Increased Aortic Pulse Wave Velocity Is Associated With the Presence of Angiographic Coronary Artery Disease in Overweight and Obese Patients

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**BACKGROUND**

Increased arterial stiffness assessed by carotid–femoral pulse wave velocity (CFPWV) and central augmentation index (AIx), has been associated with a worse cardiovascular prognosis and increased prevalence of angiographic coronary artery disease (CAD). Obesity, a well-recognized cardiovascular risk factor, has been related to increased arterial stiffness, although not consistently. The aim of this work was to investigate the association of arterial stiffness indices with obesity measures in patients undergoing coronary angiography and to study any potential association of arterial stiffness with angiographic CAD in relation to obesity.

**METHODS**

Three hundred ninety-three patients with suspected stable CAD (aged 61 ± 10 years; n = 303 men) referred for diagnostic coronary angiography were included. Body mass index (BMI), waist circumference (WC), and traditional cardiovascular risk factors were measured. Arterial stiffness was assessed by CFPWV and AIx using applanation tonometry in all patients.

**RESULTS**

CFPWV was not associated with obesity measures in multiple-adjusted logistic regression analysis (\(P > 0.05\)), whereas AIx was inversely associated with BMI and WC (\(P < 0.05\) for both). Increased CFPWV was associated with CAD in overweight and obese patients (BMI ≥25 kg/m\(^2\); WC ≥94 cm in men and ≥80 cm in women; \(P < 0.05\)). No association of AIx with CAD was found (\(P > 0.05\)).

**CONCLUSIONS**

Arterial stiffness indices were not consistently associated with obesity, opposite to what might have been expected. The association of increased CFPWV with the presence of angiographic CAD in patients with increased BMI or WC values warrants further research.

**Keywords:** arterial stiffness; augmentation index; blood pressure; coronary artery disease; hypertension; obesity; pulse wave velocity.

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Atherosclerotic vascular disease has been associated with a progressive stiffening of arteries. Increased arterial stiffness assessed by carotid–femoral pulse wave velocity (CFPWV) and central augmentation index (AIx) has been associated with a worse cardiovascular prognosis in the general population\textsuperscript{1–3} and specific groups of patients with hypertension,\textsuperscript{4,5} chronic kidney disease,\textsuperscript{6,7} and diabetes and glucose intolerance.\textsuperscript{8} CFPWV reflects central arterial stiffening, whereas AIx is a composite measure of both the amplitude and the timing of wave reflections returning to the ascending aorta from peripheral reflecting sites.\textsuperscript{2,3,9,10} Increased arterial stiffness evaluated by CFPWV\textsuperscript{11–13} and AIx\textsuperscript{11,14} has been also associated with the presence of coronary atherosclerosis and angiographic coronary artery disease (CAD).

Obesity, currently recognized as a risk factor for cardiovascular diseases (CVD),\textsuperscript{15–17} has also been suggested to have an effect on the mechanical properties of large arteries, such as an increase in large artery stiffness\textsuperscript{18–22} and arterial wave reflections.\textsuperscript{23} However, an adverse effect of obesity on arterial stiffness indices has not been consistently shown in several studies that included measurement of both CFPWV and AIx.\textsuperscript{20,24–28} Furthermore, whether a possible adverse effect of obesity on large artery mechanics may also be associated with a higher cardiovascular risk has not been previously studied.

The aims of the present study were to investigate (i) the relation of obesity measures with arterial stiffness indices (CFPWV and AIx) and (ii) the association of arterial stiffness indices with the presence of angiographic CAD in relation to obesity in patients with suspected stable CAD undergoing diagnostic coronary angiography.

