Cardiovascular risk as defined in the 2003 European blood pressure classification: the assessment of an additional predictive value of pulse pressure on mortality

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Objectives This study determines the predictive value of brachial pulse pressure for cardiovascular stroke and coronary mortality in a large population categorized by blood pressure level.

Methods The population was composed of 69 989 subjects aged more than 50 years and divided into 'optimal', 'normal' and 'normal high' normotensive subjects, and grades 1, 2, 3 hypertensive subjects as defined in the 2003 European Guidelines for Management of Hypertension. Hazard ratios for mortality were evaluated using Cox regression models before and after adjustment for pulse pressure. To further assess the role of pulse pressure in mortality, subjects were also classified as 'normotensive' and 'hypertensive' whether they were with or without elevated pulse pressure (≥60 mmHg).

Results By comparison with 'optimal' values, before adjustment for pulse pressure, the hazard ratio for cardiovascular, coronary and stroke mortality increased markedly for blood pressure groups as defined by the European blood pressure classification. For cardiovascular and coronary mortality, the hazard ratio was significant both in the 'high normal' and hypertensive ranges. For stroke mortality, hazard ratio was significant only in the hypertensive ranges. After adjustment to pulse pressure, hazard ratio remained unmodified for stroke mortality. For coronary mortality, the risk was attenuated in 'high normal' and all hypertensive groups. A study of the pulse pressure classification in subjects dichotomized as normotensive and hypertensive subjects indicated that pulse pressure was an independent risk factor for cardiovascular mortality.

Conclusion Increased pulse pressure predicts cardiovascular mortality, acting more on coronary than cerebral vessels. This finding involves all blood pressure ranges, including subjects with low diastolic but normal systolic blood pressure. *J Hypertens* 26:1072–1077 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

In subjects over 60 years of age, brachial artery pulse pressure (PP) is considered as a significant independent predictor of cardiovascular risk, mainly for myocardial infarction (see review in [1]). Because systolic blood pressure (SBP) and PP are strongly interrelated, SBP alone is often considered as a more potent predictor of cardiovascular risk than PP [2–4]. In fact, in most cohorts in the literature, even in those including the largest populations [4], the level of significance of SBP and PP as cardiovascular risk factors is greatly influenced by age. This finding is due not only to the elevation of SBP with age, but also to the spontaneous drop in diastolic blood pressure (DBP) with age, particularly above 50–60 years [1]. Indeed, SBP and DBP are both influenced by the same hemodynamic mechanism: an age-induced increase in aortic stiffness. Thus, the lowered DBP may contribute greatly to the independent predictive value of PP as a cardiovascular risk factor. Nevertheless, the validity of this finding has never been quantitatively established. More specifically, a high PP (≥60 mmHg), even in the presence of a normal SBP (≤140 mmHg), as defined according to standard international definitions [5–9], may be a consistent and independent predictor of cardiovascular risk.

One of the most widely accepted classifications of brachial BP was undertaken in 2003 in Europe [7] and involved six ranges and/or groups of subjects. First, three normotensive groups were defined as having an SBP and DBP less than

140 and 90 mmHg, respectively. These are 'optimal' (<120/<80 mmHg), 'normal' (120–129/80–84 mmHg), and 'high normal' (130–139/85–89 mmHg) groups. Second, three hypertensive groups were divided into three grades: grade 1 (140–159/90–99 mmHg), grade 2 (160–179/100–109 mmHg), and grade 3 ($\geq$180/$\geq$110 mmHg). The purpose of this study was, in a large population of normotensive and hypertensive subjects classified according to the above well established definitions, to determine the hazard ratio in each of the six groups in terms of all-cause, cardiovascular, stroke and coronary mortality; and to determine the additional predictive value of PP for cardiovascular, stroke and coronary mortality according to BP values. Finally, in order to assess further the role of PP in cardiovascular risk, normotensive and hypertensive subjects, defined according to the 2003 European classification, were subclassified according to the presence or absence of elevated PP ($\geq$60 mmHg). In the present study, only brachial (and not central) PP was used as a marker of the pulsatile component of blood pressure [5–11].

