

## ORIGINAL ARTICLE

# Obesity as an independent influential factor for reduced radial arterial wave reflection in a middle-aged Japanese male population

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This study aimed to examine whether obesity, including abdominal obesity, is an influential factor for radial arterial wave reflection, as expressed by the augmentation index (AI), in middle-aged Japanese men. Radial arterial pressure waveform was measured using automated applanation tonometry in 828 men (mean age:  $47 \pm 5$  years) during an annual health examination at a company. Radial AI was calculated from the waveforms. AI appeared to be similar between subjects with and without obesity (body mass index (BMI)  $\geq 25$  and  $< 25 \text{ kg m}^{-2}$ , respectively). However, after adjusting for age, height, heart rate, mean blood pressure, low- and high-density lipoprotein cholesterol, fasting plasma glucose, white blood cell count and other potential confounders, AI was significantly lower in subjects with obesity (71.6%, 95% confidence interval (CI); 70.2–73.0%) than in those without (75.2%, 95% CI; 74.4–76.0%,  $P < 0.001$ ). In a multiple linear regression analysis, BMI was negatively associated with AI ( $\beta = -0.20$ ,  $P < 0.001$ ); other factors associated with AI were heart rate ( $\beta = -0.56$ ), mean blood pressure ( $\beta = 0.44$ ), height ( $\beta = -0.24$ ), age ( $\beta = 0.15$ ), current smoking ( $\beta = 0.09$ ), white blood cell count ( $\beta = 0.06$ ) and low-density lipoprotein cholesterol ( $\beta = 0.06$ ). Similar associations were found when waist circumference (WC, an index of abdominal obesity) was substituted for BMI in the analysis ( $\beta = -0.12$ ,  $P < 0.001$ ). BMI closely correlated with WC ( $r = 0.87$ ), thus suggesting that approximately 76% (a square of 0.87) of BMI can be explained by WC. In conclusion, although it does not have a major impact, obesity, including abdominal obesity, may be an influential factor for reduced radial AI, independently of well-known confounders, in middle-aged Japanese men.

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**Keywords:** augmentation index; obesity; pulse-wave analysis; risk factors

## INTRODUCTION

A growing number of studies have shown arterial stiffness to be an independent predictor for cardiovascular mortality and morbidity, not only in a specific patient group<sup>1–6</sup> but also in the general population.<sup>7–9</sup> The measurement of arterial stiffness may therefore be useful for evaluating the risk of cardiovascular disease (CVD). Indeed, in Japan, the measurement of arterial stiffness has been increasing in routine physical examinations, and it is also becoming known as the measurement of ‘vascular aging’ among Japanese people.<sup>10–12</sup>

Arterial wave reflection represents the timing and intensity of the backward wave from the periphery, which is partly determined by systemic arterial stiffness.<sup>13</sup> The augmented arterial wave reflection, as expressed by the augmentation index (AI), increases left ventricular afterload<sup>13</sup> and is recognized as a surrogate marker of cardiovascular risk. AI is well known to be influenced by several hemodynamic and anthropometric parameters such as blood pressure (BP), heart rate and height,<sup>13</sup> but the influence of obesity on AI is still controversial.<sup>14–22</sup> Moreover, to our knowledge, no reports have evaluated the association

between obesity, including abdominal obesity, and AI in a non-hospital-based, apparently healthy Japanese population. Understanding this association could enable us to more accurately interpret the AI value for each individual in a variety of clinical settings.

This study aimed to examine whether obesity, including abdominal obesity, is an influential factor for radial AI in middle-aged Japanese men.

## METHODS

### Study population

This study was conducted during an annual health examination at a company in Kanagawa, Japan, in 2007. A total of 944 male workers between 40 and 61 years of age received the examination. The jobs of all the participants consisted of daytime desk work. Subjects on medication for hypertension, dyslipidemia, or diabetes mellitus ( $n = 111$ ) and those with a history or presence of CVD ( $n = 5$ ) were excluded. As a result, 828 subjects participated in this study. This study was approved by the institutional review board, and all participants gave their informed consent.

