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Pulse Pressure Amplification

A Mechanical Biomarker of Cardiovascular Risk

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Objectives The aim of this study was to determine whether the carotid/brachial (C/B) ratio is an independent predictor of cardiovascular (CV) risk.

Background Brachial and carotid pulse pressure (PP) are independent predictors of CV risk, mainly in elderly patients. Because PP is physiologically lower at the brachial than at the carotid arterial site, PP amplification is represented by the C/B ratio and could independently predict CV risk.

Methods In a Paris population (n = 834), brachial and carotid PP were measured from sphygmomanometry and pulse wave analysis. With stepwise multiple regression, carotid PP was calculated from a nomogram including age, sex, body height, brachial PP, and plasma glucose. This model was applied to 125,151 subjects, followed for 12 years, during which 3,997 deaths occurred (735 of CV origin). With Cox regression analysis, multi-adjusted hazard ratios (HRs) were calculated for 1 SD increase of brachial PP, calculated carotid PP, and C/B ratio.

Results Brachial PP was significantly associated with both CV and all-cause mortality (HR: 1.16, 95% confidence interval [CI]: 1.13 to 1.19, and HR: 1.13, 95% CI: 1.10 to 1.17, respectively). Calculated carotid PP predicted a similar risk (HR: 1.21, 95% CI: 1.15 to 1.28, and HR: 1.18, 95% CI: 1.12 to 1.25, respectively). Finally, the C/B ratio was a strong risk predictor (HR: 1.22, 95% CI: 1.12 to 1.32, and HR: 1.41, 95% CI: 1.14 to 1.73, respectively). Addition of drug treatment and other confounding variables did not statistically modify the results.

Conclusions Brachial PP, calculated carotid PP, and C/B PP amplification all predict CV mortality. In contrast to brachial and carotid PP, the C/B ratio is less dependent on blood pressure calibration and thus can be directly applicable to large population studies. (J Am Coll Cardiol 2010;55:1032–7) © 2010 by the American College of Cardiology Foundation

Physiologically, central pulse pressure (PP) is lower than brachial PP for the same mean blood pressure (MBP) and diastolic blood pressure (DBP) (1–5). The difference between brachial and central PP, called PP amplification, is approximately 14 mm Hg (4,5) and might be expressed as either the difference or the ratio of these 2 pressures. Recent studies have shown that PP amplification (i.e., here the carotid/brachial [C/B] ratio) might be a risk factor superior to the values of brachial or central alone, particularly in subjects with advanced renal failure or with essential hypertension and old age (1–3).

For the same MBP and DBP, peripheral (brachial) PP becomes higher than central PP as the pulse passes through arterial conduits that are characterized by progressive reduction in diameter and increased stiffness. Arterial wave reflections from the periphery, however, exert the main influence on PP amplification by augmenting the peripheral systolic blood pressure (SBP) more than the central SBP.

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Therefore, under physiological conditions, the pulsatile burden is lower in central than in peripheral arteries, thus protecting the heart against excess load (4–6). With aging, the cardiac load tends to increase, because of a disproportional augmentation of central than brachial arterial stiffness that raises central PP and thus reduces peripheral PP augmentation (4). This process favors the development of cardiac hypertrophy and/or congestive heart failure.

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Reduced pulse rate is associated with a retiming of central wave reflections into systole due to the longer cardiac cycle length. The resulting higher central peak SBP reduces amplification and increases cardiac work (4,6). By contrast, an increased pulse rate significantly enhances carotid-brachial amplification, a finding that is observed independent of age (6). Therefore, PP amplification is due not only to the propagation and reflection of pressure waves along the arterial tree but also to the frequency dependence of the corresponding transfer function (4,6). Finally, it has been shown that there is a different effect of pulse rate changes on central and peripheral PP that depends upon the arterial stiffness levels. In addition, the respective effect of pulse rate changes on wave reflection also depends on arterial stiffness (7,8).

In recent years, it has been proposed that carotid PP could be directly measured with pulse wave analysis (4,6,9), but carotid PP also might be evaluated from appropriate stepwise multiple regressions initiated from brachial PP (4,6,9–12). This procedure might be difficult to apply for repeat determinations in individuals but is of major interest for the development of inexpensive investigations in large populations with long-term follow-up.

