

Carotid–Femoral Pulse Wave Velocity Is Not Increased in Obesity

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BACKGROUND

There are conflicting results in the literature concerning the relationship between obesity and arterial stiffness, assessed by carotid–femoral pulse wave velocity (PWV). The discrepancies could be due to differences in carotid–femoral distance measurement and/or to the presence of pathologies frequently associated with obesity and which increase arterial stiffness. In this study, we examine the relationship between PWV and weight, without and with associated cardiovascular risk factors (diabetes and/or dyslipidemia).

METHODS

PWV was assessed with a Complior SP device (Alam Medical, France) in 2,034 patients referred for ambulatory blood pressure monitoring. The carotid–femoral distance used to calculate PWV was measured with a flexible tape and from the estimated straight carotid–femoral distance obtained with a published equation.

RESULTS

In the whole cohort, PWV did not differ significantly according to weight (9.6 ± 2.1 , 9.8 ± 2.2 and 9.7 ± 1.9 m/s in normal weight,

overweight and obese subjects, respectively, with the distance measured with a tape). PWV was significantly higher in the four groups of patients with cardiovascular risk factors (e.g., 11.1 ± 2.4 , 11.0 ± 2.7 and 10.4 ± 2.0 m/s in normal weight, overweight, and obese subjects, respectively, in the group treated for diabetes and dyslipidemia) than in the group of patients without cardiovascular risk factors (8.5 ± 1.6 , 8.8 ± 1.7 and 8.5 ± 1.2 in normal weight, overweight, and obese subjects, respectively). There was no relationship between PWV value and weight status, whether or not there were cardiovascular risk factors, and whatever the distance used to calculate PWV.

CONCLUSIONS

In our cohort, obesity *per se* was not associated with increased arterial stiffness.

Keywords: arterial stiffness; blood pressure; body mass index; hypertension; pulse wave velocity; obesity.

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Obesity is a world-wide epidemic with massive socioeconomic consequences; in particular, it increases the likelihood of associated pathologies including cardiovascular disease, type 2 diabetes, dyslipidemia, and sleep apnea. Early vascular aging and therefore elevated arterial stiffness, an independent marker of cardiovascular events and mortality, has been found to be associated with all these pathologies.^{1–8}

Therefore, obesity could be expected to be directly related to increased arterial stiffness. However, conflicting results have been reported: in adults, some studies found a positive relationship between obesity and arterial stiffness, assessed as the carotid–femoral pulse wave velocity (PWV)^{9–15} whereas others found no such relationship^{16–21} or even a negative relationship.^{22,23} A recent review²⁴ indicated that only 13% of the relevant publications reported a positive association between body mass index (BMI) and PWV. It is possible that the conflicting results are a consequence of different methodologies being used to measure carotid–femoral distance. Surface

measurements in obese subjects can lead to overestimation of the arterial length.²⁵ From magnetic resonance imaging (MRI) studies, the latest expert consensus advises using the direct distance multiplied by 0.8, and to use sliding calipers if the distance cannot be measured in a straight line with a tape.²⁶ Another possible explanation for the discrepancies between studies is the probable presence of associated cardiovascular risk factors in obese patients such as diabetes and dyslipidemia, contributing to increased arterial stiffness, independently of obesity.

In this study, we examine the relationship between PWV and weight in a large and unselected cohort of patients with a large range of weights, and without or with associated cardiovascular risk factors.

METHODS

Patients were recruited between 2008 and 2012 at the Clinical Pharmacology Unit of Henri Mondor Hospital

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(Créteil, France) where they were referred for 24-hour ambulatory blood pressure monitoring (ABPM). Informed consent was obtained from all patients. The study was approved by local ethics review boards.

All patients referred to the clinical pharmacology unit filled in a standardized questionnaire on their medical history and their cardiovascular risk factors, and underwent a thorough clinical examination by the physician in charge.

