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Sex Difference in Cardiovascular Risk

Role of Pulse Pressure Amplification

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Objectives The study was to explore whether the brachial/carotid pulse pressure (B/C-PP) ratio selectively predicts the sex difference in age-related cardiovascular (CV) death.

Background Hypertension and CV complications are more severe in men and post-menopausal women than in pre-menopausal women. C-PP is lower than B-PP, and the B/C-PP ratio is a physiological marker of PP amplification between B and C arteries that tends toward 1.0 with age.

Methods The study involved 72,437 men (ages 41.0 ± 11.1 years) and 52,714 women (39.5 ± 11.6 years). C-PP was calculated for each sex by a multiple regression analysis including B-PP, age, height and risk factors, and a method validated beforehand in a subgroup of 834 subjects. During the 12 years of follow-up, 3,028 men and 969 women died.

Results In the total population, the adjusted hazard ratios (HR) (95% confidence interval [CI]) of B/C-PP ratio were: 1) for all-cause mortality: men, HR: 1.51 (95% CI: 1.47 to 1.56), women; HR: 2.46 (95% CI: 2.27 to 2.67) ($p < 0.0001$); and 2) for CV mortality: men, HR 1.81 (95% CI: 1.70 to 1.93); women, HR: 4.46 (95% CI: 3.66 to 5.45) ($p < 0.0001$). The B/C-PP impact on mortality did not significantly increase from younger men to those ≥55 years of age, from: HR: 1.44 (95% CI: 1.31 to 1.58) to HR 1.65 (95% CI: 1.48 to 1.84), but increased significantly with age in women: HR: 3.19 (95% CI: 2.08 to 4.89) versus HR: 5.60 (95% CI: 4.17 to 7.50) ($p < 0.01$). Thus, the mortality impact of B/C-PP ratio was 3-fold higher in women than in men ≥55 years old.

Conclusions PP amplification is highly predictive of differences in CV risk between men and women. In post-menopausal women, the attenuation of PP amplification, mainly related to increased aortic stiffness, contributes to the significant increase in CV risk. (J Am Coll Cardiol 2012;59:1771–7) © 2012 by the American College of Cardiology Foundation

A greater incidence of hypertension and cardiovascular (CV) complications is widely observed in men and post-menopausal women compared with pre-menopausal women. This epidemiological finding suggests that the female sex hormone estrogen and, to a lesser extent, the sex hormones progesterone and testosterone, possess, under clinical situations, significant vascular protective properties that disappear after menopause (1–7). However, recently, the effects of menopausal hormonal therapy (MHT), as well as data from randomized clinical trials such as the Women's Health Initiative study, challenged the hypothesis of the potential CV benefits of estrogen treatment (6,7). In these studies, the major role of blood pressure (BP) was poorly taken into consideration: more than one-third of the patients were hypertensive (38%).

Studies of pulsatile arterial hemodynamics have shown that BP in women presents very particular hemodynamic characteristics. First, there are classically 2 distinct components of BP: mean arterial pressure (MAP) and pulse pressure (PP) (8). Although MAP refers exclusively to steady pressure, vascular resistance and, hence, small arteries, PP refers to pulsatile pressure that has 3 determinants: stroke volume, arterial stiffness, and wave reflections. Only the latter 2 factors impinge on PP in large arteries and, in post-menopausal women, the role of PP predominates over that of MAP in the mechanism of high BP. Second, physiologically, PP and systolic BP (SBP) are consistently higher in peripheral than in central arteries for the same

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Abbreviations and Acronyms

B/C = brachial/carotid
BP = blood pressure
B-PP = brachial pulse pressure
CI = confidence interval
C-PP = carotid pulse pressure
CV = cardiovascular
DBP = diastolic blood pressure
HR = hazard ratio
MAP = mean arterial pressure
MHT = menopausal hormonal therapy
PP = pulse pressure
SBP = systolic blood pressure

MAP and diastolic BP (DBP) (8,9). This aspect, called SBP or PP amplification, is due to the changes in arterial stiffness, principally affecting the propagation of the pressure wave and wave reflections along the arterial tree (9). In post-menopausal women (10–12), SBP and PP amplification are considerably attenuated because central SBP and PP increase more rapidly with age than do brachial SBP or PP. Consequently, the brachial to carotid PP ratio (B/C) decreases with aging and arterial stiffness.