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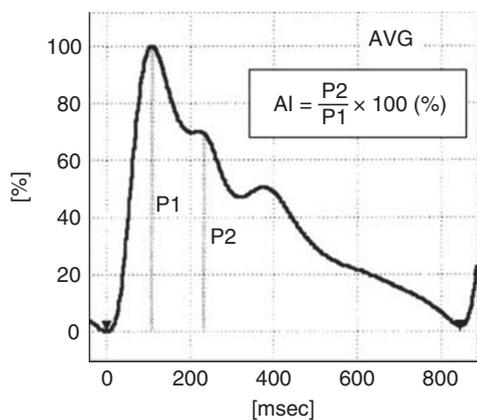
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### Collection of the subjects' data

A self-reported questionnaire was used to collect the subjects' data regarding their smoking status, frequency of alcohol intake, family history, exercise habits and medical information, including prescribed drugs. All anthropometric measurements and blood sampling were conducted in a room maintained at  $22 \pm 2^\circ\text{C}$ . Waist circumference (WC) was measured at the level of the umbilicus after expiration. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as  $\text{BMI} \geq 25 \text{ kg m}^{-2}$ , and abdominal obesity was defined as  $\text{WC} \geq 85 \text{ cm}$ . Blood samples were obtained from the antecubital vein after overnight fasting. Standard enzymatic methods were used to measure the serum total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and plasma glucose levels. The serum high-density lipoprotein (HDL) cholesterol level was measured using a direct method. White blood cell (WBC) count was measured using an automatic cell counter. 'Current smoking' was defined as smoking every day for at least 1 year. Regular exercise was defined as continuous exercise for at least 15 min 3 days or more per week for at least 1 year. The frequency of alcohol intake was categorized as follows: 0–1 day per week, 2–5 days per week or 6–7 days per week.

### Blood pressure measurement and radial pulse-wave analysis

Brachial BP and radial pulse wave were simultaneously measured, after at least 5 min of rest in the sitting position, using a HEM-9000AI device (Omron Healthcare Co., Kyoto, Japan). This device consists of a main unit, a cuff for measuring BP by the oscillometric method and a wristwatch-like tonometry sensor unit. The right brachial BP was automatically measured two times. The average of two readings was used to determine the systolic and diastolic BP. The left radial arterial pressure waveform was obtained using the automated applanation tonometric method. The detailed methodology for measuring radial pulse waveform with the device has been described elsewhere.<sup>11,23</sup> In brief, the tonometry sensor unit has a pressure sensor consisting of an array of 40 microtransducer elements. When the sensor unit is placed on the subject's wrist, one of these 40 sensor elements is automatically selected to obtain optimal radial arterial pressure waveforms. Multiple waveforms were measured during continuous 15-s periods, and the measurement was repeated two times. Each radial AI, which corresponds to each waveform obtained during the recording period, was automatically calculated by the main unit using the following formula:  $(\text{second systolic peak} - \text{bottom}) / (\text{first systolic peak} - \text{bottom}) \times 100 (\%)$  (Figure 1). Thereafter, the mean AI was calculated from the multiple AI values. Finally, the average AI was determined from the two mean AI values, and this value was used in the statistical analyses. The intra-observer coefficient of variation of AI was 3.4% in this study. Radial AI was reported to show a close linear correlation with central AI ( $r=0.82-$



**Figure 1** A representative radial arterial pressure waveform measured using a HEM-9000AI device. Augmentation index (AI) is calculated as  $P2/P1 \times 100 (\%)$ , where P1 indicates the difference between first systolic peak and bottom and P2 indicates the difference between second systolic peak and bottom.

$0.96)^{11,23-25}$  thus suggesting similar clinical utility between central and radial AI.

### Statistical analysis

All statistical tests were performed using the SPSS software program, version 11.0.1 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean  $\pm$  s.d. or the mean (95% confidence interval (CI)), as appropriate. Categorical data were expressed as the percentage of total. The unpaired Student's *t*-test was used to test the difference in continuous variables between subjects with and without (abdominal) obesity. The  $\chi^2$  test was used to compare the categorical variables. Pearson's moment correlation coefficient was analyzed to determine the simple correlation between BMI and WC. The analysis of covariance was used to test the difference in AI between the groups, with multiple confounders as covariates. A multiple linear regression analysis was conducted to determine the independent associations of AI with BMI, WC and other clinical parameters. All statistical tests were two-sided, and a *P*-value of less than 0.05 was considered to be significant.