**METHODS**

**Study population and study design**

This cross-sectional study enrolled 393 consecutive subjects with suspected stable CAD who underwent coronary
angiography by a single operator. The study was conducted in the Department of Cardiology, University Hospital of Ioannina during a 6-month period. Patients were referred because of symptoms and/or a positive stress test indicating high risk for stable CAD. Patients with suspected or documented acute coronary syndrome or peripheral vascular disease, any previous history of CAD, cerebrovascular disease, valvular heart disease, prosthetic valves, congenital heart disease, hypertrophic obstructive cardiomyopathy, and those on hemodialysis, were excluded from the study. The diagnosis of peripheral vascular disease was mainly based on review of the patient’s medical record, history, and physical examination. Further screening was implemented in patients who reported symptoms or had signs (in physical examination) suggestive of peripheral vascular disease.

In all subjects, a full medical history was taken and a complete physical examination was performed. Cardiovascular risk factors and medications were recorded in detail, and all patients underwent coronary angiography. Blood samples were drawn from all patients early in the morning after an overnight fast and just before coronary angiography. Assessment of arterial stiffness indices was performed on all patients.

The study protocol was approved by the local ethics committee. The study complied with the Declaration of Helsinki, and all participants provided written informed consent.

**Cardiovascular risk factor assessment**

The cardiovascular risk factors assessed in the present study were age, sex, smoking habits, hypertension, hypercholesterolemia, and diabetes mellitus. Smokers were defined as those who were smoking at the time of enrollment or those who had stopped for <12 months. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg during the initial examination or administration of antihypertensive medications. Hypercholesterolemia was defined as low density lipoprotein cholesterol >160 mg/dl or total cholesterol >240 mg/dl or administration of anticholesterolemic medications. Diabetes was defined as a fasting blood glucose concentration ≥126 mg/dl or administration of antihyperglycemic medications. Diabetes was defined as having a previous diagnosis of diabetes mellitus or being on antidiabetic medications. 

Heart disease, hypertrophic obstructive cardiomyopathy, valvular heart disease, any previous history of CAD, cerebrovascular disease, any previous history of CAD, and those on hemodialysis, were excluded from the study. The diagnosis of peripheral vascular disease was mainly based on review of the patient’s medical record, history, and physical examination. Further screening was implemented in patients who reported symptoms or had signs (in physical examination) suggestive of peripheral vascular disease.

In all subjects, a full medical history was taken and a complete physical examination was performed. Cardiovascular risk factors and medications were recorded in detail, and all patients underwent coronary angiography. Blood samples were drawn from all patients early in the morning after an overnight fast and just before coronary angiography. Assessment of arterial stiffness indices was performed on all patients.

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**Coronary angiography**

Coronary angiography was performed according to the standard Judkins technique. All coronary angiograms were visually assessed by 2 experienced angiographers, and a consensus was reached. The reviewers were blinded to the results of arterial stiffness analysis. Significant CAD was defined as ≥50% stenosis in the internal diameter of at least 1 coronary artery (≥30% for the left main coronary artery).

**Assessment of arterial stiffness**

Measurement of arterial stiffness indices was done early in the morning 1 day before coronary angiography with patients fasted and before the administration of scheduled medications. The assessment of arterial stiffness was performed noninvasively with the commercially available Sphygmocor system (Version 7.01; At Cor Medical, Sydney, Australia) by a single operator who was blinded to the results of coronary angiography and other findings. CFPWV and central AIx were measured. All measurements were taken in the supine position in a quiet, temperature-controlled room (approximately 22°C) after a brief period of rest in the morning before the catheterization.

Pressure waveforms were recorded from the carotid and femoral arteries using applanation tonometry. Wave transit time (t) was calculated by the system software, using the R wave on the simultaneously recorded electrocardiogram as reference frame. The distance travelled by the pulse wave was measured over the body surface as the distance between the 2 recording sites, and the distance from the suprasternal notch to the carotid was subtracted. CFPWV was calculated as distance/transit time and was assessed by measuring carotid – femoral arteries.

