

# Pulse Pressure and Aortic Pulse Wave Are Markers of Cardiovascular Risk in Hypertensive Populations

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**Background:** Pulse pressure (PP) and aortic pulse wave velocity (PWV) are significant markers of cardiovascular risk, but a similar role for central wave reflections has never been investigated.

**Procedures:** To determine the factors influencing PP, PWV, and carotid wave reflections, a cohort of 1087 patients with essential hypertension either treated or untreated was studied cross-sectionally. Atherosclerotic alterations (AA) were defined on the basis of clinical events and PWV evaluated from an automatic device. The carotid amplification index (CAI), a quantitative estimation of the magnitude of central wave reflections, was measured non-invasively from pulse wave analysis using radial and carotid aplanation tonometry.

**Results:** In the overall population, age and mean arterial pressure represented 30.4%, 32.3%, and 5.6% of the

variance of, respectively PP, PWV, and CAI. For the latter, body weight and heart rate represented 22.9% of variability. On the basis of logistic regression, AA were associated, in addition to age, plasma creatinine and HDL cholesterol levels, and tobacco consumption to three mechanical factors, increased PP, increased PWV, and low diastolic blood pressure, but not by CAI (adjusted odds ratio: 1.00; 95% confidence intervals: 0.99-1.01).

**Conclusion:** In cross-sectional hypertensive populations, PP and PWV, but not CAI, are significantly and independently associated with cardiovascular complications. Am J Hypertens 2001;14:91-97 © 2001 American Journal of Hypertension, Ltd.

**Key Words:** Cardiovascular risk, hypertension, pulse pressure, aortic pulse wave velocity, carotid wave reflections.

**I**ncreased brachial pulse pressure (PP) is an independent marker of cardiovascular (CV) risk, mainly for myocardial infarction, congestive heart failure, and CV deaths.<sup>1-6</sup> The predictive value of PP is influenced both by an increase of systolic blood pressure (SBP) and a decrease of diastolic blood pressure (DBP). Epidemiologic studies have shown that CV mortality is positively related to the level of SBP.<sup>7-9</sup> However, at any given value of SBP, CV mortality is higher when DBP is lower.<sup>9</sup> In fact, the predictive value of PP might result from two different pathophysiologic mechanisms. On one hand, increased SBP influences the level of end-systolic stress and promotes cardiac hypertrophy.<sup>1,5</sup> On the other hand, reduced DBP alters coronary perfusion and therefore, favors myocardial ischemia.<sup>2,5,6,10,11</sup>

Increased PP is the result of both cardiac and arterial factors, including ventricular ejection, arterial stiffness,

and modifications of the amplitude and timing and site of wave reflections.<sup>11</sup> Because in older subjects, ventricular ejection is normal or even decreased, the main determinants of PP in such conditions are increased arterial stiffness and altered wave reflections. The role of arterial stiffness as a marker of CV risk has been documented substantially in subjects with end-stage renal disease and in subjects with essential hypertension and preserved renal function.<sup>12-15</sup> In addition to pulse pressure and other confounding variables, aortic pulse wave velocity (PWV) is an independent identifier of CV risk. The only mechanical factor acting on CV risk in addition to PWV is a low (and not high) DBP.<sup>12-14</sup> In contrast, the role of wave reflections as a marker of CV risk has not been extensively explored. It has been reported that an early return of the backward pressure wave is a factor influencing the degree of cardiac hypertrophy in hypertension,<sup>11</sup> but the link of

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**Table 1.** Population description ( $n = 1087$ )