The purpose of the present study was: 1) to develop a noninvasive multiple regression analysis to calculate carotid PP from brachial PP measured with a simple standard sphygmomanometer; and 2) with this procedure, to evaluate the predictive value of PP amplification on overall and cardiovascular (CV) mortality in a large French population (4).

Methods

The present study described 2 different steps. The first step involved a population in whom indirect noninvasive measurements of carotid PP were obtained and subjected to a multiple regression analysis relating carotid PP (measured by tonometry) with brachial PP (measured by sphygmomanometry) and a series of hemodynamic, biochemical, and standard risk factors. The second step was to apply this analysis to a large French cohort, whose members were followed for an average of 12 years, and study the impact of brachial PP, calculated carotid PP, and PP amplification (C/B ratio) on all-cause and CV mortality.

First step: evaluation of multiple regression analysis.

POPULATION DESCRIPTION. The studied population included 834 subjects referred to the Diagnosis Center of Broussais and/or Hôtel-Dieu hospital (Paris) for an evaluation (check-up) ordered by their physician because of the presence of CV risk factors and/or family history of CV disease.

Patients with all forms of secondary hypertension, with cancer, or with severe renal insufficiency (plasma creatinine >300 μmol/l) were excluded from the study (10). Treated hypertensive patients entered the study irrespective of their BP level. At inclusion, patients had a thorough review of their medical history for the detection of clinical events and/or signs related to the presence of CV risk factors. Venous blood samples were obtained from all patients after an overnight fast for routine biochemical investigations, including plasma total cholesterol, triglycerides, low-density and high-density lipoprotein cholesterol, and glucose and creatinine levels, all determined by standard methods (3,10).

Abbreviations and Acronyms

BP = blood pressure
C/B = carotid/brachial
CI = confidence interval
CV = cardiovascular
DBP = diastolic blood pressure
HR = hazard ratio
MBP = mean (arterial) blood pressure
PP = pulse pressure
SBP = systolic blood pressure

BRACHIAL AND CENTRAL CAROTID BP MEASUREMENTS. All measurements were performed in the morning at stable room temperature (20°C to 22°C), after an overnight fast. Brachial BP determinations were performed in the supine position after a 15-min rest in the laboratory by traditional mercury sphygmomanometry, with the first and the fifth Korotkoff sounds for SBP and DBP measurements, respectively. The average of the last 2 (of 3) consecutive BP measurements was used for data analysis.

For central BP determinations, radial artery and carotid artery applanation tonometry was applied with a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments, Houston, Texas) as described previously (3,4,6,10). Briefly, the derived pressure waveforms were recorded on a Gould 8188 recorder (Gould Electronic, Ballainvilliers, France) at a paper speed of 100 mm/s. Radial artery pressure waveform calibrated from brachial artery SBP and DBP was used for determination of peripheral MBP via application of an integration method. Because DBP and MBP differences throughout the arterial tree are of minor value (ascending aorta to radial artery differences do not exceed 2 to 3 mm Hg) (4,6,10–12), the obtained carotid BP wave was calibrated with brachial diastolic and radial mean BP. Mean BP of the carotid pressure waveform, computed from the area method, was assumed to be equal to peripheral mean BP to calculate the amplitude of the carotid pressure waveform as well as carotid PP and SBP. Carotid PP was considered as a close surrogate of aortic PP. This point has been previously validated with invasive measurements as well as the use of mathematical transformation (4,6,9,10,13,14).

Reproducibility of all hemodynamic measurements has been published in detail elsewhere, particularly regarding carotid PP (10,12–14). The PP amplification between carotid PP and brachial PP (mm Hg) was calculated as the C/B ratio. In the present population (n = 834), the carotid PP measured by pulse wave analysis was compared with carotid PP calculated from the multiple regression analysis deduced from the 834 studied patients (Tables 1 and 2).