AIx was derived from the radial pressure waveform acquired from the right radial artery using the Sphygmocor’s tonometer. After acquisition of 15–20 waveforms, a validated generalized transfer function was used to generate the corresponding pressure waveform. The central AIx was derived from the reconstructed central pressure waveform and was calculated as the difference between the second and first systolic peaks observed on the central pulse waveform. AIx was expressed as a percentage of the central pulse pressure and was finally corrected for heart rate (AIx at 75). Only high quality recordings, defined as an in-device quality index ≥80% (derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform) and acceptable curves on visual inspection were included in the analysis.

According to the Bland and Altman method,31 mean differences between consecutive CFPWV and AIx performed
on 2 different days were −0.5 m/sec and 1.3% respectively; the coefficient of repeatability (i.e., 2 times the SD of the differences between the two measurements) for CFPWV and AIx at 75 were 1.4 m/second and 9.0%, respectively.

Statistical analysis
Continuous data are presented as mean ± SD. Kolmogorov–Smirnov Z test was used to identify continuous variables that were not normally distributed: age, height, heart rate, glucose, high-density lipoprotein cholesterol, triglycerides, and pulse wave velocity. Univariate and multiple-adjusted associations of arterial stiffness measures with obesity measures were assessed with linear regression analysis. The natural logarithm of CFPWV (dependent variable) was used and linear regression analysis was performed. Normal distribution of residuals and no skewness in the scatterplot of standardized residuals vs. standardized predicted values were fulfilled in all linear regression models and precluded the need for log transformation of independent variables. The covariates included in the multiple-adjusted linear regression models were parameters and medications known to be related to arterial stiffness:32 age, sex, smoking, height, heart rate, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting glucose, history of diabetes, mean arterial blood pressure, estimated glomerular filtration rate, and use of antihypertensive medications, statins, and nitrates. In analyses including BMI, height was left out; similarly heart rate was left out in analyses with AIx at 75. Logistic regression analysis was used to assess the CFPWV- and AIx-related multiple-adjusted risk for the presence of significant CAD in relation to obesity measures in all subjects. An interaction term of arterial stiffness measures (pulse wave velocity or AIx at 75) and BMI or WC subgroups was included in each model. Other covariates included in the adjusted logistic regression models were cardiovascular risk factors known to be related with the presence of CAD: male sex, age, smoking, presence of diabetes, presence of hypertension, presence of hypercholesterolemia, estimated glomerular filtration rate, heart rate, high-density lipoprotein cholesterol, and triglycerides. To avoid excessive multicollinearity, the standardized values (Z scores) of the continuous variables were used in multiple-adjusted regression models, and a stepwise method (stepwise logistic regression analysis and backward conditional logistic regression analysis) was also implemented. P values were always 2-sided, and P < 0.05 was considered significant. The SPSS statistical software package (version 15.0 for Windows; SPSS Inc. Chicago, IL) was used.

RESULTS
The median age of our patients was 62 years and most of the patients were men (75%), were smokers (62%), had hypertension (79%), had hypercholesterolemia (70%); about one-third of the total population (34%) had type 2 diabetes. Significant angiographic CAD was found in 202 (51%) patients. The characteristics of our population are shown in Table 1. The descriptive data by subgroups are presented in Supplementary Table 1 online.

CFPWV was positively associated with AIx at 75 (r = 0.163, P = 0.001) in the whole population. The associations (univariate and multivariate) of arterial stiffness indices and obesity measures are presented in detail in Table 2. CFPWV was not associated with BMI in univariate (P = 0.70) or multivariate (P = 0.93) analysis. CFPWV was positively associated with WC in univariate analysis (P = 0.04). This association was no longer significant after adjustment for multiple risk factors and medications known to be related with arterial stiffness (P = 0.35). AIx at 75 was inversely associated with BMI and WC before (P = 0.02 and P < 0.001, respectively) and after multiple adjustment for other risk factors and medications (P < 0.001 for both BMI and WC). CFPWV and AIx values in various obesity subgroups are shown in Figure 1.

