Pulse Pressure and Cardiovascular Mortality in Normotensive and Hypertensive Subjects

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Pulse Pressure and Cardiovascular Mortality in Normotensive and Hypertensive Subjects

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Abstract—There is now increasing evidence that high pulse pressure, which is an indicator of large artery stiffness, is an independent risk factor for cardiovascular mortality, especially coronary mortality, in different populations. We have recently shown in a large French population that in male subjects aged 40 to 69 years, increased pulse pressure was a strong predictor of cardiovascular mortality, especially coronary mortality. In the present report, we analyzed the effect of pulse pressure in men and women of the same cohort after classifying them as normotensive (systolic blood pressure [SBP] <140 mm Hg and DBP <90 mm Hg) or hypertensive (SBP ≥160 mm Hg or DBP ≥95 mm Hg). After adjustment for age, mean blood pressure, and other risk factors, the relative risk (95% confidence limits) for cardiovascular mortality for an increase of 10 mm Hg of pulse pressure was 1.20 (1.01 to 1.44) in normotensives and 1.09 (1.03 to 1.14) in hypertensives. Cardiovascular and coronary death rates were similar in the group of normotensive men with a pulse pressure >50 mm Hg and in the group of hypertensive men with a pulse pressure <45 mm Hg. No association between cardiovascular mortality and pulse pressure was observed in either normotensive or hypertensive women (0.85 [0.60 to 1.21] and 1.0 [0.91 to 1.11], respectively). Low mortality rates could explain this observation in normotensive but not in hypertensive women, in whom cardiovascular mortality rates were relatively high. Because a high pulse pressure in men is an independent predictor of cardiovascular mortality in both hypertensives and in those considered as having normal blood pressure, this parameter could aid in evaluating cardiovascular risk. **(*Hypertension*. 1998;32:560-564.)**

Key Words: cardiovascular diseases ■ coronary artery disease ■ mortality ■ blood pressure ■ normotension ■ hypertension, essential

Aging and environmental and genetic factors are responsible for structural and functional changes of the arterial wall media leading to decreased elasticity and increased stiffness.[1,2] The alteration of large artery elasticity has deleterious effects on the heart and is responsible for an inadequate increase in systolic pressure and a relative decrease in aortic diastolic pressure at any given value of mean arterial blood pressure (MBP).

We have recently shown in a large French population that in male subjects aged 40 to 69 years, increased pulse pressure (PP) was a strong predictor of general and cardiovascular mortality, especially coronary mortality.[3] An analysis of the Survival and Ventricular Enlargement (SAVE) study showed that PP measured at the site of the brachial artery was a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function.[4] These data, in addition to data from previous studies in hypertensives,[5] suggest that PP itself could be a major predictor of cardiac risk in different populations.

Compared with our previous analysis, the purpose of this study was to evaluate whether the role of PP on cardiovascular mortality is significant in normotensive and hypertensive subjects of both genders. We therefore analyzed the effect of PP in men and women after classifying them as normotensive (systolic blood pressure [SBP] <140 mm Hg and diastolic blood pressure [DBP] <90 mm Hg) and hypertensive (SBP ≥160 mm Hg or DBP ≥95 mm Hg).

Methods

Subjects

The French public healthcare system (Securité Sociale–Caisse Nationale d'Assurance Maladie [CNAM]) provides all working and retired persons and their families with a free health examination every 5 years. The Centre d'Investigations Préventives et Cliniques (IPC) is one of the largest medical centers of this kind in France, having performed approximately 15 000 examinations per year since 1970 for persons living in the Paris area. In this study, we present data of the normotensive and hypertensive men and women aged 40 to 69 years who had a health checkup at the IPC Center during the period of May 1972 through May 1977. The general characteristics of this population have been described previously.[3]

In the present analysis, we included male and female subjects defined as normotensive or hypertensive. Normotensives were subjects with SBP <140 mm Hg and DBP <90 mm Hg and without any antihypertensive treatment (5503 women and 7128 men). Hypertensives were subjects with SBP ≥160 mm Hg or DBP ≥95 mm Hg (1945 women and 5379 men). All other subjects with intermediate blood pressure values were excluded from the present analysis.