Recently, our group showed that brachial (B) PP, carotid (C) PP, and the B-PP/C-PP ratio (or B/C ratio) are all significant and independent CV risk factors and that the most powerful predictor of CV death is the B/C ratio (13). In the present study, our aim was to compare the respective impacts of C-PP, B-PP, or B/C ratio on mortality rates. Our working hypothesis is that the B/C ratio should be more significantly associated with the sex difference in age-dependent CV risk than C-PP or B-PP. To assess the observed mortality rates in both sexes in the general low-to-moderate risk population, we studied a large sample of 125,151 subjects. We determined mathematically the central carotid artery PP by an equation established in an independent sample of 834 subjects. Calculated for epidemiological purpose, this equation is not applicable to evaluation of C-PP in clinical practice.

Methods

Subjects. Subjects were examined at the IPC ("Investigations Preventives et Cliniques") Center (Paris, France). This medical center, which is subsidized by the French national health care system (Sécurité Sociale-CNAMTS), offers a free medical examination to working and retired individuals and their families and, thus, carries out approximately 25,000 health examinations per year for inhabitants of the Paris area.

The IPC study population consisted of 72,437 men (age 41.0 ± 11.1 years) and 52,714 women (age 39.5 ± 11.6 years) who had a health checkup at the IPC Center between January 1981 and December 1988 (Table 1). Subjects with previous CV disease were excluded, to focus on primary prevention. Although the specific date of menopause was not available in our global database, in a more recent cohort of 35,000 women examined in the IPC center, we found that after the age of 55 years, 98% had gone through menopause (data not shown). As a consequence, in the present study, women >55 years of age were considered as being post-menopausal.

Antihypertensive drug therapy (present or past) involved 4,499 patients (3.60% of the IPC population). The follow-up ended in 1998. During this period (mean duration: 12.1 ± 2.2 years), 3,028 men and 969 women died. Among these deaths, CV disease was responsible in 600 men and 135 women. The measurement methods employed were described in detail elsewhere (14). Briefly, supine BP was measured in the right arm using a manual mercury sphygmomanometer, after a 10-min rest period. The first and the fifth Korotkoff sounds were used to define SBP and DBP. The mean of 3 measurements was considered as the peripheral BP value. B-PP was calculated as SBP − DBP. Heart rate was classified in the database, according to categories with arbitrary cutoff points: <60, 60 to 80, 80 to 100, and >100 beats/min. Height (using a wall-mounted stadiometer) and weight (using calibrated scales) were recorded by a nurse. Standard biological parameters, including total plasma cholesterol, triglycerides, and glycemia, were measured under fasting conditions, and a resting electrocardiogram was recorded. Heart rate was measured on the electrocardiogram. Tobacco consumption (present: yes/no), physical activity (exercising >1 h of walking per day: yes/no), and personal medical history were assessed using a self-administered questionnaire. All clinical and biological parameters were evaluated on the same day of the examination.

Brachial and central carotid blood pressure measurements. To assess the mortality rates associated with CV causes in such a low-to-moderate CV risk population, we needed a large sample of subjects. As direct measurements of central carotid artery PP are not available in such a large population, at least in our institution, and at the time of recruitment, we determined this parameter mathematically from B-PP, using an equation first evaluated in an independent sample of 834 subjects and then validated in a second independent population of 285 individuals.

To assess a method of calculating C-PP, we selected a population of 834 subjects, taken from the Hotel Dieu Hospital population (MES), who had C-PP measured by applanation tonometry. The aim was to develop a method to determine C-PP by calculation, using multiple regression analysis associating B-PP (measured by sphygmomanometry), some significant risk factors, and other hemodynamic and biochemical variables (11,12,15,16), and to validate the method by comparison with C-PP values measured directly by tonometry. A complete description of the procedure is given in Benetos et al. (13).