Table 1. Descriptives of the population (N = 393)

<table>
<thead>
<tr>
<th>Age, years</th>
<th>62 (35, 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, no. (%)</td>
<td>295 (75)</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>245 (62)</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>312 (79)</td>
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<tr>
<td>Antihypertensive medications, no. (%)</td>
<td></td>
</tr>
<tr>
<td>ACE-I/ARBs</td>
<td>145 (37)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>111 (28)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>210 (53)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>63 (16)</td>
</tr>
<tr>
<td>Nitrates, no. (%)</td>
<td>127 (32)</td>
</tr>
<tr>
<td>Hypercholesterolemia, no. (%)</td>
<td>275 (70)</td>
</tr>
<tr>
<td>Statins, no. (%)</td>
<td>175 (45)</td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>133 (34)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.67 (1.37, 1.90)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>28.39 ±3.59</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>103 ±10</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>65 (45, 100)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>140 ±18</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>82 ±10</td>
</tr>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>101 ±12</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.7 (3.3, 16.4)</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>77.8 ±13.4</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.6 ±1.1</td>
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<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1 (0.3, 2.3)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.7 ±1.1</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.5 (0.5, 4.0)</td>
</tr>
<tr>
<td>Carotid–femoral pulse wave velocity, m/sec</td>
<td>9.1 (3.5, 19.7)</td>
</tr>
<tr>
<td>Augmentation index at 75, %</td>
<td>24.2 ±9.1</td>
</tr>
<tr>
<td>Presence of angiographic CAD, no. (%)</td>
<td>202 (51)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD unless otherwise stated. Not normally distributed continuous variables are presented as median (minimum, maximum).

Abbreviations: ACE-I, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Table 2. Univariate and multivariate associations of arterial stiffness indices and obesity measures

<table>
<thead>
<tr>
<th></th>
<th>Carotid–femoral pulse wave velocity, m/sec</th>
<th>Augmentation index at 75, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Body mass index, kg/m²</td>
<td>Waist circumference, cm</td>
</tr>
<tr>
<td>Univariate analysis</td>
<td>β = 0.020, P = 0.70</td>
<td>β = 0.103, P = 0.04</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td>β = 0.004, P = 0.93</td>
<td>β = 0.041, P = 0.35</td>
</tr>
</tbody>
</table>

Data are presented as standardized coefficient (β), p value. Natural logarithm of pulse wave velocity was used in linear regression models. Standardized values (Z scores) for body mass index and waist circumference were used in linear regression models.

Figure 1. Values of carotid–femoral pulse wave velocity and augmentation index at 75 in various subgroups of overall and central obesity. (a) Carotid–femoral pulse wave velocity in groups with varying body mass indexes and waist circumferences. (b) Augmentation index at 75 in groups with varying body mass indexes and waist circumferences. One way analysis of variance was used to compare arterial stiffness indices among groups (P values). Post hoc analysis was performed with the Bonferroni test. *P < 0.05 vs. both overweight and obese patients in post hoc analysis. †P = 0.04 vs. group 3 in post hoc analysis.
Increased CFPWV was independently associated with the presence of CAD in the entire population in models including either BMI (OR = 1.40, 95% CI = 1.06–1.86, P = 0.019) or WC (OR = 1.49, 95% CI = 1.11–1.99, P = 0.007) as covariates. The association of CFPWV and CAD differed significantly in various obesity-related subgroups (P = 0.04 and P = 0.03 for the interaction of CFPWV with BMI and WC subgroups, respectively). CFPWV was not related with the presence of CAD in normal-weight (P = 0.11) or normal-waist (P = 0.46) subjects but was significantly associated with the presence of CAD in overweight (P = 0.05) and obese (P = 0.02) subjects as well as in subjects with moderate (P = 0.02) and severe (P = 0.01) central obesity. AIx at 75 was not associated with CAD presence either in the entire population or in any of the obesity subgroups (P > 0.05 for all).