A nurse measured supine blood pressure in the right arm using a manual sphygmomanometer. After a 10-minute rest period, blood pressure was measured 3 times, and the mean of the last 2

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TABLE 1. Description of Population According to PP: Normotensive Subjects (SBP <140 and DBP <90 mm Hg)

	Women				Men			
	PP≤45	45<PP≤50	PP>50	*P*, ANOVA	PP≤45	45<PP≤50	PP>50	*P*, ANOVA
n	2609	1976	918		2676	2910	1542	
Age, y*	48.9±6.9	50.8±7.7	51.8±8.5	<0.0001	49.3±7.1	49.9±7.4	50.5±7.8	<0.001
BMI, kg/m^2†	22.8±0.06	23.1±0.07	23.1±0.10	<0.0001	24.3±0.05	24.6±0.05	24.6±0.07	<0.001
SBP, mm Hg†	117±0.13	126±0.16	129±0.23	<0.0001	120±0.10	128±0.10	131±0.14	<0.0001
DBP, mm Hg†	75.9±0.13	75.5±0.15	72.3±0.22	<0.0001	78.5±0.10	77.8±0.10	73.7±0.14	<0.0001
Cholesterol, mg/dL†	215±0.67	217±0.78	216±1.15	NS	217±0.68	217±0.65	218±0.90	NS

*Mean±1 SD; †Adjusted by age and presented as mean±1 SEM.

measurements was calculated. The first and fifth Korotkoff phases were used to define SBP and DBP. Smoking status and physical activity were assessed using a self-administered questionnaire containing dichotomic (yes or no) questions regarding tobacco use. Plasma cholesterol was measured with a Technicon SMA-12.

The follow-up study period ended in December 1994 (mean follow-up was 19.5 years). Deceased subjects were identified through the mortality records of the Institut National de Statistiques et d'Etudes Economiques (INSEE) following the procedure previously detailed.[3] Following this procedure, it was determined that 3135 subjects of our cohort had died during the follow-up period. Causes of mortality were taken from the death certificates. These data were provided by the Department of Mortality of INSERM (Unit SC 8). Causes of death were codified according to the *International Classification of Disease* (8th revision until 1978 and 9th revision after 1979).

Data Analysis

In each of the 4 groups identified according to gender and presence or absence of hypertension, the role of PP was studied either as a qualitative parameter (separation according to the 4 quartiles of PP defined in the whole population) or as a continuous quantitative parameter. The qualitative separation was accomplished by dividing each group into PP quartiles defined as $PP_1 \leq 45$; $45 < PP_2 \leq 50$; $50 < PP_3 < 65$; and $PP_4 \geq 65$ mm Hg. This classification is the closest to the quartile distribution in the whole population by steps of 5 mm Hg. However, in normotensives the number of PP_4 was too low, leading us to regroup PP_3 and PP_4.

The following statistical tests were used for comparisons among the PP groups: (1) After adjustment for age, mean values of body mass index (BMI), blood pressure, and total cholesterol were compared using a 1-way ANOVA. (2) Deaths for the different causes of mortality were compared using a trend χ^2 test. (3) The role of PP as a quantitative or qualitative variable for the different causes of mortality was tested using a multivariate Cox regression controlling for age, MBP, total cholesterol, and tobacco consumption.

Results

Tables 1 and 2 summarize the mean values of age, BMI, blood pressure, and total cholesterol (values were adjusted for age) in the different groups according to the PP level. In all groups, age and SBP increased progressively from the first to the fourth PP group, whereas DBP was significantly lower in the subgroups with the higher PP. BMI was slightly but significantly higher in the higher PP groups.

All-cause and total cardiovascular mortality were consistently more elevated in the higher PP groups both in normotensive men (Table 3) and in hypertensive men and women (Table 4). However, the multivariate Cox regression analysis controlling for age alone (Table 5a) or age and other risk factors such as MBP, total cholesterol, and tobacco consumption (Table 5b) showed that the association between cardiovascular mortality and PP was significant in the 2 groups of men but not in women. The Cox analysis showed that in hypertensive women, MBP was a significant determinant for cardiovascular mortality with a relative risk (RR) for an increase in 10 mm Hg of 1.16 (95% confidence limits, 1.02 to 1.32). In normotensive women, undoubtedly due to the low mortality rates, only age had a predictive value in the different causes of mortality.

In men, an elevation in PP of 10 mm Hg significantly increased the RR of cardiovascular mortality by 20% in normotensives and by 9% in hypertensives (Table 5). Comparing this with the effects of MBP, we observed that an elevation in MBP of 10 mm Hg significantly increased the RR of cardiovascular mortality in hypertensive (RR, 1.14 [95% confidence limits, 1.07 to 1.21]) but not in normotensive men (1.10 [0.88 to 1.40]). The effects of PP on the cardiovascular mortality were related to its influence on coronary mortality but not cerebrovascular mortality. The latter was influenced by MBP levels (data not shown) but not by PP levels (Table 5). When PP was considered as a qualitative parameter, the RR for cardiovascular mortality in male subjects with a PP >50 mm Hg versus those with a PP