Briefly, in 834 subjects, brachial BP determinations were performed in the supine position after a 15-min rest in the laboratory by traditional mercury sphygmomanometry. Central BP determinations were made by performing radial and carotid artery applanation tonometry using a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments, Houston, Texas) (8,11,12,17–19). The derived

Table 1 Characteristics of the Population According to Sex and Age

	Men		Women				
	Age <55 yrs (n = 62,888)	Age ≥55 yrs (n = 9,549)	Age <55 yrs (n = 46,187)	Age ≥55 yrs (n = 6,527)	Age Effect	Gender Effect	Age–Gender Interaction
Age (yrs)	38.3 ± 9.1	58.9 ± 4.7	36.8 ± 9.5	58.9 ± 4.9			
Weight (kg)	73.7 ± 10.6	75.4 ± 10.8	58.1 ± 9.4	61.2 ± 10.2	<0.0001	<0.0001	<0.0001
Height (cm)	174.2 ± 6.7	171.2 ± 6.6	161.1 ± 6.2	158.0 ± 6.0	<0.0001	<0.0001	<0.0001
Body mass index (kg/m^2)	24.3 ± 3.2	25.7 ± 3.2	22.4 ± 3.5	24.5 ± 3.9	<0.0001	<0.0001	<0.0001
Plasma glycemia (g/l)	1.02 ± 0.12	1.07 ± 0.20	0.95 ± 0.10	1.03 ± 0.14	<0.0001	<0.0001	<0.0001
Plasma creatinine (mg/l)	10.41 ± 1.25	10.66 ± 1.48	8.46 ± 1.15	8.76 ± 1.35	<0.0001	<0.0001	0.0008
Plasma cholesterol (g/l)	2.17 ± 0.45	2.37 ± 0.42	2.00 ± 0.39	2.49 ± 0.42	<0.0001	<0.0001	<0.0001
Systolic blood pressure (mm Hg)	133.8 ± 12.8	142.5 ± 16.3	126.6 ± 12.9	139.9 ± 17.2	<0.0001	<0.0001	<0.0001
Diastolic blood pressure (mm Hg)	82.2 ± 9.8	87.8 ± 10.6	77.3 ± 9.6	85.3 ± 10.4	<0.0001	<0.0001	<0.0001
Mean arterial pressure (mm Hg)	99.4 ± 10.2	106.0 ± 11.9	93.8 ± 10.1	85.3 ± 10.4	<0.0001	<0.0001	<0.0001
Heart rate ≥80 beats/min	10,142 (16.1)	1626 (17.0)	9,269 (20.1)	1173 (18.0)	<0.0001	<0.0001	<0.0001
Brachial PP (mm Hg)	51.6 ± 8.3	54.7 ± 10.1	49.3 ± 8.1	54.7 ± 10.9	<0.0001	<0.0001	<0.0001
Carotid PP (mm Hg)	33.5 ± 7.0	38.8 ± 8.8	39.9 ± 7.1	47.2 ± 9.4	<0.0001	<0.0001	<0.0001
Brachial/carotid PP	1.56 ± 0.10	1.43 ± 0.09	1.24 ± 0.04	1.16 ± 0.01	<0.0001	<0.0001	<0.0001
Hypertensive subjects	26,530 (42.2)	6,495 (68.1)	10,301 (22.3)	3,883 (59.7)	<0.0001	<0.0001	<0.0001
Antihypertensive treatment*	1,459 (2.32)	967 (10.1)	1134 (2.46)	939 (14.4)	<0.0001	<0.0001	<0.0001
Current smokers	22,238 (35.4)	2,269 (23.8)	11,670 (25.3)	702 (10.8)	<0.0001	<0.0001	<0.0001
Subjects with aspirin treatment or anti-inflammatory agent	4,879 (7.8)	990 (10.4)	6,468 (14.0)	1,318 (20.2)	<0.0001	<0.0001	<0.0001
All-cause mortality	1,929 (3.1)	1,099 (11.5)	604 (1.3)	365 (5.6)	<0.0001	<0.0001	<0.0001
Cardiovascular mortality	313 (0.5)	287 (3.0)	57 (0.12)	78 (1.2)	<0.0001	<0.0001	<0.0001

Values are mean ± SD or n (%). *With or without antidiabetic or hypolipidemic agent.
PP = pulse pressure.