	Mean $\pm$ Standard Deviation	Min-Max
Men:women ( $n$ , %)	616 (57%):471 (43%)	
Age (yr)	58.46 $\pm$ 13.67	45–90
Weight (kg)	75.5 $\pm$ 14.9	39–157
Height (m)	1.68 $\pm$ 0.09	1.40–2.00
BMI (kg/m <sup>2</sup> )	26.64 $\pm$ 4.35	17.15–46.37
SBP (mm Hg)	143.59 $\pm$ 19.74	97–213
DBP (mm Hg)	81.94 $\pm$ 11.97	50–136
MBP (mm Hg)	102.49 $\pm$ 12.61	71–153
PP (mm Hg)	61.65 $\pm$ 17.30	30–143
Heart rate (beats/min)	67.60 $\pm$ 10.35	41–112
Total plasma cholesterol (mmol/L)	5.56 $\pm$ 1.08	1.18–11.22
HDL plasma cholesterol (mmol/L)	1.34 $\pm$ .40	0.55–3.33
Plasma glucose (mmol/L)	6.08 $\pm$ 1.53	3.70–21.60
Tobacco consumption (pack/yr)	11.9 $\pm$ 18.3	0–107
Plasma creatinine ( $\mu$ mol/L)	91.48 $\pm$ 29.12	38–300
Carotid amplification index (%)	21.5 $\pm$ 21.0	–35–69
PWV (m/sec)	12.63 $\pm$ 3.10	6.40–30.19

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure; PWV = pulse wave velocity.

altered wave reflections with CV events has never been investigated in the literature.

The purpose of the present cross-sectional study is, in a population of subjects with essential hypertension either treated or untreated, to investigate whether arterial stiffness measured from aortic PWV or carotid wave reflections, evaluated with tonometry, were significant and independent markers of CV risk.

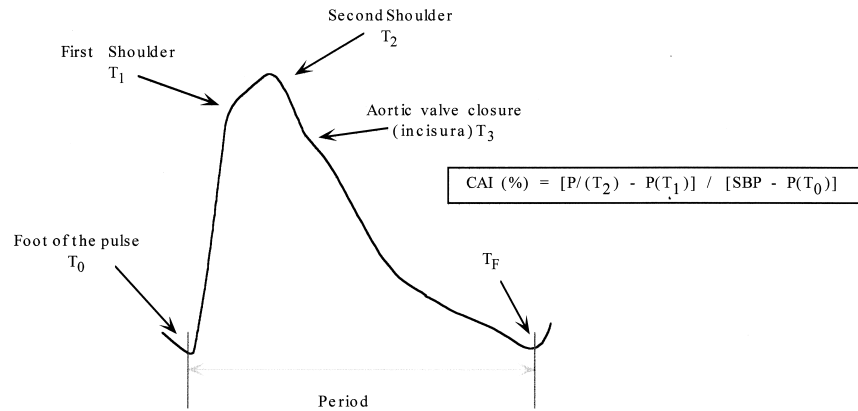
## Methods

### Study Cohort

From January 1997 to June 1999, 1470 patients entered the Department of Internal Medicine of Broussais Hospital for a CV check-up ordered by their general practitioner or their cardiologist because of the presence of one or several CV risk factors involving high blood pressure (BP), smoking, dyslipidemia, diabetes mellitus, a family history of premature CV disease, with or without previously identified atherosclerotic alterations (AA). From those 1470 patients, only subjects with essential hypertension ( $n = 1087$ ) were selected. In never-treated hypertensive subjects ( $n = 217$ ), high BP was defined as a SBP  $\geq 140$  mm Hg or a DBP  $\geq 90$  mm Hg, measured by mercury sphygmomanometry in the supine position with a minimum of three casual measurements during the past month. In treated hypertensive subjects ( $n = 870$ ), patients were included regardless of whether or not BP was well controlled (SBP  $< 140$  mm Hg and DBP  $< 90$  mm Hg). Patients with all forms of secondary hypertension on the basis of classic laboratory and radiology tests<sup>12,13</sup> were not included. Patients with cancer (other than basal cell carcinoma), with insulin-dependent diabetes, or with severe renal insufficiency (plasma creatinine  $> 300$  mmol/L) were

not included in this study. The study cohort was composed of 1087 consecutive hypertensive patients (616 men, 471 women) with mean age ( $\pm 1$  standard deviation [SD]) of  $58 \pm 14$  years. From the 870 (80%) patients treated with antihypertensive therapy at inclusion, the mean number of antihypertensive drugs was  $1.51 \pm 1.02$  per patient. The antihypertensive drugs included calcium antagonists (43%), diuretics (38%),  $\beta$ -blocking agents (37%), angiotensin converting enzyme inhibitors (32%), central-acting agents (14%), angiotensin II antagonists or  $\alpha$ -blockers (2%), either alone or in combination. One hundred fifty-seven patients (14%) were medically treated for dyslipidemia (drugs including statins or fibrates). Seventy-three (7%) patients were medically treated for diabetes mellitus (drugs including sulfamids or biguanids). Each subject provided informed consent for the study, which was approved by our institutional review board. Clinical characteristics of the population are indicated in Table 1.