### RESULTS

The characteristics of the study participants are noted in Table 1. For the study population as a whole, the mean age was  $47 \pm 5$  years. The mean values of BMI, WC, systolic and diastolic BP, lipid profile and fasting plasma glucose levels were all within the normal range. BMI closely correlated with WC ( $r=0.87$ ,  $R^2=0.76$ ,  $P<0.001$ ). The mean AI for the overall study population was  $74.3 \pm 12.5\%$ . Obesity, as classified by BMI, was present in 214 subjects. When classified by WC, 279 subjects were regarded as having abdominal obesity. The subjects with abdominal obesity were older and taller, and the prevalence of regular exercise was lower than in those without abdominal obesity, whereas no significant differences in these values were found between subjects with and without obesity. BP, total and LDL cholesterol levels, triglyceride level, fasting plasma glucose level and WBC count were higher and HDL cholesterol level was lower in subjects with abdominal obesity than in those without, as well as in subjects with obesity in comparison to those without.

The mean AI was found to be similar between subjects with and without either obesity or abdominal obesity (Table 1). However, as shown in Figure 2, when adjusting for multiple potential confounders such as age, height, heart rate, mean BP, LDL and HDL cholesterol levels, fasting plasma glucose, WBC count, smoking status, frequency of alcohol intake and exercise and family history of CVD, the mean AI was significantly lower in subjects with obesity (71.6%, 95% CI: 70.2–73.0%) than in those without (75.2%, 95% CI: 74.4–76.0%,  $P<0.001$ ). A significant difference in the adjusted mean AI was also found when compared between subjects with and without abdominal obesity (73.0%, 95% CI: 71.8–74.2%, and 74.9%, 95% CI: 74.1–75.8%, respectively,  $P=0.015$ ).

Table 2 notes the results of a multiple linear regression analysis for the association between AI and various parameters, including BMI and WC. In Model 1 (with BMI as an independent variable), heart rate, height and BMI were negatively associated, and mean BP, age, smoking status, WBC count and LDL cholesterol level were positively associated with AI. The absolute value of the standardized regression coefficient of BMI ( $-0.20$ ) was smaller than those of heart rate, mean BP and height, but larger than that of age. Similar associations were found when WC was substituted for BMI (Model 2), except that the absolute value of the standardized regression coefficient of WC ( $-0.12$ ) was smaller than that of age.

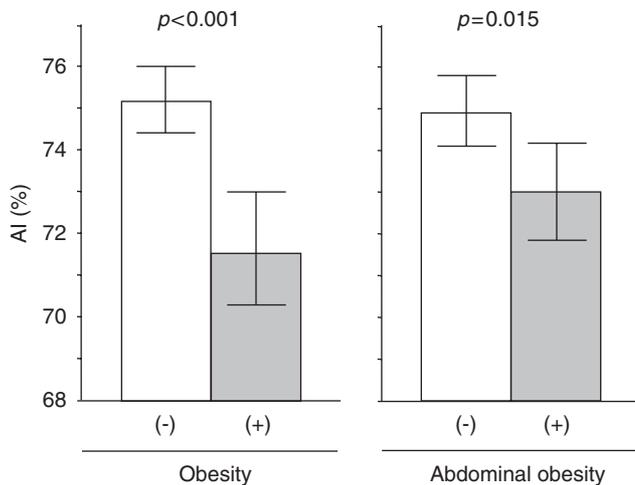
### DISCUSSION

This study demonstrated that in Japanese working men ranging from 40 to 61 years, radial AI was significantly lower in subjects with obesity