pressure waveforms were recorded on a Gould 8188 recorder (Gould Electronic, Boulainvilliers, France) at a paper speed of 100 mm/s. Radial artery pressure waveform, calibrated from brachial artery SBP and DBP, was used for the determination of peripheral MAP via application of an integration method. Because DBP and MAP differences throughout the arterial tree do not exceed 2 to 3 mm Hg (8,17,20,21), the resulting carotid BP wave was calibrated using brachial DBP and MAP. MAP, 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 C-PP and SBP. C-PP is considered a close surrogate of aortic PP (22,23).

The reproducibility of hemodynamic measurements has been published in detail elsewhere, particularly regarding C-PP (22,23). PP amplification between C-PP and B-PP (mm Hg) was calculated as the B/C ratio. In the present subpopulation, the C-PP measured by tonometry and pulse wave analysis was compared with the values calculated from a sex-specific multiple regression analysis deduced from the same 834 patients studied, including 480 men and 354 women (equations are shown in the expanded Methods section; please see the Online Appendix). To further validate the C-PP evaluation, we applied these equations to another distinct population of 285 individuals (147 men, 138 women), investigated in the Nancy Hospital (France) (24,25) (please see the expanded Methods in the Online Appendix). We calculated the correlation between the evaluated C-PP and the measured C-PP using the same methodology (applanation tonometry) but performed by another trained investigator. The observed R^2 values were 0.888 ($p < 0.0001$) in men and 0.889 ($p < 0.0001$) in women. The Bland-Altman analysis for comparison of both methods for central PP determination showed that the 2 SDs for individual differences was 12.18 mm Hg in men and 12.45 mm Hg in women, without any drift of the regression lines (please see the expanded Methods section in the Online Appendix). The mean value for the individual difference in C-PP was −0.50 mm Hg in men and −6.45 mm Hg in women. After this validation, the calculation of C-PP was then applied to the total IPC population.

Statistical analysis. The impact of B-PP and C-PP and PP amplification (B/C ratio) on all-cause and CV mortality was evaluated using Cox regression models, including age, sex, height, weight, and risk factors (smoking, physical activity, cholesterol, and diabetes mellitus). Additional adjustment for MAP in the Cox regression model was also performed. Because the B/C ratio is known to be highly influenced by pulse rate (13), models also included pulse rate as an adjusting factor. Hazard ratios (HR) for all-cause and CV mortalities (HR and 95% confidence interval [CI]) were calculated for each increase of 1 SD of B-PP, C-PP, and the B/C ratio. All quantitative variables used in the regression model or in the C-PP equation were normally distributed, and colinearity assessment was taken into account in multivariate analysis. The presence or absence of antihypertensive therapy did not modify the results. For overall mortality, a single model for C-PP showed, in the total population, a sex

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interaction for the B/C ratio ($p < 0.0001$; data not shown) that allowed us to perform a separate analysis in men and women. To evaluate the effect of sex, Cox regression models were carried out separately in men and women. To compare the effect of sex in both age classes, a Cox regression model, including an interaction term between sex and B/C ratio, was calculated.

Secondly, the effect of age was investigated by dividing men and women into 2 categories (<55 or ≥55 years of age) and analyzing men and women separately. The threshold of 55 years of age was chosen for this analysis because of its link with the menopause. HRs were adjusted for height, weight, risk factors (smoking, physical activity, cholesterol, and diabetes mellitus), and heart rate. The interaction of age was calculated.

All statistical analyses, including interactions, were performed with SAS statistical software (version 8.2, SAS Institute, Cary, North Carolina), and a p value <0.05 was considered significant.

Results

Clinical characteristics of the population. The population was composed of 72,437 men (age 41.0 ± 11.1 years) and 52,714 women (age 39.5 ± 11.6 years). MAP was 100.3 ± 10.7 mm Hg in men and 95.0 ± 10.8 mm Hg in women. B-PP was 52.0 ± 8.6 mm Hg and 49.9 ± 8.7 mm Hg, calculated C-PP was 34.2 ± 7.5 mm Hg and 40.8 ± 7.8 mm Hg, and the B/C ratio was 1.54 ± 0.11 and 1.23 ± 0.05 in men and women, respectively ($p < 0.0001$).