TABLE 2. Description of Population According to PP: Hypertensive Subjects (SBP ≥160 or DBP ≥95 mm Hg)

	Women					Men				
	PP≤45	45<PP≤50	50<PP<65	PP≥65	*P*, ANOVA	PP≤45	45<PP≤50	50<PP<65	PP≥65	*P*, ANOVA
n	199	288	388	1070		827	1018	1198	2336	
Age, y*	52.5±7.9	54.2±8.4	56.4±8.0	60.6±7.2	<0.0001	50.1±7.1	51.8±7.7	53.2±8.0	56.4±8.6	<0.001
BMI, kg/m^2†	24.8±0.30	25.1±0.25	25.9±0.21	25.7±0.13	<0.001	26.2±0.11	26.6±0.10	26.7±0.10	26.7±0.07	<0.01
SBP, mm Hg†	143±1.02	153±0.84	163±0.71	177±0.44	<0.0001	145±0.50	154±0.44	165±0.40	178±0.30	<0.0001
DBP, mm Hg†	103±0.74	102±0.61	104±0.52	99±0.32	<0.0001	105±0.40	104±0.36	106±0.33	102±0.24	<0.0001
Cholesterol, mg/dL†	233±2.77	239±2.29	236±1.94	239±1.20	NS	222±1.29	225±1.16	229±1.06	227±0.77	<0.001

*Mean±1 SD; †Adjusted by age and presented as mean±1 SEM.

TABLE 3. Mortality Rates in Normotensive Subjects (SBP <140 and DBP <90 mm Hg) According to PP Levels

	Women				Men			
	All-Cause (P=0.01)	Cardiovascular (NS)	Coronary (NS)	Stroke (NS)	All-Cause (P=0.003)	Cardiovascular (P=0.001)	Coronary (P=0.004)	Stroke (NS)
PP≤45	133 (5.1)	28 (1.1)	11 (0.4)	6 (0.2)	307 (11.5)	73 (2.7)	31 (1.2)	13 (0.5)
45<PP≤50	131 (6.6)	24 (1.2)	9 (0.5)	7 (0.4)	370 (12.7)	102 (3.5)	56 (1.9)	15 (0.5)
PP<50	69 (7.5)	17 (1.9)	7 (0.8)	3 (0.3)	233 (15.1)	74 (4.8)	39 (2.5)	12 (0.8)
Total	333 (6.1)	69 (1.3)	27 (0.5)	16 (0.3)	910 (12.8)	249 (3.5)	126 (1.8)	40 (0.6)

Values are number of deaths (%).

≤50 mm Hg was increased by 40% in normotensives and 48% in hypertensives (Figure). This association was related to an increase in coronary mortality but not in cerebrovascular mortality in both normotensive and hypertensive men.

Comments

The main finding of this study is that in a large unselected population, PP is an independent predictor of cardiovascular mortality in both normotensive and hypertensive men. Therefore, PP measurement may help in the evaluation of individual risk and therefore in therapeutic decision-making. In women, the same association between PP and cardiovascular mortality was observed in those with hypertension. The higher the PP, the higher the cardiovascular mortality. However, after adjustment for age alone or age and other risk factors, this association lost its significance. This lack of association can be explained only partially by the low statistical power of our analysis. In normotensive women, we are unable to draw any conclusions because cardiovascular mortality rates are very low in this particular subpopulation. However, in hypertensive women, we observed that mortality rates from cardiovascular disease, especially coronary heart disease, were higher than in normotensive men. In this latter subpopulation, PP is a strong predictor of cardiovascular and coronary mortality. Moreover, in hypertensive women, MBP was a predictor of the different causes of mortality. Interestingly, several studies,[6] showed similar gender differences concerning heart rate; for example, increased heart rate was a significant predictor of cardiovascular mortality, especially coronary mortality, in men but not in women. Larger studies are needed to evaluate whether gender can influence the role of cyclic stress (depending on PP and heart rate) on the cardiovascular system.