**Table 1** Characteristics of study participants, overall and classified by the obesity or abdominal obesity status

	Overall (n=828)	Obesity		Abdominal obesity	
		(-) (n=614)	(+) (n=214)	(-) (n=549)	(+) (n=279)
Age (years)	47 ± 5	47 ± 5	47 ± 5	47 ± 5	48 ± 5***
Height (cm)	171 ± 6	171 ± 6	171 ± 5	170 ± 6	172 ± 6*
Weight (kg)	68.0 ± 9.5	64.3 ± 6.8	78.4 ± 8.6*	63.6 ± 6.5	76.6 ± 8.7*
BMI (kg m <sup>-2</sup> )	23.3 ± 2.9	22.0 ± 1.8	26.9 ± 2.1*	22.0 ± 2.0	25.9 ± 2.4*
WC (cm)	82.1 ± 8.1	79.0 ± 6.0	90.9 ± 6.6*	77.6 ± 4.9	90.8 ± 5.4*
Heart rate (b.p.m.)	69 ± 10	69 ± 10	69 ± 10	68 ± 10	70 ± 9
Systolic BP (mm Hg)	120 ± 14	117 ± 13	126 ± 15*	117 ± 13	125 ± 15*
Diastolic BP (mm Hg)	75 ± 11	73 ± 11	79 ± 11*	73 ± 10	79 ± 11*
Mean BP (mm Hg)	90 ± 12	88 ± 11	95 ± 12*	88 ± 11	94 ± 12*
AI (%)	74.3 ± 12.5	74.3 ± 12.4	74.2 ± 13.1	74.3 ± 12.4	74.2 ± 13.0
Total cholesterol (mg dl <sup>-1</sup> )	209 ± 33	206 ± 32	216 ± 34*	204 ± 32	218 ± 33*
HDL cholesterol (mg dl <sup>-1</sup> )	58 ± 14	60 ± 14	52 ± 10*	60 ± 15	53 ± 10*
LDL cholesterol (mg dl <sup>-1</sup> )	135 ± 39	131 ± 41	144 ± 32*	130 ± 42	144 ± 30*
Triglycerides (mg dl <sup>-1</sup> )	113 ± 95	102 ± 85	144 ± 114*	97 ± 73	143 ± 122*
Fasting plasma glucose (mg dl <sup>-1</sup> )	92 ± 14	91 ± 12	96 ± 18**	91 ± 13	95 ± 16*
WBC count (×10 <sup>9</sup> per liter)	5.6 ± 1.5	5.5 ± 1.4	6.1 ± 1.5*	5.5 ± 1.5	5.9 ± 1.5*
Current smoking, (%)	28.7	27.5	32.2	27.0	32.3
Family history of CVD, (%)	23.3	23.9	21.5	23.0	24.0
Regular exercise, (%)	25.6	26.7	22.4	28.4	20.1**
<i>Frequency of alcohol intake</i>					
0–1 day per week, (%)	39.3	38.8	40.7	41.3	35.1
2–5 days per week, (%)	36.1	35.5	37.8	35.2	38.0
6–7 days per week, (%)	24.6	25.7	21.5	23.5	26.9

Abbreviations: AI, augmentation index; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC, white blood cell; WC, waist circumference. Values are mean ± s.d. or percent of total. Obesity and abdominal obesity were defined as BMI ≥25 kg m<sup>-2</sup> and WC ≥85 cm, respectively. \*P<0.001, \*\*P<0.01, and \*\*\*P<0.05 vs. obesity (-) or abdominal obesity (-), as appropriate.



**Figure 2** Comparison of the adjusted mean augmentation index (AI)\* between subjects with and without obesity (body mass index ≥25 and <25 kg m<sup>-2</sup>, respectively) or abdominal obesity (waist circumference ≥85 and <85 cm, respectively). Error bars indicate 95% confidence interval. \*Adjusted for age, height, heart rate, mean blood pressure, low- and high-density lipoprotein cholesterol, fasting plasma glucose, white blood cell count, smoking status, frequency of alcohol intake, exercise habits and family history of cardiovascular disease.

**Table 2** Multiple linear regression analysis for the association with AI

Independent variables	Model 1		Model 2	
	β	P-value	β	P-value
Heart rate	-0.56	<0.001	-0.54	<0.001
Mean BP	0.44	<0.001	0.40	<0.001
Height	-0.24	<0.001	-0.21	<0.001
BMI	-0.20	<0.001	—	—
Age	0.15	<0.001	0.17	<0.001
WC	—	—	-0.12	<0.001
Current smoking (Yes=1)	0.09	0.002	0.09	0.002
WBC count	0.06	0.028	0.06	0.032
LDL cholesterol	0.06	0.037	0.06	0.049
Frequency of alcohol intake <sup>a</sup>	0.04	0.169	0.05	0.112
HDL cholesterol	-0.04	0.210	-0.01	0.753
Regular exercise (No=1)	0.02	0.384	0.03	0.236
Family history of CVD (Yes=1)	0.01	0.630	0.01	0.708
Fasting plasma glucose	0.01	0.710	0.00	0.969
	(Model adjusted R <sup>2</sup> =0.43)		(Model adjusted R <sup>2</sup> =0.41)	

Abbreviations: AI, augmentation index; β, standardized regression coefficient; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC, white blood cell; WC, waist circumference. Model 1 and Model 2 include BMI and WC, respectively. <sup>a</sup>Classified as follows: 0–1 day per week=0, 2–5 days per week=1, and 6–7 days per week=2.

than in those without, when adjusted for multiple potential confounders such as age, height, mean BP and heart rate. Similarly, radial AI was significantly lower in subjects with abdominal obesity than in those without. Moreover, both BMI and WC were independently and inversely associated with radial AI in the multiple linear regression analysis. However, the BMI and WC associations with radial AI were not as strong as those of height and heart rate. These findings suggest that although it does not have a major impact, obesity, including abdominal obesity, is an influential factor for reduced radial arterial wave reflection in a non-hospital-based, middle-aged Japanese male population.