Table 1 shows the characteristics of the population divided into 2 categories of age. The younger men had the highest mean value of B/C ratio (1.56 ± 0.10), whereas the older women showed the lowest (1.16 ± 0.01). The sex–age interaction was significant, with a greater decrease in B/C ratio with age in men than in women. A sex–age interaction was also observed for B-PP and C-PP separately. The mortality risk increased with age, particularly the CV risk of death: 0.5% in men <55 years of age, and 3.0% in men ≥55 years of age, and 0.12% and 1.2% in women, respectively. The age–sex interaction was significant with a greater increase in CV mortality with age in women than in men.

Risk of mortality according to sex. For all-cause mortality and CV mortality (Table 2), the HRs for B-PP, calculated C-PP, and B/C ratio were highly significant in the overall population.

Concerning all-cause mortality, the B/C ratio HR was significantly different between men and women after adjustment for age, height, weight, smoking, physical activity, cholesterol, diabetes mellitus, and heart rate; the HR was higher in women than in men ($p < 0.0001$). However, the differences observed for B-PP and C-PP HRs between sexes were not statistically significant. The CV mortality risk associated with the B/C ratio was also higher in women than in men ($p < 0.0001$) and moreover, similar significant sex differences in HR were observed for both B-PP and C-PP.

Table 2 Adjusted Risk (HR) of All-Cause Mortality and CV Mortality According to Sex in the Overall Population

	Men	Women	p Value
All-cause mortality HR			
Brachial PP	1.17 (1.14–1.21)	1.07 (1.01-1.14)	0.31
Carotid PP	1.39 (1.35–1.44)	1.35 (1.28-1.42)	0.88
B/C ratio	1.51 (1.47–1.56)	2.46 (2.27–2.67)	<0.0001
CV mortality HR			
Brachial PP	1.18 (1.11–1.25)	1.25 (1.12–1.40)	0.02
Carotid PP	1.50 (1.42–1.59)	1.72 (1.57–1.89)	0.01
B/C ratio	1.81 (1.70–1.93)	4.46 (3.66–5.45)	<0.0001

Adjusted risk of all-cause mortality and cardiovascular (CV) mortality (hazard ratio [HR] and 95% confidence interval) associated with the increase of 1 SD in brachial pulse pressure (PP), carotid PP, and carotid/brachial (B/C) ratio. Adjustments were made for age, height, weight, smoking, physical activity, cholesterol, diabetes mellitus, and heart rate. Additional adjustment for gender was performed for the overall group analysis. *Men versus women.

Sex interaction of risk according to age. The p values of sex interactions in the total population showed, for overall mortality, a sex interaction observed for the B/C ratio in patients both <55 and ≥55 years of age ($p < 0.0001$). For CVD mortality, p values were significant for C-PP ($p = 0.04$) in those ≥55 years of age and for the B/C ratio in those <55 and ≥55 years of age ($p = 0.008$ and $p < 0.0001$, respectively).

Figure 1 shows values of HRs for CV risk associated with the B/C ratio and sex interactions in men and women in the 2 age groups (<55 and ≥55 years of age). This HR was higher for women than for men. In men, the change in HR with age was not statistically significant (HR: 1.44 [95% CI: 1.31 to 1.58] vs. HR: 1.65 [95% CI: 1.48 to 1.84]), but for women it significantly increased (HR: 3.19 [95% CI: 2.08 to 4.89] vs. HR: 5.60 [95% CI: 4.17 to 7.50]) ($p < 0.01$). The mortality impact of the B/C ratio was 3-fold higher in women than in men ≥55 years of age ($p < 0.0001$). The inclusion of MAP as a covariate (data not shown) or a supplementary adjustment on MAP did not alter these results (men <55 years: HR: 1.29 [95% CI: 1.17 to 1.42]; men ≥55 years: HR: 1.56 [95% CI: 1.39 to 1.74]; women, <55 years: HR: 2.59 [95% CI: 1.67 to 4.02]; women ≥55 years: HR: 5.83 [95% CI: 4.29 to 7.92]).