Second step: mortality study. Subjects were examined at the "Investigations Preventives et Cliniques" (IPC) Center (Paris-France) (15). This medical center, which is subsi-

Table 1 Step 1: Main Characteristics of the Population With Multiple Regression Analysis

	Men (n = 480)	Women (n = 354)	All (n = 834)	p Value (Men vs. Women)
Age, yrs (min–max)	56.7 (15–90)	57.9 (21–91)	57.2 (15–91)	0.23
Weight, kg	82.0 (13.1)	68.1 (13.3)	76.1 (14.9)	<0.0001
Height, cm	174 (7)	161 (7)	168 (9)	<0.0001
BMI, kg/m^2	27.1 (3.9)	26.2 (5.1)	26.8 (4.5)	0.003
Glycemia, g/l	1.12 (0.29)	1.07 (0.29)	1.10 (0.28)	0.06
Creatinine, mg/l	10.5 (4.4)	7.66 (2.8)	9.3 (4.0)	<0.0001
Cholesterol, g/l	2.08 (0.37)	2.13 (0.46)	2.10 (0.42)	0.08
Brachial SBP, mm Hg	142.5 (19.2)	141.0 (21.1)	141.9 (20.1)	NS
Brachial DBP, mm Hg	82.9 (12.7)	79.4 (11.5)	81.4 (12.3)	<0.0001
Brachial MAP, mm Hg	102.8 (13.3)	100.0 (12.6)	101.6 (13.1)	0.002
Brachial PP, mm Hg	59.5 (15.4)	61.6 (18.9)	60.4 (17.0)	0.09
Pulse rate, beats/min	66.2 (11.0)	68.0 (10.6)	67.0 (10.8)	0.01
Carotid PP, mm Hg	47.6 (14.9)	52.9 (18.3)	49.9 (16.7)	<0.0001
C/B ratio	0.79 (0.10)	0.86 (0.12)	0.82 (0.11)	<0.0001
Hypertensive subjects, % (n)	92.1 (442)	93.8 (332)	92.8 (774)	NS
Antihypertensive treatment % (n)*	77.7 (373)	74.3 (263)	76.3 (678)	NS
Current or former smokers, % (n)	59.8 (286)	33.6 (119)	48.6 (405)	<0.0001
Hypolipidemic treatment, % (n)†	12.2 (61)	11.6 (41)	12.2 (102)	NS
Antidiabetic treatment, % (n)‡	6 (29)	7.1 (25)	6.5 (54)	NS
Subjects with aspirin or anti-inflammatory treatment, % (n)	18.3 (88)	15.0 (53)	16.9 (141)	NS

Values are mean (SD) unless otherwise indicated. *28.9% with beta-blockers, 25.4% with angiotensin blockade, 45.7% with calcium blockade. †Fibrate or statin. ‡Insulin and/or oral administration. BMI = body mass index; C/B = carotid/brachial; DBP = diastolic blood pressure; MAP = mean arterial pressure; NS = not significant; PP = pulse pressure; SBP = systolic blood pressure.

dized by the French national health care system (Securite Sociale-CNAMTS), offers all working and retired individuals and their families a free medical examination every 5 years. It is 1 of the largest medical centers of this kind in France, carrying out approximately 25,000 health examinations/year for people living in the Paris area.

The IPC study population was composed of 72,437 (age 41.0 ± 11.1 years) men and 52,714 (age 39.5 ± 11.6 years) women who had a health checkup at the IPC Center between January 1981 and December 1988 (Table 3). To focus on primary prevention, subjects with previous CV disease were excluded. Antihypertensive drug therapy involved 4,499 patients (3.60%). The follow-up ending occurred in 1998; during this period (mean duration: 12.1 ± 2.2 years), 3,028 men and 969 women died. Among them, 600 men and 135 women died from CV disease. Measurement methods have been described in detail elsewhere (15).

Table 2 Carotid PP: Multiple Regression Analysis in Step 1

Parameters	Standard Regression Coefficients (SEM)	Partial R^2	p Value
Intercept	0.064 (6.7)		
Brachial PP, mm Hg	0.86 (0.02)	0.835	<0.0001
Pulse rate, beats/min	—		
Height, m	−6.62 (3.36)	0.0007	0.05
Glycemia, g/l	−0.33 (0.15)	0.0001	0.03
HDL cholesterol, g/l	—		
Age, yrs	0.13 (0.02)	0.010	<0.0001
Sex (M = 1; F = 2)	2.83 (0.62)	0.012	<0.0001
Pulse wave velocity, m/s	—		
MBP, mm Hg	—		
DBP, mm Hg	—		
BMI, kg/m^2	—		
Model R^2	0.858		

BMI = body mass index; DBP = diastolic pulse pressure; HDL = high-density lipoprotein; MBP = mean blood pressure; PP = pulse pressure.