Information compiled from the questionnaire filled out at inclusion included gender, age, weight and height, body mass index, family (first-degree relatives) history of premature CV events ( $< 55$  years old in men and  $< 60$  in women), personal history of diabetes mellitus or dyslipidemia, smoking habits, previous diseases, and use of medications including antihypertensive drugs. From the clinical questionnaire and the findings of the check-up during hospitalization, AA was present in 248 patients and absent in 839 patients. For a description of AA in hypertensive patients, the usual criteria were used according to the International Classification of Diseases (ninth revision) for coronary heart disease (CHD), cerebrovascular disease, peripheral vascular disease, and abdominal aortic aneurysm. Dyslipidemia was defined as a total/HDL cholesterol ratio  $> 5$  or the presence of a hypocholesterolemic



**FIG. 1.** Carotid pressure waveform analysis with applanation tonometry. After the foot of the pulse ( $T_0$ ) indicating the onset of ejection, the pressure wave increases to an initial peak where it forms a shoulder ( $T_1$ ). It then proceeds to a second shoulder ( $T_2$ ), which often constitutes the peak pressure in the elderly. The former point is related to timing of peak flow, whereas the second shoulder to reflected waves. The end of ejection ( $T_3$ ) is associated with closure of the aortic valve.  $T_F$  represents the end of the pulse.  $P$  = pressure; SBP = systolic blood pressure; CAI = carotid amplitude index.

drug (statins or fibrates). Diabetes mellitus was defined as a fast glycemia  $>7.8$  mmol/L or the presence of hypoglycemic agents (sulfamids or biguanids).

Two hundred forty-eight patients had AA involving at least one vascular site, including CHD (134 patients), peripheral vascular disease (76 patients), cerebrovascular disease (38 patients), and abdominal aorta aneurysm (43 patients). The extent of atherosclerosis was assessed as the number of vascular sites involved by AA: 0 (839 patients), 1 (174 patients), 2 (56 patients), or 3 (18 patients).

### Hemodynamic and Biological Investigations

The measurements were performed in the morning after an overnight fast, each patient being in supine position. Brachial BP was measured in both arms with a mercury sphygmomanometer after 15 min of rest. Phases I and V of the Korotkoff sounds were considered, respectively, as SBP and DBP. The mean BP (MBP) was calculated as  $MBP = DBP + (SBP - DBP)/3$ . Five measurements 2 min apart were averaged. Pulse pressure was the difference between SBP and DBP.

Heart rate was determined from the three-lead orthogonal electrocardiogram. Venous blood samples were obtained in subjects after an overnight fast. Plasma was separated without delay at  $4^\circ\text{C}$  in a refrigerated centrifuge and stored at  $4^\circ\text{C}$  (for the determination of routine chemistry profile by standard methods) until analysis. Total cholesterol and triglycerides were determined with the use of standard methods,<sup>12–14</sup> and HDL cholesterol was measured in the supernatant after precipitation of apolipoprotein B-containing lipoproteins with heparin-manganese chloride. Low-density lipoprotein cholesterol was calculated for patients with serum triglyceride concentration  $<4.0$  mmol/L, as previously described.<sup>13</sup>

After BP determination, the PWV measurement was performed before the three-lead orthogonal electrocardio-

gram and blood sample in a controlled environment at  $22 \pm 2^\circ\text{C}$ . Aortic pulse wave velocity was determined with the use of an automatic device: the Complior (Colson, Paris, France), which allowed an online pulse wave recording and automatic calculation of PWV with two transducers, one positioned at the base of the neck for the common carotid artery and the other over the femoral artery, as previously published.<sup>16</sup> The validation of this automatic method and its reproducibility have been described previously, with an intraobserver repeatability coefficient of 0.935 and an interobserver reproducibility coefficient of 0.890.<sup>16</sup>