PWV was measured after the patient had been resting in supine position for 15 minutes in a quiet, temperature-controlled room. PWV was measured along the carotid–femoral arterial segment by our trained and highly experienced research nurses, using the Complior SP device (Alam Medical, France), on the right side of the patient. For each subject, the mean of two measurements was used. If the difference between the two PWV values exceeded 0.5 m/s, the test with the lowest tolerance was used—the tolerance being a quality parameter provided by the Complior software and representing beat-to-beat variation. We successfully obtained a PWV value for every subject, including obese individuals. Pulse transit time was automatically measured by the validated foot-to-foot method from simultaneous carotid and femoral recordings as previously published.^{27–29} As advised by the latest expert consensus,²⁶ carotid–femoral distance was calculated as surface tape measurements multiplied by 0.8 and used to obtain PWV values (PWVtape).

In obese patients, surface measurements can lead to overestimation of the arterial distance.^{25,26} To overcome this limitation, we determined the straight line surface carotid–femoral distance from the distance measured with a sliding caliper, by applying the recently published equation:²⁵ $D_{0.8\text{-caliper}} = 0.76 \times D_{\text{tape}} - 0.12 \times \text{BMI} + 2.73$, where $D_{0.8\text{-caliper}}$ is the caliper distance multiplied by 0.8 and D_{tape} the surface distance measured with a tape. We then calculated the estimated caliper PWV from the estimated straight line caliper distance (PWVcal).

Weight and height were measured with a digital scale in a standing position without shoes and are expressed in kilograms and centimeters, respectively. Waist and hip circumferences were measured in a standing position using a flexible tape measure. BMI was calculated as the weight divided by the height in meters squared. Subjects were classified according to World Health Organization (WHO) standards as normal (BMI < 25 kg/m²), overweight (25 ≤ BMI < 30 kg/m²), or obese (BMI ≥ 30 kg/m²).

We also divided our cohort into five groups according to cardiovascular risk factors which are potentially confounding factors with obesity: patients with no known cardiovascular risk factor and no history of clinical cardiovascular disease; patients treated for type 2 diabetes; patients treated for dyslipidemia; patients treated for both type 2 diabetes and dyslipidemia; and patients with cardiovascular risk factors (CVD group) other than type 2 diabetes and dyslipidemia, including hypertension or personal history of stroke or coronary artery disease or peripheral vascular disease. Patients were classified as diabetic or dyslipidemic if currently treated with antidiabetics or drugs used for treating dyslipidemia, respectively. Patients were classified as hypertensive if currently treated with antihypertensive drugs or diagnosed as hypertensive on the basis of 24-hour ABPM

according to European guidelines, i.e., systolic blood pressure day ≥ 135 mm Hg and/or diastolic blood pressure day ≥ 85 mm Hg or systolic blood pressure night ≥ 120 mm Hg and/or diastolic blood pressure night ≥ 70 mm Hg.

Data were analyzed using SAS software (SAS 9.0, Cary, NC). Continuous values are expressed as means ± SD. Qualitative data are expressed as numbers (percentage). Comparisons involved using t-tests for normally distributed data, Wilcoxon Rank Sum tests for non-normal continuous data and chi-square tests for qualitative variables. Velocities were not normally distributed, so associations between velocities and continuous values were assessed with Spearman correlations. The PWV values presented are uncorrected, but for calculation of correlations, PWV values were adjusted for age and mean arterial pressure, calculated as [diastolic pressure + (systolic pressure – diastolic pressure)/3] with systolic and diastolic blood pressure values measured just before PWV measurements. Differences were considered to be statistically significant if $P < 0.05$ and coefficients of correlations were defined as negligible if $R < 0.2$ even if statistically significant ($P < 0.05$).

RESULTS

The study included 2,304 patients. The characteristics of this study population according to the BMI are shown in Table 1. The mean age was 56 years, consistent with populations of patients referred for 24 hours blood pressure monitoring generally. The BMI range was from 16.7 to 49.7 kg/m² (mean ± SD: 28.7 ± 5.0 kg/m²). The proportions of patients with hypertension, type 2 diabetes, and dyslipidemia increased with body weight (Table 1).