Methods

Population

All subjects were examined at the Centre d'Investigations Préventives et Cliniques (IPC) [5], a medical center subsidized by the French national health service (Sécurité Sociale-CNAM, Paris), which provides a free medical examination every 5 years to all working and retired persons and their families. The IPC Center is one of the largest medical centers in France, having carried out approximately 20 000–25 000 examinations per year since 1970 on people living in the Paris area. The population was composed of 41 473 men and 28 516 women ($n = 69\,989$) aged more than 50 years (Table 1) who underwent a standard health check-up at the IPC Center between 1972 and 1988.

Supine brachial SBP and DBP were measured three times in the right arm, and after a 10-min rest period, using a manual sphygmomanometer, and the appearance and disappearance of the Korotkov sounds for the SBP and DBP determinations were noted. The mean of the last two measurements were used in the analyses for SBP, DBP and PP which were calculated as the difference of the mean values of the last two measurements of SBP and DBP. PP at over 60 mmHg was considered to be a cardiovascular risk factor according to previously published epidemiological data [5,6,8]. The 60 mmHg threshold level reflects

the mean value of PP in large populations, with the addition of two standard deviations [9] (Table 2). Heart rate was measured by an electrocardiogram after a 5–7-min rest in the supine position. Data pertaining to physical activity were obtained from a self-administered questionnaire. Subjects who reported regular physical activity of more than 2 h per week were considered as physically active. Tobacco use (current consumption of more than 10 cigarettes/day) and personal and family history of heart disease were also obtained from the self-administered questionnaire. At the time of examination, blood samples were collected for the measurement of plasma cholesterol, glucose, creatinine, uric acid and triglycerides at the IPC Center under fasting conditions.

The IPC Center received approval from the national ethical committee (Comité National d'Informatique et des Libertés–CNIL) to conduct all these analyses. All subjects included gave their informed consent at the time of the examination. Mortality data were obtained for all subjects, for the period that extended from inclusion up to December 1997 (mean follow-up 15.3 $\pm$ 4.7 years). These data were obtained from the mortality records at the Institut National de Statistiques et d'Etude Economiques (INSEE), following a previously established procedure [5,10]. In order to validate the procedure, we took a random sample of 250 subjects in this cohort and compared our mortality data with those found in city hall registries. A discordance was found in only two subjects (< 1%), indicating that we had an essentially complete follow-up for the entire study population. The description of the IPC cohort has been detailed previously [5,11].

During this follow-up period, 10 657 subjects died (3079 from cardiovascular cause) (Table 3). Antihypertensive drug therapy involved 7047 patients (10.1%).

Statistical evaluation

In order to determine the role of PP (the difference between systolic blood pressure and diastolic blood pressure), two different analyses were carried out. First, among the six groups of the European BP classification, risks for all-cause, cardiovascular, coronary and stroke mortality were evaluated before and after adjustment for PP. Second, to further take into account the relationship between PP and BP, the population was divided into four groups: normotensive (HT–) and hypertensive subjects (HT+) were subclassified according to PP less than 60 mmHg (PP–) and PP at least 60 mmHg (PP+). Time-to-death for

Table 1 Number of subjects according to sex and blood pressure classifications [7]

	Optimal	Normal	High normal	Grade 1	Grade 2	Grade 3
Men	1079 (2.6)	18 399 (44.3)	3071 (7.4)	13 492 (32.5)	4163 (10.0)	1269 (3.1)
Women	1884 (6.6)	14 424 (50.6)	2032 (7.1)	7519 (26.4)	2097 (7.4)	560 (2.0)

Percentage values are shown in parentheses.