In 548 patients, the radial artery pressure waveform was recorded noninvasively with a tonometer involving a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments, Houston, TX) on a Gould 8188 recorder (Gould Electronics, Ballainvilliers, France) at 100 mm/sec. Then the common carotid artery pressure waveform was obtained using a validated transfer function.<sup>11,17</sup> The carotid pressure wave was analyzed according to Murgu et al<sup>18</sup> and the carotid augmentation index (CAI in percent), which represents the effect of arterial wave reflections on BP in central arteries,<sup>11,19</sup> was calculated according to Fig. 1. In 50 subjects, we verified that CAI measured using either transfer function or local carotid tonometry gave similar results. Validation and reproducibility of the measures have been published previously in detail,<sup>11,17,20,21</sup> making CAI an index at least as sensitive as PWV. Systolic BP and PP may increase from central to peripheral arteries, whereas the diastolic or mean BP decreases from the ascending aorta to the radial artery, but the decrease does not exceed 2 to 3 mm Hg.<sup>21</sup> Therefore, the carotid pressure wave was calibrated assuming that brachial and carotid diastolic and mean BP were equal. The mean BP on the carotid pressure wave was computed from the area of the carotid pressure wave in the corresponding heart period

**Table 2.** Stepwise linear regression of pulse pressure ( $n = 1087$ )

	Reg. Coeff.	SE	Part. Adj R <sup>2</sup>	Sum. Adj. R <sup>2</sup>	P
Age (yr)	0.50	0.03	16.3%	16.3%	.0001
MBP (mm Hg)	0.52	0.04	14.2%	30.4%	.0001
Plasma glucose (mmol/L)	1.48	0.30	1.3%	31.7%	.0001
Weight (kg)	-0.07	0.03	0.6%	32.3%	.0023
Heart rate (beats/min)	-0.09	0.04	0.2%	32.6%	.0633
Gender (M:W)	2.39	1.05	0.3%	32.8%	.0525
Tobacco consumption (pack/yr)	0.04	0.03	0.2%	33.0%	.1235

Body height, HDL cholesterol, creatininemia, and antihypertensive treatment were not significantly linked to pulse pressure.

M = men; W = women; Reg. Coef = regression coefficient; SE = standard error; Part adj = partially adjusted; Sum. adj = Sum of all partial r<sup>2</sup> at each step of the stepwise regression.

Abbreviations: see text and Table 1.

and set equal to the brachial BP. The CAI was then computed from DBP and the position of MBP on the carotid pressure wave.<sup>21</sup> The hemodynamic and biologic characteristics of the population are detailed in Table 1.

### Statistical Analysis

Data are expressed as mean  $\pm$  SD or percentage if there were categorical variables. In this latter case, the  $\chi^2$  test of repartition was used. Adjusted  $\chi^2$  test of Fisher's test exact repartition was used when the expected number was less than 5. "r" test of correlation was used to test whether the correlation of the slopes of PP, PWV, or CAI was different from zero compared with other parameters. Analysis of variances and F test was used to identify whether the mean of PP, PWV, or CAI was different in relation to other categorical variables. Multiple linear stepwise regression was used to find which parameter explained PWV, PP, or CAI variations (considered as independent one from the other) among CV factors (clinical or biochemical). Prognostic variables for the presence of AA was searched by a multiple logistic stepwise regression involving parameters when simple comparison coefficients were more than 0.15. When necessary, adjustments were made in these analyses with pertinent parameters. In the case of antihypertensive drug treatment, the adjustment was made both in terms of number of drugs and class of drug. For the final model in the stepwise regression, we have encoded the arterial parameters and the age according to the standard deviation

of each parameter. Therefore, units for the logistic regression were 1 SD. Studies were performed with SAS 6.7 version (Cary, NC) using Windows NT. A value of  $P = .05$  was considered significant.