Discussion

In this study, we investigated a large sample of the general population in whom we measured B-PP noninvasively and also calculated C-PP. The validation of the methodological basis of the C-PP calculation was already published (13). C-PP was measured using a tonometric sensor in a first unrelated population of 834 patients to evaluate the determinants of C-PP, among the classical parameters available in a large cohort of subjects. We further confirmed this validation in a second unrelated population.

Both C-PP and B-PP individually had significant predictive value on overall and CV mortality, independently of

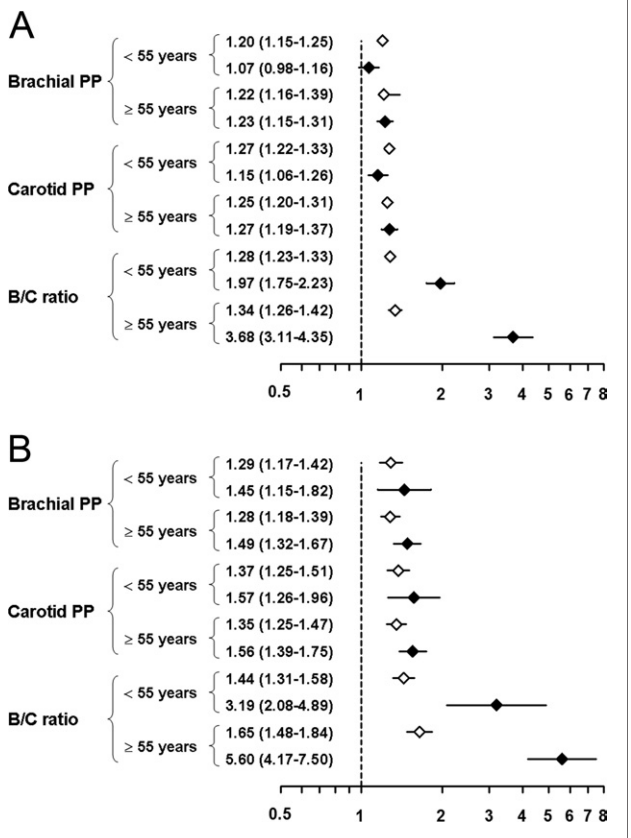

Figure 1 **Forest Plot**

Adjusted risk of all-cause **(A)** and cardiovascular mortality **(B)** according to sex and age (**open diamonds** = men; **solid diamonds** = women). Hazard ratio (95% confidence interval) associated with the increase of 1 SD in brachial pulse pressure (PP), carotid PP, and/or the decrease of 1 SD in brachial/carotid (B/C) PP ratio. Adjustments were made for height, weight, risk factors (smoking, physical activity, cholesterol, and diabetes mellitus), and heart rate.

standard CV risk factors. Furthermore, PP amplification, expressed as the B/C ratio, was strongly associated with both CV and overall mortality risk, with a much higher HR for the B/C ratio compared with that of B-PP or C-PP alone. Thus, after adjustment for age, height, standard risk factors, drug treatment, and heart rate, a decrease in PP amplification of 1 SD was associated with an increase of 51% for all-cause mortality, an 81% increase for CV mortality in men, a 146% increase for women for overall mortality, and a 346% increase for CV mortality. In our population, heart rate was not included in the equation for calculation of C-PP because in the database it was classified according to categories with arbitrary cut-off points (i.e., <60, 60 to 80, 80 to 100, and >100 beats/min), and, as such, it accounted for only 2% of variability of C-PP. However, the results were adjusted for heart rate. The CAFE (Conduit Artery Function Evaluation) study showed that heart rate explained 9% of central pulse pressure measured with Sphygmocor (AtCor, Sydney, Australia) (26). The facts that the population studied was a hypertensive population with high risk and that the beginning of the arterial study took place after the first year of the inclusion and treatment probably explains this unexpectedly high impact. Finally, the disappearance of PP amplification indicated a significantly higher risk of CV mortality in women than in men. Because only a relatively small number of subjects, particularly women, died during the observation period, this finding was probably slightly underestimated.