Table 2 Mean ± SD of clinical and biological variables according to the 2003 European classification [7]

	Optimal	Normal	High normal	Grade 1	Grade 2	Grade 3
N	2963	32 823	5103	21 011	6260	1829
Age (years)	54.8 (4.5)	55.9 (5.4)	55.6 (5.1)	57.1 (6.0)	58.0 (6.4)	59.2 (6.6)
SBP (mmHg)	111 (0.2)	131 (0.05)	132 (0.1)	148 (0.06)	168 (0.1)	193 (0.2)
DBP (mmHg)	68 (0.1)	80 (0.03)	83 (0.08)	92 (0.04)	103 (0.07)	118 (0.1)
MBP (mmHg)	82.1 (0.09)	96.8 (0.03)	98.9 (0.07)	110.6 (0.04)	124.9 (0.07)	142.7 (0.1)
PP (mmHg)	43.1 (0.2)	51.6 (0.05)	49.1 (0.1)	56.2 (0.06)	64.1 (0.1)	75.4 (0.2)
PP ≥ 60 mmHg (%)	0.4 (n = 11)	23.2 (n = 7600)	31.0 (n = 1582)	38.9 (n = 8170)	82.5 (n = 5164)	97.4 (n = 1829)
Weight (kg)	64.5 (0.2)	68.2 (0.06)	68.7 (0.1)	71.1 (0.07)	73.0 (0.13)	74.6 (0.2)
Height (cm)	166.2 (0.1)	166.2 (0.03)	166.2 (0.03)	165.9 (0.04)	165.7 (0.08)	165.6 (0.1)
BMI (kg/m^2)	23.2 (0.06)	24.6 (0.02)	24.8 (0.05)	25.7 (0.02)	26.5 (0.04)	27.0 (0.08)
Expiratory ratio[a]	1.04 (0.003)	1.03 (0.001)	1.03 (0.003)	1.02 (0.001)	1.00 (0.002)	0.98 (0.004)
Capacity ratio[a]	0.92 (0.003)	0.92 (0.0008)	0.91 (0.002)	0.90 (0.001)	0.89 (0.002)	0.87 (0.003)
Cholesterol (g/l)	2.24 (0.007)	2.33 (0.002)	2.33 (0.006)	2.38 (0.003)	2.41 (0.005)	2.38 (0.009)
Triglycerides (g/l)	1.02 (0.02)	1.11 (0.004)	1.12 (0.01)	1.24 (0.006)	1.34 (0.01)	1.38 (0.02)
Glycaemia (g/l)	1.01 (0.005)	1.04 (0.001)	1.03 (0.003)	1.07 (0.002)	1.10 (0.003)	1.12 (0.007)
Gamma-Gt (UI)	19.5 (0.7)	23.5 (0.2)	24.7 (0.5)	28.5 (0.3)	35.4 (0.5)	39.0 (1.2)
Uricemia (mmol/l)	53.2 (0.2)	55.5 (0.06)	56.1 (0.2)	57.8 (0.08)	59.6 (0.1)	60.6 (0.3)
Treated for hypertension (%)	0.81	4.82	5.57	13.9	26.1	33.8
Regular physical activity (%)	26.6	24.3	24.5	20.3	17.5	13.7
Current smokers (%)	17.9	17	16.1	16.1	14.2	10.9
Wine drinkers[b] (%)	1.1	2.6	3	4.6	5.9	7.5
80 bpm (%)	7.42	14.9	15.1	23.3	31.8	37.2
Diabetics (%)	6.4	8.5	8.4	10.4	12.6	11.7
Cardiovascular disease (%)	3.5	4.2	3.7	5.8	7.7	9.4
LVH (%)	0.4	0.9	1	1.7	2.8	4.5

[a] ratio of expiratory volume observed to expiratory volume expected; ratio of vital capacity observed to vital capacity expected. [b] Drink more than 1 l of wine per day. ***$P < 0.0001$ among groups except for height, capacity ratio and smoking status. DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; MBP, mean blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

the Cox analyses was defined as the length of follow-up in years from the time of the subject's visit in the IPC Center until death or censoring as of December 1997.

Regarding the first analysis, subjects were divided into six groups according to the European BP classification, as described earlier [7]. This study did not analyze men and women separately. In the six groups, mean values for a series of clinical and biological parameters were compared using a multivariate analysis of variance, including age as covariate. Percentages were compared with χ^2-test. Cox regression models including age, sex, cholesterol, diabetes, physical activity, alcohol, tobacco consumption and antihypertensive drug treatment were used to evaluate all-cause and stroke, coronary and cardiovascular mortality among the six BP groups. Hazard ratio with a confidence interval (CI) was computed for the variable time-to-death before and after adjustment to brachial PP. The 'optimal' group was used as the reference.