### Results

Tables 2, 3, and 4 show the stepwise linear regression of brachial PP, PWV, and CAI. Factors influencing PP were age ( $P < .0001$ ), MBP ( $P < .0001$ ), plasma glucose ( $P < .0001$ ), body weight ( $P < .0023$ ), heart rate ( $P < .0633$ ), and gender ( $P < .0525$ ) (Table 2). Age and MBP represented 30.4% of the total variance and the remaining factors represented only 2.6%. Factors influencing PWV were age ( $P < .0001$ ), MBP ( $P < .0001$ ), plasma creatinine ( $P < .0001$ ) and glucose ( $P < .0001$ ) levels, heart rate ( $P < .0001$ ), gender ( $P < .0001$ ), and tobacco consumption ( $P = .035$ ) (Table 3). Age and MBP represented 32.3% of the total variance and all the remaining factors 6.8%. Factors influencing CAI were body height ( $P < .0001$ ), heart rate ( $P < .0001$ ), MBP ( $P < .0001$ ), age ( $P < .0009$ ), gender ( $P < .0003$ ), and tobacco consumption ( $P < .0078$ ) (Table 4). Body height, heart rate, MBP, age, and gender represented 30.3% of the total variance. For PP, PWV, and CAI, plasma HDL cholesterol, and the presence of antihypertensive treatment (either in term of number or of class of drug) did not enter into any of the three stepwise linear regressions.

**Table 3.** Stepwise linear regression of pulse wave velocity ( $n = 1087$ )

	Reg. Coeff.	SE	Part. Adj R <sup>2</sup>	Sum. Adj. R <sup>2</sup>	P
Age (yr)	0.114	0.006	25.5%	25.5%	.0001
MBP (mm Hg)	0.052	0.006	6.8%	32.3%	.0001
Plasma Creatinine (mmol/L)	0.013	0.003	2.3%	34.6%	.0001
Plasma glucose (mmol/L)	0.265	0.050	2.0%	36.6%	.0001
Heart rate (beats/min)	0.037	0.008	1.3%	37.9%	.0001
Gender (M:W)	-0.570	0.174	1%	38.9%	.0001
Tobacco consumption (pack/yr)	0.009	0.004	0.3%	39.1%	.0350

Body height, weight, plasma HDL cholesterol, and antihypertensive treatment were not significantly linked to pulse wave velocity. Abbreviations: see text and Tables 1 and 2.



**Table 4.** Stepwise linear regression of carotid index amplification ( $n = 548$ )

	Reg. Coeff.	SE	Part. Adj R <sup>2</sup>	Sum. Adj. R <sup>2</sup>	P
Body height (m)	-57.12	10.92	11.4%	11.4%	.0001
Heart rate (beats/min)	-0.75	0.08	11.4%	22.9%	.0001
MBP (mm Hg)	0.42	0.06	4.2%	27.1%	.0001
Gender (M:W)	8.27	2.09	1.8%	28.9%	.0003
Age (yr)	0.21	0.06	1.4%	30.3%	.0009
Tobacco consumption (pack/yr)	0.11	0.04	0.9%	31.2%	.0078
Plasma creatinine ( $\mu\text{mol/L}$ )	-0.05	0.03	0.3%	31.5%	.1065

Body weight, plasma HDL cholesterol, plasma sugar, and antihypertensive treatment were not significantly linked to carotid amplification index.

Abbreviations: see text and Tables 1 and 2.

In the logistic stepwise regression of AA, age ( $P < .0001$ ), gender ( $P < .0109$ ), tobacco consumption ( $P < .004$ ), plasma HDL cholesterol ( $P < .0343$ ) and plasma creatinine ( $P < .0001$ ) levels were significantly associated with AA. Diabetes entered in the logistic regression only in the absence of plasma creatinine. Among the mechanical factors influencing AA, two models could be described involving either PP alone ( $P < .0001$ ) or PWV ( $P < .0001$ ) together with DBP ( $P < .0001$ ). However, it is important to note that DBP entered only as a negative correlation. Mean blood pressure and CAI did not enter into the logistic regression.