An important advantage of the present C-PP calculation results from the use of a validated stepwise multiple regression, which associates hemodynamic and biological variables with a very high proportion of explained variance (86%) (13). When PP amplification is calculated as the B/C ratio, this ratio is influenced only by the reliability of detection of the B-PP by the auscultatory method and the methodology used to estimate the central aortic or carotid pulse (9,20,21).

The present study confirms that all-cause mortality and CV mortality (Table 1) are higher in men than in women, both at <55 and ≥55 years of age. However, there is a greater increase in CV mortality with age in women than in men, and the major finding of this study concerns the impact of the B/C ratio on CV mortality. This impact is largely increased in women ≥55 years compared with younger women. Such an increase was not observed in men. At ≥55 years of age, the impact of the B/C ratio on CV mortality was 3-fold higher in women than in men. The main putative cause of this sex difference is the menopausal change, particularly via its effects on large artery behavior (1–7) and CV events. The fact that the most important observations of this study concerned the large arteries of older women (≥55 years), suggests that, independently of the standard aging process, the loss of estrogenic action in the carotid and brachial arterial wall might play a specific deleterious role, increasing arterial stiffness and reducing elasticity, as previously observed by others (27–29). We show, for the first time, that in men, the well-established increase in aortic stiffness with age (30,31) does not result in the same epidemiological consequences as in women. We propose that the B/C ratio should be interpreted, taking into account estrogenic status as recently demonstrated by our group in the metabolic syndrome, which is mainly associated with hormonal changes and inflammation (32).

Study limitations. Some limitations of the study should be acknowledged. As mentioned, we were not able to directly measure the carotid artery PP by applanation tonometry in these 125,151 subjects. However, we tried hard to circumvent this limitation by a calculation based on a subgroup of 834 subjects of both sexes and to validate the sex equations in 285 individuals studied in the Nancy Hospital (V.R., P.L.). We did not include heart rate in the calculation of C-PP because it was classified into categories with arbitrary cutoff points and accounted for no >2% in the variability. A second limitation is the lack of data on morbidity for these 125,151 subjects, particularly in the CV domain. Our database does not include such data. However, the mortality

data are robust and have been previously validated. The cause of death is drawn from the only official French institution that documents French mortality, the Cepid INSERM (SC8 department of the National French Institute of Health and Medical Research). It is clear that in the field of CV disease, particularly in the 1980s, the CV mortality rate did not correspond to the general impact of the disease because of the many successful interventional coronary and arterial procedures. However, we are convinced of the robustness of the data, despite this limitation, particularly in view of the large size of the sample studied. The menopause status was not specifically assessed in our questionnaire. However, we have obtained data in a different subpopulation of the IPC cohort, suggesting that at 55 years of age 98% of women have gone through menopause. The last limitation is the lack of high-density lipoprotein and low-density cholesterol data for assessing risk factors and CV mortality. Unfortunately, our database at the period of this cohort did not include the measurement of high-density lipoprotein cholesterol. We thus adjusted for total cholesterol in our analysis.

Conclusions

This epidemiological study shows that a large scale evaluation of central to peripheral pulsatility amplification is independently associated with CV mortality. However, it is not applicable to the individual calculation of carotid artery PP for clinical use. In the past, studies of BP in menopausal and post-menopausal women have largely been based on its steady component, MAP, and consequently on its principal determinant, total peripheral resistance (small arteries) (33). Using the B/C ratio, our findings show that 3 major components of arterial pressure are involved in hemodynamics and prognosis: steady pressure, PP, and regional distribution of pulsatility. We show for the first time that the latter component is a major contributor to mortality risk, principally in women (30,34). For this reason, the effects of menopausal hormonal therapy in controlled trials should be analyzed in older women on the following basis: 1) the choice of drugs acting on arterial stiffness and wave reflections, which depends on the status of pre-existing CV disease; 2) the specific analysis of the type of estrogen used, and its dose and mode of administration (probably acting differently on small and large arteries); and 3) epidemiological findings principally evaluated in women. We speculate on such a basis, that the optimal antihypertensive drug therapy of hypertension should differ markedly between men and women.

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

APPENDIX

For the expanded Methods section, please see the online version of this article.