Regarding the second analysis, hazard ratio and 95% CI were computed for time-to-death for the various mortality measures using Cox regression models including the same covariates as for the first analysis. The group normotensive (HT−) and PP less than 60 mmHg (PP−) was used as the comparator, optimal group.

All statistical analyses were performed using the SAS (8.02) statistical software package (SAS Institute Inc., Cary, North Carolina, USA).

Results
Study of the 2003 European classification
Table 1 represents the number and percentage of subjects in each group of the 2003 European classification [7] according to sex.

Table 2 shows the mean values of the various clinical and biological parameters in the six groups. All of them increased significantly ($P < 0.0001$) according to the 2003 European BP classification [7], apart from body height, capacity ratio and smoking habits. The percentage of physical activity was significantly lower in grade 1, 2 and 3 hypertensive subjects compared with normotensive subjects. In the 'optimal' group, the number of subjects with PP at least 60 mmHg was low, and the percentage of

Table 3 All-cause, cardiovascular, coronary and stroke mortality rate according to the 2003 blood pressure classification [7]

	Optimal	Normal	High normal	Grade 1	Grade 2	Grade 3
n	2963	32 823	5103	21 011	6260	1829
All-cause mortality (%)	8.5	12.1	11.7	17.5	23.8	36.3
Cardiovascular mortality (%)	1.6	2.8	3.0	5.4	8.6	15.7
Coronary mortality (%)	0.51	1.2	1.3	2.3	3.3	6.8
Stroke mortality (%)	0.51	0.7	0.6	1.3	2.3	4.2

Table 4   Hazard ratio (± 95% confidence interval) for all cardiovascular, coronary and stroke risk mortality according to the 2003 European blood pressure classification

	Optimal	Normal	High normal	Grade 1	Grade 2	Grade 3
Before adjustment to PP						
HR CV mortality	1	1.30 (0.96–1.75)	1.48 (1.05–2.07)	1.95 (1.45–2.63)	2.96 (2.16–4.07)	4.85 (3.41–6.90)
HR coronary risk	1	1.52 (0.91–2.56)	1.88 (1.06–3.34)	2.33 (1.39–3.92)	2.92 (1.68–5.07)	6.05 (3.36–10.90)
HR stroke risk	1	0.98 (0.58–1.66)	0.97 (0.51–1.84)	1.52 (0.89–2.59)	2.90 (1.65–5.12)	4.23 (2.21–8.12)
After adjustment to PP						
HR CV mortality	1	1.12 (0.83–1.52)	1.37 (0.96–1.97)	1.86 (1.37–2.53)	2.33 (1.64–3.31)	4.26 (2.76–6.57)
HR coronary risk	1	1.30 (0.77–2.20)	1.74 (0.96–3.18)	2.26 (1.33–3.86)	2.38 (1.30–4.34)	5.86 (2.90–11.86)
HR stroke risk	1	0.84 (0.49–1.45)	0.93 (0.46–1.86)	1.51 (0.87–2.63)	2.32 (1.23–4.40)	4.29 (1.92–9.60)

Hazard ratio (HR) was adjusted to age, sex, cholesterol, diabetes, physical activity, alcohol and tobacco consumption, and antihypertensive drug treatment but not to pulse pressure (PP). CV, cardiovascular.

subjects with PP at least 60 mmHg increased linearly from the 'normal' (23.2%) to grade 3 (97.4%). In Table 3, the percentage of deaths increased from the 'optimal' group to grade 3. This was observed for all-cause, cardiovascular, coronary and stroke mortality.

Before adjustment to PP (Table 4), the hazard ratio for all (data not shown) and each specific mortality factor increased with a linear trend across the six BP classes. As an example, from the 'high normal' group [hazard ratio: 1.48 (1.05–2.07)] to grade 3 [hazard ratio: 4.85 (3.41–6.90)], these trends were significant for cardiovascular mortality. Risk of coronary mortality increased significantly from 'high normal' [hazard ratio: 1.88 (1.06–3.34) ($P = 0.03$)] to grade 3 [hazard ratio: 6.05 (3.36–10.90)]. Compared with the optimal group, for stroke mortality, the hazard ratio value was significant only in grade 2 [hazard ratio: 2.90 (1.65–5.12)] and grade 3 [hazard ratio: 4.23 (2.21–8.12)]. We noted that, compared with the optimal group, hazard ratio in grade 3 group was 6.05 for coronary mortality and only 4.23 for stroke mortality.