As expected, in the population as a whole, PWVtape was higher than PWVcal (0.6 ± 0.2 m/s, $P < 0.001$), PWVtape and PWVcal increased with age (for both, $R = 0.49$, $P < 0.001$) and mean blood pressure (for both, $R = 0.25$, $P < 0.001$). Similar

Table 1. Patient characteristics according to BMI category

	Normal weight	Overweight	Obese
<i>N</i>	561	905	838
Women (%)	50	34	42
Age (years)	54.6 ± 14.4	58.1 ± 12.1	56.6 ± 12.1
BMI (kg/m ²)	22.8 ± 1.8	27.5 ± 1.4	34.1 ± 3.5
Waist circumference (cm)	82.4 ± 8.0	95.6 ± 7.3	109.5 ± 10.2
Waist-to-hip ratio	0.86 ± 0.07	0.92 ± 0.07	0.96 ± 0.08
Hypertension (%)	77	82	90
Diabetes (%)	15	28	40
Dyslipidemia (%)	29	42	49
Heart rate (bpm)	66 ± 11	65 ± 11	67 ± 12
MAP (mm Hg)	99 ± 11	100 ± 11	102 ± 11

Data are means + SD. $P < 0.05$ between the three groups for all values.

Abbreviations: BMI, body mass index; MAP, mean arterial pressure.

results were obtained within each BMI group. Carotid–femoral transit time increased slightly but significantly with increasing BMI (Table 2). The difference between surface tape measurement distance and estimated straight line distance increased with increasing BMI (0.4 ± 0.1 , 0.5 ± 0.1 and 0.7 ± 0.2 m/s for normal weight, overweight, and obese respectively, $P < 0.001$). However, neither PWVtape nor PWVcal differed significantly within the three BMI groups (Table 2). There was no increase in PWVtape or PWVcal with BMI as a continuous variable, or with waist circumference or waist-to-hip ratio. In addition, we did not observe any difference in the relationship of PWV with central or peripheral obesity (PWVtape: $R = -0.02$, $P = 0.64$; PWVcal: $R = -0.02$, $P = 0.61$).

The characteristics of the patients according to their cardiovascular risk factors are shown in Table 3. Patients with dyslipidemia, diabetes, or both were older and had a higher BMI than patients with no cardiovascular risk factor. PWVtape and PWVcal were higher in the four groups of patients with cardiovascular risk factors than in the group of patients with no cardiovascular risk factor (Table 3, $P < 0.001$). However, PWVtape did not differ significantly according to BMI within each cardiovascular risk group (Figure 1). The findings were similar with PWVcal and when waist circumference and waist-to-hip ratio were used as measured of obesity.

DISCUSSION

Obesity is directly related to the occurrence of pathologies, generally leading to early vascular aging. However, in our cohort of more than 2,300 patients, we did not find any relationship between PWV and BMI, whatever the measure of the carotid–femoral distance used for the calculation of PWV (whether surface measurement with a flexible tape or straight line distance estimated by using an equation we recently published).²⁵ In addition, we did not find any relationship between PWV and BMI in subgroups of patients classified according to the presence or absence of various cardiovascular risk factors.

We tested the hypothesis that the positive association between BMI and PWV found by some authors might be due to the use of surface distance measurements; this approach may overestimate PWV and hence lead to artificially high PWV values for obese subjects. Indeed, none of the published studies used the recently recommended D0.8 method

and all studies finding a positive relationship between obesity and PWV used tape measurements; also, at least two of these studies reported an influence of BMI in women but not in men.^{17,19} As large breasts could lead to overestimation of the distance,³⁰ this would be coherent with errors in distance measurements. As we previously reported,²⁵ correcting for carotid–femoral straight-line distance measurements with a caliper has a larger influence on PWV values for obese than normal weight subjects. Nevertheless, we did not find any relationship between arterial stiffness and BMI, whether surface measurements or estimated straight line distance was used. Our results are in agreement with those of Rider *et al.*¹⁸ who measured aortic PWV with MRI and hence had access to the true distance. What is more, they measured PWV in segments of the aorta, a pure elastic artery which is thus more prone than muscular arteries to vascular aging. However, they did not observe any difference in aortic PWV between obese and normal patients, entirely consistent with our results.