The IPC center received approval from the national ethical committee (Comite National d 'Informatique et des Libertes–CNIL) to conduct all these analyses. All subjects included gave their informed consent at the time of the examination. Mortality data were obtained from the mortality records at the "Institut National de Statistiques et d'Etude Economiques" (INSEE), following a previously established procedure (15).

Statistical analysis. In the first step, stepwise regressions analysis was carried out to evaluate the function estimating carotid PP values. In the second step (epidemiological study), the impact of brachial and carotid PP and PP amplification (C/B PP ratio or C/B ratio) on all-cause and CV mortality were evaluated with Cox regression models including age, sex, height and weight, and risk factors (smoking, physical activity, cholesterol, and diabetes mellitus). Because the C/B ratio is known to be highly influenced by pulse rate (4), models also included pulse rate as an adjusting factor. Hazard ratios (HRs) were calculated for each increase of 1 SD of brachial and carotid PP and of the C/B ratio. All quantitative variables used in the regression model or in the carotid PP equation were conformed to a normality distribution, and colinearity assessments were taken into account in multivariate analysis. All statistical analyses, including interactions, were performed with the version 8.2 of the SAS statistical software

Table 3 Step 2: Main Characteristics of the IPC Population According to Sex

	Men (n = 72,437)	Women (n = 52,714)	All (n = 125,151)
Age, yrs (min–max)	41.0 (16–95)	39.5 (16–95)	40.4 (16–95)
Weight, kg	73.9 (10.7)	58.5 (9.6)	67.4 (12.7)
Height, cm	173.8 (6.8)	162.0 (6.0)	168.3 (9.2)
BMI, kg/m^2	24.5 (3.2)	22.7 (3.6)	23.7 (3.5)
Plasma glycemia, g/l	1.03 (0.13)	0.97 (0.10)	1.00 (0.13)
Plasma creatinine, mg/l	10.44 (1.28)	8.49 (1.18)	9.62 (1.24)
Plasma cholesterol, g/l	2.19 (0.45)	2.07 (0.42)	2.14 (0.44)
Brachial SBP, mm Hg	134.0 (13.6)	128.3 (14.2)	132.1 (14.3)
Brachial DBP, mm Hg	82.9 (10.1)	78.3 (10.1)	81.0 (10.3)
Brachial MAP, mm Hg	100.3 (10.7)	95.0 (10.8)	98.0 (10.7)
Brachial PP, mm Hg	52.0 (8.6)	49.9 (8.7)	51.1 (8.7)
Pulse rate, beats/min	69.4 (12.8)	73.2 (10.3)	71.0 (12.0)
Carotid PP, mm Hg	39.2 (7.6)	40.7 (7.9)	39.8 (7.8)
C/B ratio	0.79 (0.03)	0.85 (0.03)	0.82 (0.42)
Hypertensive subjects, % (n)	45.6 (33,025)	26.9 (14,184)	37.8 (47,209)
Antihypertensive treatment, % (n)*	3.35 (2,426)	3.94 (2,073)	3.60 (4,499)
Current smokers, % (n)	33.8 (24,507)	23.5 (12,372)	29.5 (36,879)
Subjects with aspirin treatment or anti-inflammatory agent, % (n)	8.1 (5,869)	14.8 (7,786)	10.9 (13,655)

Values are mean (SD) unless otherwise indicated. *With or without antidiabetic or hypolipidemic agent.
Abbreviations in Table 1.

(SAS Institute, Cary, North Carolina). A p value <0.05 was considered significant.