After adjustment to PP, the excess of coronary risk decreased. The result was observed in all groups (cardiovascular, coronary, stroke mortality), and a nonsignificant level among 'high normal subjects' was reached ($P = 0.07$). However, the interaction between hypertension and PP on cardiovascular or coronary mortality was not significant (data not shown). Regarding stroke mortality risk, no consistent hazard ratio modification was observed after adjustment to PP.

Study of the pulse pressure classification

Regarding the PP classification, Fig. 1 represents hazard ratio for cardiovascular mortality in each group compared to the reference group composed of normotensive subjects (HT−) with PP less than 60 mmHg (PP−). The number of subjects was 31 696 in HT−PP−, 9193 in HT−PP+, 13 985 in HT+PP− and 15 123 in HT+PP+ group. Compared with the reference group, in normotensive subjects, an elevated PP (PP ≥ 60 mmHg) was associated with an increased risk of cardiovascular mortality after adjustment of age, sex, cholesterol, diabetes, physical activity, alcohol, tobacco consumption and antihypertensive drug treatment
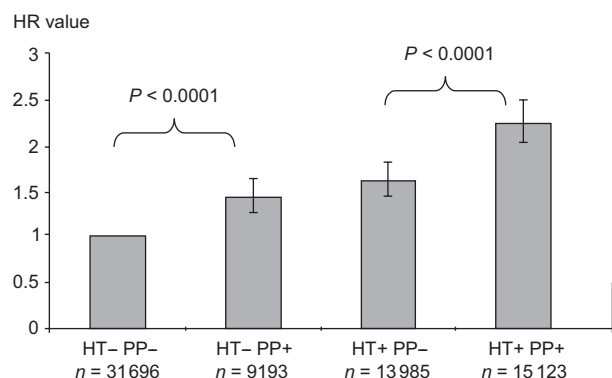
[hazard ratio: 1.42 (1.25–1.61); $P < 0.0001$ (Fig. 1)]. In hypertensive subjects, the adjusted hazard ratio for cardiovascular mortality associated with the presence of elevated PP was 1.35 (1.22–1.49; $P < 0.0001$) (comparison between HT+PP− and HT+PP+) (Fig. 1). Similar results were found for cardiovascular and coronary mortality (data not shown).

Discussion

This study showed that, in a large French population ($n = 69\,989$ subjects) with a mean 15-year follow-up period, the profile of mortality risk values for cardiovascular, coronary and stroke mortality differed markedly when the 2003 European classification was used. By comparison with the 'optimal' control group, hazard ratio for stroke mortality in normotensive ranges did not differ from controls. Furthermore, the hazard ratio increased linearly from grades 1 to 3 but was poorly modified before and after adjustment to PP (except for grade 2). In contrast, before PP adjustment, hazard ratio for cardiovascular and coronary mortality was constantly significant from the 'normal high' group to grade 3. However, the hazard ratio was reduced after PP adjustment and in fact, did not differ from the reference group in the 'high normal' group. Taken together, these results suggest that the epidemiological profiles of stroke and coronary mortality differ markedly, suggesting differences for pathophysiological mechanisms and mostly clinical management; and in subjects with 'high normal' BP, that is, with SBP less than 140 mmHg, the excess risk for coronary mortality is in part explained by PP and not exclusively by SBP.