Table 5 shows that, after adjustment to plasma glucose, HDL cholesterol, plasma creatinine, tobacco consumption, age, and gender, only three parameters related to mechanical factors emerged as significant: increased PP, increased PWV, and decreased DBP. The adjusted odds ratios for CAI (1.00; confidence intervals: 0.99–1.01) and MBP (data not shown) were not significant.

**Table 5.** Stepwise logistic regression of atherosclerotic alterations with principal (significant) arterial or biological parameters

	Adjusted OR	95% CI Lower	95% CI Upper
Tobacco consumption (pack/yr)	1.424	1.205	1.682
Plasma creatinine ( $\mu\text{mol/L}$ )	1.404	1.208	1.630
HDL cholesterol (mmol/L)	0.810	0.682	0.961
Age (yr)	1.495	1.221	1.831
Pulse pressure (mm Hg)	1.202	1.024	1.411
DBP (mm Hg)	0.786	0.662	0.933
PWV (m/sec)	1.354	1.139	1.610

OR = odd ratio adjusted to all the other parameters indicated in the logistic regression; CI = confidence intervals; other abbreviations: see text and Tables 1 and 2.

Plasma glucose (g/L, unit = 1 SD), Plasma triglyceridemia (g/L, unit = 1 SD) were not significantly linked to the presence of AA.

All units in the model were equal to 1 SD of each parameter.

## Discussion

The studied population was composed of patients entering the Department of Internal Medicine of Broussais Hospital for a CV check-up, and including young and old hypertensive subjects, with and without hypertensive drug treatment. Although a significant proportion of patients (25%) had confirmed AA, this proportion was probably underestimated, including unrecognized silent myocardial ischemia or cerebrovascular disease, as invasive explorations were not systematically performed. Taking into account these observations, the salient finding of this study was that, in this cohort of hypertensive subjects, increased PP and aortic PWV, but not increased CAI, were significantly and independently associated with the presence of CV diseases. The findings were not influenced by the presence of antihypertensive drug treatment.

In the present study we used PWV as a direct marker of aortic stiffness, because it is related to the square root of the elasticity modulus and to the thickness-to-radius ratio of the aorta.<sup>11</sup> For a given ventricular ejection and CAI, PP may be considered only as an indirect marker of arterial elasticity. The PWV determined using a foot-to-foot transit time in the aorta offers a simple, reproducible, and noninvasive evaluation of regional aortic stiffness.<sup>11,13,16</sup>

This noninvasive superficial measurement allows only an estimate of the distance traveled by the pulse, and accurate measurements of this distance are obtained only with invasive procedures. As a result of this fact, some investigators suggested a possible correction based on anatomic dimensions of the body, whereas other researchers recommended subtracting the distance between the suprasternal notch to the carotid location from the total distance when the carotid pulse is recorded instead of the aortic arch pulse, because the pulse travel is in the opposite direction.<sup>11,16</sup> In fact, because arteries become longer and tortuous with age, the path lengths determined from superficial linear measurements are underestimated. Repeatability studies, checks made with Bland and Altman diagrams,<sup>22</sup> and modern computer technology,<sup>16</sup> now make it feasible to simply investigate aortic stiffness in CV epidemiologic studies. Because the two principal factors modulating the level of PWV

and PP were age and MBP (Tables 3 and 4),<sup>11</sup> clinical results should be adjusted to these two variables, which represent about 30% of total variance.