A number of studies have shown the relationship of AI to BMI and/or WC,<sup>14–22</sup> but the results are inconclusive. The differences in the characteristics of the study subjects and in the methodology for measuring AI among the studies may have caused these discrepancies. Moreover, only a few of studies have investigated the relationship with a statistical adjustment for major confounders.<sup>18–21</sup> In this regard, to our knowledge, this is the first study to show a significant inverse association of radial AI with BMI and WC using a multivariate analysis with a sufficient adjustment for various confounders in a relatively large Japanese male population. Smoking status, WBC count and LDL cholesterol level were also independently associated with AI in this study. These results are consistent with those in previous studies conducted in other ethnic groups,<sup>26–28</sup> and indicate that the relationships are also valid in the present population.

Possible mechanisms for the association of AI with BMI and/or WC have been considered. Maple-Brown *et al.*<sup>19</sup> showed an inverse association between AI and central obesity and noted that the external pressure from adipose tissue encapsulating small conduit arteries might decrease arterial transmural pressure, thus reducing arterial wave reflection. In contrast, insulin resistance and increased circulating levels of leptin and proinflammatory cytokines following excess accumulation of visceral adipocytes are thought to augment arterial wave reflection.<sup>29</sup> The net effect of these pathophysiological actions may determine the association between AI and WC. Snijder *et al.*,<sup>30</sup> however, reported that larger leg lean mass, as assessed by dual-energy X-ray absorptiometry, is a significant determinant of lower AI, possibly because of an increased blood supply and subsequent size adaptation of the arteries in response to increased muscle mass. Because BMI is not an index that can distinguish between excess fat accumulation and lean muscle mass, body composition may, at least partly, determine the association between AI and BMI. In this regard, in this study, the association between AI and BMI is thought to be influenced by visceral fat accumulation, because the correlation coefficient between BMI and WC was 0.87, suggesting that approximately 76% of BMI is explained by WC. Importantly, a number of studies have shown that arterial stiffness, assessed mainly by pulse-wave velocity (PWV), a standard and reliable index of arterial stiffness, is increased in subjects with abdominal obesity.<sup>29</sup> Moreover, obesity has been known to increase the risk of CVD.<sup>31</sup> It can therefore not be determined whether the inverse association between AI and the obesity indices seen in the present study indicates decreased arterial stiffness in subjects with obesity.

There are potential limitations to this study. First, because this is a cross-sectional investigation, the causal relationships cannot be determined. Further longitudinal surveys are needed to examine the impact of the change in the obesity indices on AI. Second, body fat composition was not directly measured in this study. However, the purpose of the study was to evaluate the influence of the anthropometric obesity indices on AI from a clinical perspective. Third, although PWV is considered to be a standard index of arterial stiffness,

we did not measure PWV in this study. Simultaneous measurements of AI and PWV may indicate a usefulness of PWV superior to that of AI for evaluating arterial stiffness in subjects with obesity. However, these two measurements provide different information on arterial properties; namely, pulse-wave velocity, measured not only between the carotid and femoral but also between the brachial and ankle arteries,<sup>32</sup> indicates regional arterial stiffness, in particular, the stiffness of large elastic arteries, whereas AI is thought to reflect systemic arterial stiffness.<sup>13</sup> Finally, the study participants included only middle-aged, Japanese male office workers in a certain district. Therefore, the results of this study may not be accurately extrapolated to other populations, including the elderly, women and other ethnic groups.

In conclusion, this study showed both obesity indices—BMI and WC—to be independently and inversely associated with radial AI. These findings suggest that obesity, including abdominal obesity, is an influential factor for reduced radial arterial wave reflection in middle-aged, Japanese men. Because obesity has been known to increase the risk of CVD, cautious interpretation of the AI value is needed when using AI as a cardiovascular risk marker in subjects with obesity.

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