As discussed by Rodrigues *et al.*,²³ the finding of an apparent positive relationship in some groups could be the consequence of the association of obesity with diabetes and/or dyslipidemia, both of which accelerate vascular aging. It may not be the excess of body fat but rather the associated disease that increases arterial stiffness. For example, Recio-Rodriguez *et al.*¹⁰ found that an increase of BMI of 1 kg/m^2 led to an increase of 0.052 m/s in PWV, corresponding to about six months of vascular aging. However, 33% of the subjects in the study were diabetic. Our cohort was large, so we could identify subgroups of patients with and without various cardiovascular risk factors that were large enough to have sufficient statistical power to test for possible relationships between BMI and PWV. Groups with cardiovascular risk factors had higher arterial stiffness than patients with no known cardiovascular risk; within each group, there was no relationship between PWV values and weight. Therefore, elevated BMI does not appear to be associated with greater arterial stiffness. However, this does not preclude the possibility that a reduction of obesity could lead to improvement in PWV. Indeed, significant weight loss has been reported to improve PWV.^{18,31}

Cecelja *et al.*²⁴ reviewed all articles relating PWV to cardiovascular risk factors up to December 2008 and report that a relationship between BMI and PWV was found in only 13% of the studies. We extended this analysis to another ten articles, published since December 2008, specifically looking at the relationship between BMI and carotid–femoral PWV.^{10,11,13–15,17,20–23} Only 10 of the total of 62 studies (16%) found a positive association between BMI and PWV. One study looked very specifically at body fat and its relation to age and arterial stiffness:²² it found a negative relationship until middle age and then a positive relationship at older ages; this suggests a J-shape curve which would have been missed by standard multivariate analysis and might explain the discrepancies in the literature. In our cohort, we did not observe any difference with age (data not shown), but our cohort was older and with a smaller age range.

Obesity is usually considered to be a major cardiovascular risk factor and the paradoxical absence of relationship (or

Table 2. Transit time and PWV values according to BMI category

	Normal weight (n = 561)	Overweight (n = 905)	Obese (n = 838)	P value
Transit time (ms)	53 ± 11	54 ± 11	57 ± 11	<0.001
PWVtape (m/s)	9.6 ± 2.1	9.8 ± 2.2	9.7 ± 1.9	NS
PWVcal (m/s)	9.2 ± 2.0	9.2 ± 2.1	9.0 ± 1.8	NS

Data are mean + SD.

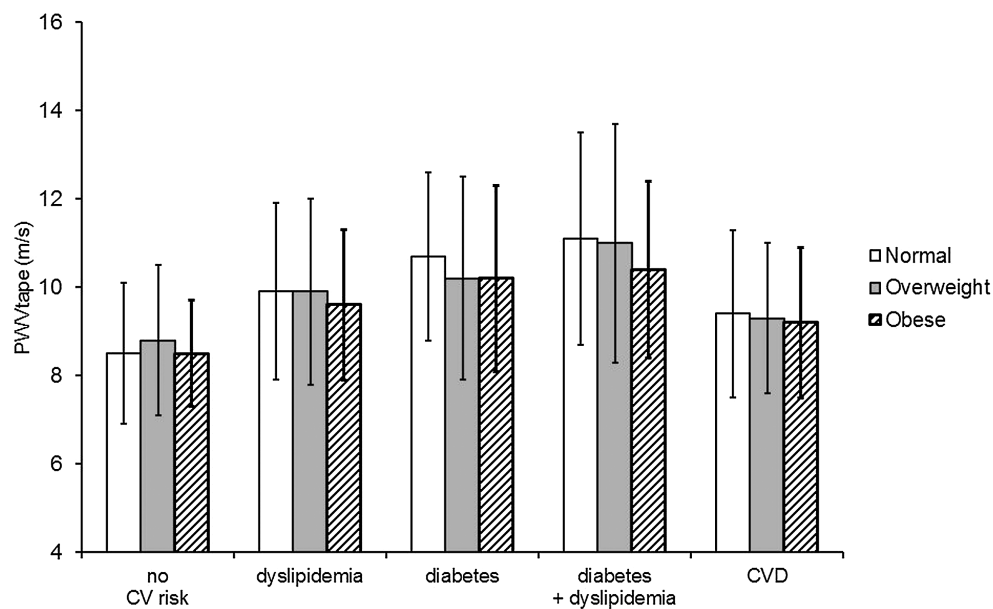
Abbreviations: PWVtape, carotid–femoral pulse wave velocity calculated from surface tape measurement; PWVcal, carotid–femoral pulse wave velocity calculated from estimated straight-line distance.