In this population, the presence of AA was influenced by conventional CV risk factors such as HDL cholesterol, tobacco consumption, and plasma creatinine. However, the dominant findings of the logistic regression were the hemodynamic pattern of the mechanical factors influencing the presence of AA. First, MBP was not involved. Second, either increased PP alone, or an association of high PWV and low DBP, had to be considered in this study. For the interpretation of the results, it is important to note that the consequences of arterial stiffening on BP are not only increased SBP and PP, but also decreased DBP at any given mean BP value.<sup>9,10</sup> In fact increased PP, decreased DBP, and increased PWV are related to the same common denominator, namely increased aortic stiffness, a parameter that is significantly associated with increased CV risk.<sup>1,2,10,12–15</sup> From this observation, it is not surprising that, in our population of hypertensive subjects, increased PP and PWV and low DBP might be significant markers of CV events. In recent longitudinal studies, we and other investigators have shown that increased PP, the major hemodynamic consequence of increased aortic PWV, was a strong independent marker of CV mortality, mainly due to myocardial infarction, in populations of normotensive and hypertensive subjects.<sup>1–6,9,10</sup> The higher degree of CV mortality was observed in subjects who developed isolated systolic hypertension and exhibited both a decrease in DBP and an increase in SBP during the long-term follow-up.<sup>23</sup>

In the present study, results were totally different for CAI, a quantitative evaluation of the alterations of the amplitude and timing of wave reflections in the central (carotid) arteries. Studies of pulsatile arterial hemodynamics indicate that the aortic BP curve may be considered as the mathematical summation of an incident pressure wave coming from the heart and propagating along the arterial tree, and a reflected wave, returning to the heart from reflection sites normally located at the level of resistant vessels.<sup>11</sup> The forward wave is influenced by the pattern of ventricular ejection and the degree of aortic stiffness. The amplitude and timing of the reflected wave depends not only on arterial stiffness but also on the distance between the reflection sites and the heart. Thus, reduced body height, a marker of the length of the arterial tree, influences significantly CAI (Table 4).<sup>11,24</sup> This index is also largely dependent on age. In healthy middle age subjects, arterial stiffening is modest and reflection points are principally located at the early narrowing of small resistant vessels, causing a return of reflection waves during the diastolic component of the aortic pressure wave with relatively low values of CAI and aortic systolic and pulse pressure.<sup>11</sup> This hemodynamic pattern favors an adequate maintenance of MBP, as well as cardiac function and coronary perfusion.<sup>11,24</sup> On the other hand, in older subjects, particularly those with hypertension, arterial stiffness

increases markedly and additional reflecting sites operate closer to the heart, causing an earlier return of reflected waves, with the appearance of a late systolic aortic peak and a significant increase in CAI (Fig. 1).<sup>11,17</sup> This hemodynamic pattern is more frequent in the presence of a reduced cardiac time (ie, an increase in heart rate), and thus may be detrimental for cardiac function and coronary perfusion, as it favors not only a high systolic peak, but also a low DBP. From this simple analysis, it appears that changes in the timing of wave reflections may have dual effects on CV risk, depending on the numerous factors influencing CAI: not only age and MBP, but mostly heart rate and body height. This interpretation agrees with our finding that CAI is not significantly associated with CV events, and thus contrasts with the two other significant indices—PP and PWV.

An important finding of the present study was the influence of plasma glucose on the level of PWV and PP (Tables 2 and 3), whereas dyslipidemia, particularly low plasma HDL cholesterol, had no specific contribution. Because foam cells are often located on focal sites and composed mainly of soft tissue, it is not surprising that a low HDL cholesterol had no statistical association with increased PWV.<sup>11,13</sup> In contrast, diffuse atherosclerotic alterations, which involve substantial amounts of collagen accumulation and calcifications, are expected to be statistically associated with increased arterial stiffness.<sup>25,26</sup> In the present study, we found that hyperglycemia influenced the level of both PWV and PP. A number of studies have previously shown that increased arterial stiffness is a characteristic feature of diabetic subjects, in addition to increased plasma levels of glucose and insulin, and possibly due to the presence of elevated amounts of vascular glycosylation end products.<sup>27–30</sup> Furthermore, in subjects with type 2 diabetes, increased ambulatory (but not occasional) pulse pressure is a common finding, never observed in patients with hypercholesterolemia.<sup>31</sup>

In conclusion, the present study has shown that in cross-sectional cohorts of hypertensive subjects, increased PP and PWV, but not altered carotid wave reflections, are significant and independent identifiers of CV risk after exclusion of the role of other confounding variables. Whether they have per se a detrimental effect cannot be shown from the present study and require further longitudinal investigations.

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