DISCUSSION

The results of this study indicate that arterial stiffness as assessed by CFPWV was not associated with obesity, whereas AIx was associated inversely with both BMI and WC. CFPWV was independently associated with angiographic CAD in patients with increased BMI (>25 kg/m²) or WC levels (≥94 cm in men and ≥80 cm in women). AIx was not associated with the presence of angiographic CAD in our population.

CFPWV was positively associated with WC, but not BMI, in univariate analysis, and this association was lost after adjustment for risk factors and medications known to affect arterial stiffness and despite a potential overestimation of the carotid–femoral distance in obese individuals. In agreement with our findings, several previous studies have reported a lack of association of CFPWV with BMI or a positive relation of CFPWV with WC that disappeared after adjustment for various confounders. In contrast, a positive association of CFPWV with obesity, as assessed by BMI, central obesity indices, or visceral fat distribution, has been previously reported. This positive association of increased stiffness to obesity was found to be stronger for central obesity measures rather than BMI and appeared to be weaker in older and hypertensive subjects. A possible explanation for the discrepancy of our finding compared with previous studies that showed an independent association of aortic stiffness and obesity may lie in the older age of our population (most patients aged >60 years), which included a higher proportion of hypertensive subjects (almost 80%), compared with those studies. These factors may have led to a uniform increase in arterial stiffness that probably masked a weak association of obesity with aortic stiffening.

Furthermore, after adjustment for risk factors and medications, we found that increasing CFPWV was associated with the presence of CAD in patients with increased BMI (≥25 kg/m²) or WC levels (≥94 cm in men and ≥80 cm in women). Such an association between arterial stiffness and CAD has been previously shown in other groups of high-risk patients (i.e., those with chronic renal disease and/or hypertension) but has not been previously reported in relation to central or overall obesity. Whether CFPWV may have a more prominent role for CAD risk stratification in patients with overall or central obesity, as opposed to normal-weight patients, warrants further research.

AIx was found to be inversely associated with measures of overall and central obesity, in contrast with what might have been expected based on the positive association between CFPWV with AIx and the weak association of CFPWV with central obesity (in univariate analysis). In agreement with our findings, increased BMI and WC have been previously related to decreased AIx, suggesting lower peripheral wave reflections in subjects with higher values of obesity measures, although not consistently. The different associations of CFPWV and AIx with obesity measures probably reflect the distinct pathophysiological processes evaluated by these two measures (i.e., arterial stiffening (CFPWV) vs wave reflection to central arteries (AIx)).

Finally, AIx was not associated with the presence of CAD in our population. Previous studies in patients undergoing coronary angiography for suspected CAD and patients with chronic kidney disease have reported conflicting results; the largest study that showed a positive, independent association of AIx with CAD presence in men had a very small control group (patients without CAD) that may have reduced the power of the study. It cannot be excluded that the variability of AIx measurements in our study, which were relatively increased compared with the CFPWV measurement, could have contributed to the lack of association of AIx with the presence of CAD.

This was an observational study that could reveal risk associations but could not establish causal relationships or explore potential mechanisms. The confinement of our study to patients at high CAD risk referred for coronary angiography, mostly men with a high percentage of diabetes and poorly controlled hypertension and dyslipidemia, may limit the applicability of our findings to the general population. The relatively small number of patients in the BMI and WC subgroups (especially in the normal-range patients) may limit the ability of the study to determine the associations of arterial stiffness with CAD or investigate the interactions with other potentially relevant parameters.

In conclusion, arterial stiffness indices were not consistently associated with obesity in our population; opposite to what might have been expected, no significant relationship between CFPWV and obesity and an inverse relation of AIx with obesity were found. Increased CFPWV was associated with the presence of angiographic CAD in patients with increased BMI or WC values. Further larger studies are needed to confirm these findings and investigate their clinical implications.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at the American Journal of Hypertension online (http://www.oxfordjournals.org/our_journals/ajh/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.
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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES


