was associated with aortic knob width independent of CAVI. These findings suggest that OSA may increase aortic knob width through an increase in arterial stiffness and other mechanisms. One such mechanism could be apnea without respiratory effort leading to aortic dilatation due to negative intrathoracic pressure¹⁷.

Clinical implications of increased aortic knob width have been suggested in previous studies targeting several patient populations other than OSA. An independent direct correlation between aortic knob width and central systolic BP has been shown in patients with known or suspected CAD¹⁸. Erkan *et al.* have reported that in 126 patients with hypertension, there was a strong direct correlation between aortic knob width and one of the well-known atherosclerotic parameters, carotid intima-media thickness (IMT)¹¹. Yun *et al.* have shown that in patients with CAD, aortic knob width was significantly and directly correlated with the extent of CAD¹². These results suggested that aor-

Table 3. Multivariate linear regression analysis of aortic knob width

	Partial correlation coefficient	<i>p</i> value
Age	0.37	<0.001
BMI	0.26	<0.001
Systolic BP	0.19	<0.001
CAVI	0.12	0.004
AHI	0.15	<0.001
Male	0.15	<0.001

AHI, apnea-hypopnea index; BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index.

tic knob width could indicate the degree of early atherosclerosis, including arterial stiffness, as well as the progression and extent of systemic atherosclerotic diseases, including CAD. Presumably, in patients with OSA, increased arterial stiffness, IMT^{19, 20}, and CAD progression²¹ can occur through pathophysiological mechanisms of OSA, such as increased oxidative stress and enhanced inflammatory response³. The dose-response relationship between aortic knob width and OSA severity in the present study suggests another means of stiffening or sclerotic process of the aorta in association with OSA.

The effect of negative intrathoracic pressure on the aorta in patients with OSA has been demonstrated based on high prevalence of OSA in patients with aortic dilatation, aneurysm, and dissection. Indeed, several studies have shown a close association between aortic disease and OSA. Sampol *et al.*⁹ have suggested that OSA is common in patients with aortic dissection. Another study has revealed that the prevalence of OSA in patients with abdominal aortic aneurysm was high and that OSA was a risk factor for the progression of the aneurysm⁸. In these studies, exaggerated negative intrathoracic pressure during obstructive respiratory events was speculated to play an important role in the possible link between OSA and aortic diseases in addition to the basal atherosclerotic change in the aorta. To further substantiate the adverse effects of exaggerated intrathoracic pressure on the aorta, an association between the OSA severity and increased aortic diameter has been reported in individuals without aortic disease²². These associations can be explained by accompanying hypertension. Hypertension is common in patients with OSA, and it is the most important cause of dilatation of the aorta in patients with aortic disease, such as thoracic aortic aneurysm. In addition, OSA promotes hypertension²³. Therefore, hypertension due to OSA contributes to the dilatation of the aorta and development of aortic disease. Indeed, in

our multivariate regression analysis, systolic BP was a significant correlate of aortic knob width independent of OSA severity and CAVI.

The association between aortic knob width and CAVI or AHI can emphasize the importance of aortic knob width in a real clinical setting. In patients with OSA, the degree of atherosclerosis may be estimated by measuring aortic knob width. This information can help stratify patients according to their underlying atherosclerotic risk. Furthermore, simple examinations, such as chest radiography, may provide novel information regarding OSA and may serve as a tool in its screening. Many patients with OSA remain undiagnosed^{24, 25)}, which represents an issue that needs to be resolved to prevent future cardiovascular diseases²³⁾. Although there are several parameters indicating the severity of atherosclerosis, most of them are evaluated to measure atherosclerosis alone. However, chest radiography is widely used in various clinical settings and during health checkups unrelated to OSA. Radiography can in fact provide information regarding OSA, which should be of interest to investigate in greater detail.

Several limitations of this study should be noted. First, because we excluded patients with aortic disease according to their medical history, some patients with dilated aortic knob width may have undiagnosed aortic disease, and this may have led to selection bias. In addition, although multivariate analysis was performed, there may be unknown confounding factors. Second, we cannot determine whether the association between aortic knob width and OSA severity includes a causal relationship due to the cross-sectional nature of this study. If aortic knob width changes following OSA treatment, it may confirm the causality between OSA and increased aortic knob width. Therefore, further longitudinal studies are warranted. Finally, we did not include any data on intrathoracic pressure or oxidative stress, which may act as mediating factors in the association between OSA severity and aortic knob width; moreover, there may be other unknown mechanisms. Collectively, this study is to some extent a proof-of-concept study, and results should be interpreted with caution.

Conclusion

In conclusion, the dilatation of aortic knob width detected using chest radiography was significantly correlated with OSA severity, independent of blood pressure and arterial stiffness. Therefore, dilated aortic knob width may be an indicator of severe OSA.

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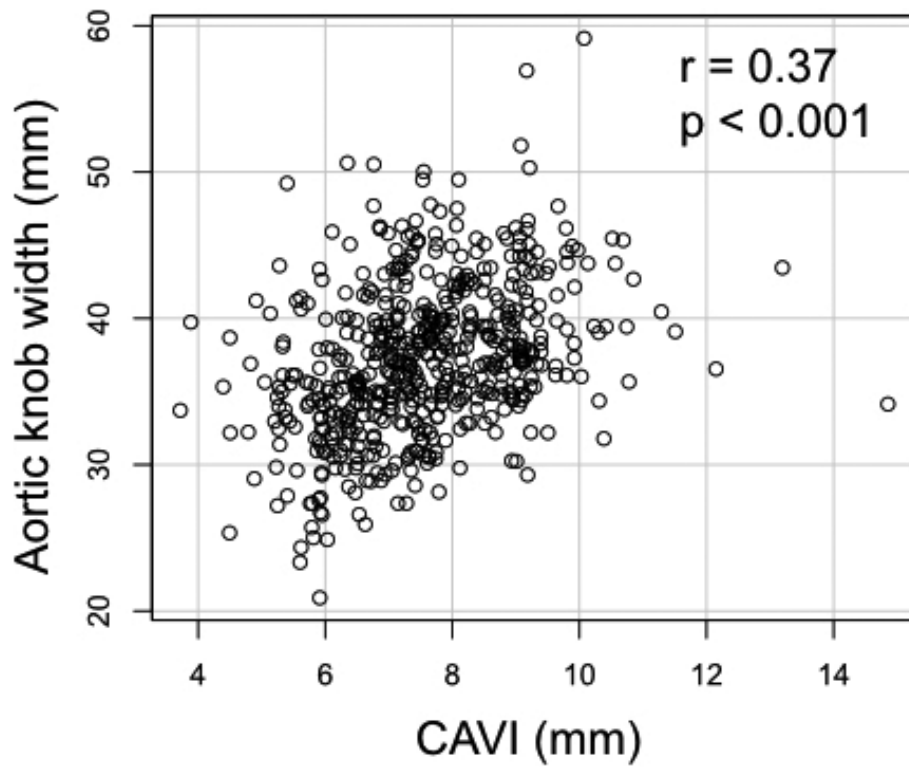
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Supplemental Fig. 1. The correlation between aortic knob width and cardio-ankle vascular index (CAVI).