Results

Step 1: models of carotid PP evaluation. The main clinical and biological characteristics of the population (n = 834) are listed in Table 1. In bivariate analysis, carotid PP was closely correlated with brachial PP (r = 0.916, p < 0.0001). Table 2 reports the results of stepwise regression analysis in this population. The major components of total variance were represented by the following parameters: brachial PP, plasma glucose, body height, age, and sex. Drug treatment, pulse rate, MBP, DBP, and body mass index had no statistical significance in the stepwise regression. The model established in the population explained 86% of carotid PP variance and was then used for the epidemiological study.

Step 2: epidemiological study. Table 3 represents the characteristics of the IPC population according to sex. Figure 1 shows the mean values of carotid and brachial PP according to age. Both PP values increase with age, but the C/B ratio trends toward 100%, because carotid PP increases more rapidly than brachial PP with age.

Table 4 shows the values of HR for CV and all-cause mortality when included in the model for brachial PP or carotid PP after adjusting for age, sex, traditional CV risk factors, and pulse rate. Both brachial and carotid PP were significant and to a similar extent predictors of CV and all-cause mortality: for brachial PP, HRs were 1.16 (95% confidence interval [CI]: 1.13 to 1.19) and 1.13 (95% CI: 1.10 to 1.17), respectively; for carotid PP, HRs were 1.21 (95% CI: 1.15 to 1.28) and 1.18 (95% CI: 1.12 to 1.25), respectively. Carotid HRs were slightly but constantly higher than brachial HR. Finally, the C/B ratio PP was also strongly predictive of prognosis (respective HRs: 1.22 [95% CI: 1.12 to 1.32] and 1.41 [95% CI: 1.14 to 1.73], for 1 SD increase). Further adjustment for drug treatment did not significantly change the results (Table 4, lower panel). A separate analysis in diabetic and nondiabetic subjects showed similar results in these groups and no interaction (data not shown).

Discussion

In this study, we used a population of outpatients in whom we simultaneously and noninvasively measured brachial and carotid PP. For this, we established a multiple regression

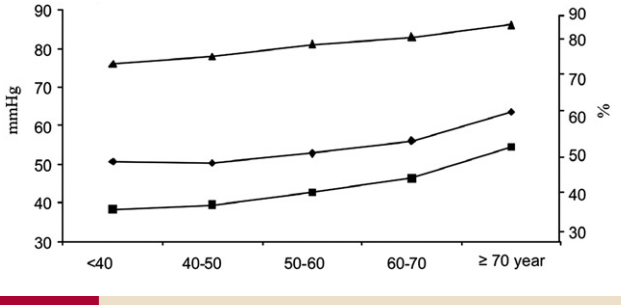

Figure 1 Step 2: Brachial PP, Carotid PP, and the C/B Ratio According to Age

Brachial pulse pressure (PP) (mm Hg) **(diamonds)**, carotid PP (mm Hg) **(squares)**, and the carotid/brachial (C/B) ratio (%) **(triangles)** according to age.

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Table 4 Adjusted Risk of All-Cause Mortality and CV Mortality Associated With the Increase of 1 SD of Brachial PP, Carotid PP, and C/B Ratio

	All-Cause Mortality	CV Mortality
Upper panel		
Brachial PP	HR 1: 1.13 (1.10–1.17)	HR 1: 1.16 (1.13–1.19)
Carotid PP	HR 2: 1.18 (1.12–1.25)	HR 2: 1.21 (1.15–1.28)
C/B ratio	HR 3: 1.22 (1.12–1.32)	HR 3: 1.41 (1.14–1.73)
Lower panel		
Brachial PP	HR 1: 1.13 (1.12–1.15)	HR 1: 1.17 (1.15–1.19)
Carotid PP	HR 2: 1.17 (1.14–1.20)	HR 2: 1.20 (1.13–1.27)
C/B ratio	HR 3: 1.19 (1.12–1.27)	HR 3: 1.30 (1.12–1.52)

Adjusted risk of all-cause mortality and cardiovascular (CV) mortality (hazard ratio [HR] and 95% confidence interval) associated with the increase of 1 SD of brachial pulse pressure (PP), carotid PP, and carotid/brachial (C/B) ratio. Upper panel: adjustments were made for age, sex, smoking, physical activity, cholesterol, diabetes mellitus, and pulse rate. Lower panel: adjustments as upper panel plus antihypertensive treatment.