The various components [SBP, DBP, mean arterial pressure (MAP), PP] of BP are nowadays well acknowledged as independent predictors of cardiovascular risk. However, all these mechanical factors are known to be measured on the same BP curve and to be significantly correlated, raising the question as to which component would be the best predictor to consider in clinical practice. The 'principal component analysis' has been proposed as a statistical method making it possible to attenuate and even suppress the statistical link between the pulsatile (PP) and the steady (MAP) components of BP [10]. MAP and PP then become 'independent' of each other in terms of the

Fig. 1

Hazard ratio (HR) for cardiovascular mortality in regard to pulse pressure classification. HR [95% confidence interval (CI)] for cardiovascular mortality in each group compared to the reference group [HT(−) PP(−)]. (See methods). HT(−): normotensive subjects; HT(+): hypertensive subjects PP(−):<60 mmHg; PP(+): ≥ 60 mmHg. Note that HT− PP+ and HT+ PP− do not differ significantly [Hazard ratio = 1.09 with 95% CI: 0.96–1.23].

predictive value. Using this procedure, we showed that PP was a significant cardiac (coronary) predictor of cardiovascular risk, independent of MAP [10]. The present results, although derived from a different method of statistical analysis, extend these earlier findings, thanks to two principal designs. First, the reference population was the 'optimal' group, in which subjects with PP at risk (≥60 mmHg) were shown to be practically absent (Table 2). Second, all the hazard ratio results were previously adjusted to all well established cardiovascular variables, such as age, sex, diabetes mellitus, dyslipidemia, obesity, tobacco consumption. More specifically, the role of standard cardiovascular risk factors could be excluded in the present results [11]. Finally, we compared the results of the 2003 European classification with the results of a PP classification on the same patients, but taking into account the direct measurement of PP.

Regarding stroke mortality, hazard ratio was significantly increased, but only in the hypertensive subjects. The increase was practically linear from grades 1 to 3. In most cases, the hazard ratio was poorly modified by adjustment to PP. These results agree with the well established finding that the totality of excess risk for stroke disappears after effective drug treatment for hypertension [12]. There is no contradiction with the observations of the Prospective Studies Collaboration [4], in which a higher relation between stroke events and BP was observed compared with the relation between coronary events and BP. However, these results were obtained using a very large and heterogeneous (multi-ethnic and multi-geographic) population.

As regards cardiovascular and coronary mortality, the situation is more complex. Before PP adjustment, hazard ratio was significantly increased from the 'high normal' ranges (as defined by the 2003 European BP classification) toward the hypertensive ranges. This finding is important to consider because it suggests that a PP, which is considered as risk (≥60 mmHg) may occur even in the presence of SBP less than 140 mmHg. Furthermore, the hazard ratio is markedly attenuated after PP adjustment, indicating a contribution of pulsatile pressure to cardiovascular and coronary mortality. Within normotensive ranges, and particularly in the 'high normal' group, the excess of risk did not persist (or remained nonsignificant) after PP adjustment. In order to assess the importance of this aspect, we proposed to investigate our overall PP classification by taking into account the PP value: above and below 60 mmHg. We showed that whatever the level of SBP or DBP, PP was an independent predictor of cardiovascular risk; further, normotensive subjects with PP at least 60 mmHg and hypertensive subjects with PP less than 60 mmHg have a nonsignificantly different cardiovascular risk (Fig. 1).

At this point, caution is required in the interpretation of the data. In this study, PP was measured only at the site of the brachial artery. It is well accepted that, both in normotensive and hypertensive subjects, brachial SBP and PP are physiologically higher than central SBP and PP, whereas MAP is quite similar in central (carotid artery, thoracic aorta) and peripheral (brachial artery) arteries. The difference, which is close to 14 mmHg, is mainly due to the increased stiffness of vessels from proximal to distal arteries and to the changes in amplitude and timing of wave reflections along the arterial tree. This PP amplification is attenuated with age, but is also markedly and independently increased in the presence of elevated heart rate [13,14]. In Table 2, it is clear that the heart rate increased consistently from normotensive to the hypertensive BP ranges. This heart rate profile which has already been observed widely in the literature [15], suggests that within the normotensive BP ranges, brachial and central PP are not necessarily very close. Thus, central BP determinations are needed to interpret more adequately the epidemiological differences in risk between cerebral and coronary circulations.

In conclusion, this study has shown that in our population, the risk profile markedly differs from stroke and coronary mortality, affecting only grade 1, 2 and 3 for stroke and being already present in the 'high normal' range for coronary mortality. This latter particularity involves SBP and probably PP too. Prospective determinations of SBP and PP at the central and brachial levels are necessary to firmly respond to this important question.

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