Table 3. Patient characteristics according to cardiovascular risk factor

	No CV risk	Dyslipidemia	Diabetes	Dyslipidemia and diabetes	CVD
<i>N</i>	240	487	197	469	911
Women (%)	60	40	46	33	45
Age (years)	49±13	63±11	57±10	63±9	52±13
BMI (kg/m ²)	27±4	29±5	31±5	31±5	28±5
BMI status (<i>n</i> (%))					
Normal	97 (40)	110 (23)	27 (14)	55 (12)	272 (30)
Overweight	102 (43)	201 (41)	70 (35)	183 (39)	349 (38)
Obese	41 (17)	176 (36)	100 (51)	231 (49)	290 (32)
Hypertension (%)	0	90	87	95	96
Heart rate (bpm)	66±10	63±11	70±12	66±12	67±11
MAP (mm Hg)	93±7	99±10	102±11	100±11	104±11
TT (ms)	60±10	54±11	53±11	51±11	56±10
PWVtape (m/s)	8.6±1.6	9.8±1.9	10.3±2.1	10.7±2.3	9.3±1.7
PWVcal (m/s)	8.2±1.5	9.3±1.9	9.6±2.0	10.1±2.2	8.8±1.7

Data are means ± SD. *P* < 0.05 between the five groups for all values.

Abbreviations: BMI, body mass index; CVD, patients with cardiovascular risk factors other than diabetes and dyslipidemia; MAP, mean arterial pressure; PWVtape, carotid–femoral pulse wave velocity calculated from surface tape measurement; PWVcal, carotid–femoral pulse wave velocity calculated from estimated straight line distance; TT, carotid–femoral transit time.

**Figure 1.** PWVtape values according to BMI group and cardiovascular risk.

even negative relationship) seems very surprising at first. However, a recent meta-analysis of obesity and mortality indicated that slightly elevated BMI was actually protective against CV diseases.³² This meta-analysis included data for 2.88 million individuals in 97 studies and found that overweight subjects (BMI of 25–30 kg/m²) had the lowest mortality whereas normal weight (BMI < 25 kg/m²) and grade 2–3 obesity (BMI > 35 kg/m²) was associated with higher mortality.

Limitations

Our recruitment was cross-sectional, based on subjects referred to our unit for ambulatory blood pressure monitoring. Despite its size, our cohort may not represent the standard general population and recruitment bias cannot be excluded. Obesity was assessed from BMI, waist circumference, and waist-to-hip ratio only. These measures might not correctly describe body fat composition and distribution,

but they do however represent standard clinical practice and are consistent with the WHO's BMI category definitions.

In our cohort, obesity *per se* is not associated with elevated arterial stiffness. Previous studies suggesting such a relationship may have suffered from technical or recruitment biases. Careful characterization of study populations and adjustment for age, blood pressure, and concomitant cardiovascular-related disease are required to elucidate the consequences of obesity for arterial structure and function.

DISCLOSURE

Sandrine Millasseau works as a freelance specialist on pulse wave analysis and receives revenues from several medical device companies including Alam Medical whose device was used in this study. None of the other authors declare any conflict of interest.

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