analysis that permitted calculation of carotid PP from brachial PP while adjusting for age, sex, body height, and plasma glucose but not MBP, DBP, pulse rate, or drug treatment (Table 2). The variance explained by the corresponding stepwise multiple regression approximated 86%. The methodology of brachial PP measurement and of carotid PP calculation was applied to the large epidemiological IPC cohort. Both carotid and brachial PP had a significant predictive value on overall and CV mortality risks, independently of CV risk factors. Finally, PP amplification, expressed as the C/B ratio, was strongly associated with both CV and overall mortality risks, with the highest HRs. Thus, after adjustment for age, sex, associated risk factors, and presence of antihypertensive treatment, an increase of 1 SD of PP amplification was associated with an increase of 19% of the all-cause mortality and of 30% of the CV mortality. All results were independent of any other confounding factors including pulse rate and drug treatment.

The methodological basis of the present study was to determine the ratio between the carotid and brachial artery PP with a validated tonometric sensor. This previously described methodology (4,16) requires at least 3 major prerequisites. First, high-quality radial artery and carotid artery BP curves should be recorded transcutaneously. Second, after calibration of the curves with the brachial artery auscultatory method, the radial and carotid curves should be considered to have the same mean BP determined by planimetry. Third, the difference between MBP and DBP measured at the brachial and carotid arterial sites are considered to be nearly identical and both of small amplitude (4,16). Finally, carotid SBP can then be deduced from the calibrated carotid BP curve and is potentially corrected from the small arterial amplification (<5 mm Hg) observed between the brachial and the radial arteries (17). Noninvasive and invasive methods have in the past extensively validated this methodology and showed that BP measured at the carotid arterial site varied in strict parallelism with thoracic aorta or carotid BP measured with a transfer function (4,14,16).

The major limitation of this methodology is related to the calibration of the carotid BP curve, which requires the use of the classical transcutaneous auscultatory method to measure the brachial artery SBP and DBP (16). With this procedure, the determination of SBP is known to be quite adequate in contrast with the determination of DBP (4,14). The DBP error is somewhat attenuated, because DBP is identical in all parts of the arterial tree. This observation minimizes the difficulties introduced by using peripheral DBP to estimate central DBP measurements. When PP amplification is calculated as the C/B ratio, this ratio becomes independent of brachial artery calibration (expressed in voltage) and is influenced only by the reliability of detection of the brachial pressure pulse by the auscultatory method and the methodology used to estimate the central aortic or carotid pulse (17). This procedure undoubtedly facilitates the comparisons of BP measurements between various laboratories and under different circumstances.

An important advantage of the present study results from the use of stepwise multiple regression model, which associates hemodynamic and biological parameters with a very high proportion of variance explained (86%). This method might then be used to better advantage for large inexpensive statistical evaluations than for repeated determinations in individuals. The major component of this variance is brachial PP, representing more than 80% of the variance, as previously reported and validated in the published data (6,12,16,18–20). The remaining components exclude the influence of other major factors, such as drug treatment, MBP, DBP, and body mass index, but also involve age, sex, and height, but among the standard CV risk factors, only plasma glucose.

The major finding of this study was to show that: 1) when brachial and carotid PP are used separately to evaluate adjusted CV risk, each of them have a consistent impact; but 2) when the C/B ratio is calculated in the same population, the HR of this ratio is greater by comparison than that obtained from each of its brachial or carotid components—especially with regard to CV mortality (Table 4). As shown earlier, the increase in PP from central to peripheral arteries physiologically contributes to reduce the cardiac pulsatile load. Aging increases central more than brachial PP, leading to an increase in the C/B ratio.

Prospective views. This study has proposed a method to calculate, in humans, central (carotid) PP from measured brachial PP and to deduce CV risk from the ratio between the 2 variables. An epidemiological study involving 125,151 subjects indicates that the C/B ratio is a powerful risk predictor. The ratio is poorly influenced by the calibration used for the BP curve measurements. Consequences in CV risk reduction strategies and titration of antihypertensive drug treatment remain yet to be further established.

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Key Words: cardiovascular risk ■ hypertension ■ pulse pressure ■ pulse pressure amplification.