There is now increasing evidence that high PP reflecting large artery stiffness is a significant independent risk factor for cardiovascular, especially coronary, mortality in different populations. Madhavan et al[5] reported that untreated hypertensive subjects with a PP >63 mm Hg had an increased risk of cardiovascular complications. In addition, they found that these subjects were at greater risk of myocardial infarction when there was too great a fall in DBP after treatment. The same group later reported that in a larger population of treated and untreated hypertensive subjects, PP was the only blood pressure measurement independently related to the in-treatment incidence of myocardial infarction.[7] The link between PP and cardiovascular complications has also been shown in subjects who had myocardial infarction with left ventricular dysfunction.[4] In this population, a single measurement of PP 3 to 16 days after myocardial infarction was a significant predictor of recurrent cardiovascular events. We recently reported that PP is a significant predictor of cardiovascular mortality in a general male population aged 40 to 69 years. The present study shows that the evaluation of PP is of interest even in individuals with normal values of SBP (<140 mm Hg) and DBP (<90 mm Hg). Our results presented in Table 5 show that evaluation of PP could be of even more interest for normotensives than hypertensives, since the odds ratios for cardiovascular and coronary mortality corresponding to the increase of 10 mm Hg of PP are higher than those for hypertensives. The lack of such a difference between normotensive and hypertensive subjects in the qualitative analysis (presented in the Figure) is explained by a larger difference in PP levels between "low" and "high" PP individuals in the hypertensive group.

As expected, hypertensive individuals globally showed higher mortality levels than normotensive men (Tables 3 and 4). However, cardiovascular, especially coronary, death rates

TABLE 4. Mortality Rates in Hypertensive Subjects (SBP ≥160 or DBP ≥95 mm Hg) According to PP Levels

	Women				Men			
	All-Cause (P=0.001)	Cardiovascular (P=0.001)	Coronary (NS)	Stroke (P=0.06)	All-Cause (P=0.001)	Cardiovascular (P=0.001)	Coronary (P=0.001)	Stroke (P=0.03)
PP≤45	16 (8.0)	8 (4.0)	4 (2.0)	3 (1.5)	138 (16.7)	50 (6.0)	18 (2.2)	13 (1.6)
45<PP≤50	47 (16.3)	15 (5.2)	6 (2.1)	6 (2.1)	207 (20.3)	73 (7.2)	49 (4.8)	13 (1.3)
50<PP<65	54 (13.9)	23 (5.9)	6 (1.6)	9 (2.3)	317 (26.5)	112 (9.4)	62 (5.2)	28 (2.3)
PP≥65	261 (24.4)	114 (10.7)	38 (3.6)	45 (4.2)	852 (36.5)	370 (15.8)	180 (7.7)	74 (3.2)
Total	378 (19.4)	160 (8.2)	54 (2.8)	63 (3.2)	1514 (28.2)	605 (11.3)	309 (5.7)	128 (2.4)

Values are number of deaths (%).

TABLE 5. Relative Risks and 95% Confidence Limits of Mortality Corresponding to an Increase of 10 mm Hg of PP

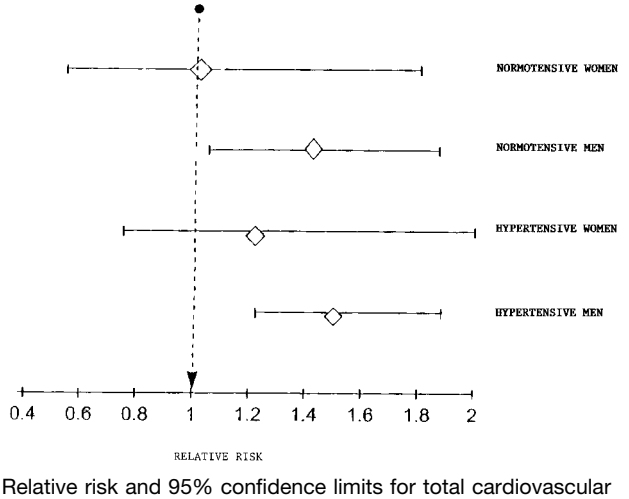
Population	All-Cause	Cardiovascular	Coronary	Stroke
Adjusted for age only				
NT women	1.00 (0.86–1.17)	0.85 (0.61–1.21)	0.87 (0.51–1.52)	0.81 (0.39–1.70)
HT women	1.10 (1.03–1.16)	1.01 (0.96–1.15)	1.10 (0.92–1.28)	1.09 (0.95–1.26)
NT men	1.07 (0.97–1.18)	1.20 (1.00–1.45)	1.26 (0.96–1.62)	1.12 (0.70–1.77)
HT men	1.11 (1.07–1.18)	1.13 (1.08–1.18)	1.12 (1.05–1.19)	1.08 (0.96–1.20)
Adjusted for age and other risk factors				
NT women	1.00 (0.86–1.17)	0.85 (0.60–1.21)	0.88 (0.51–1.52)	0.80 (0.38–1.69)
HT women	1.07 (0.99–1.14)	1.00 (0.91–1.11)	1.10 (0.92–1.30)	0.99 (0.85–1.16)
NT men	1.07 (0.97–1.18)	1.20 (1.01–1.44)	1.24 (0.97–1.61)	1.12 (0.70–1.78)
HT men	1.07 (1.04–1.11)	1.09 (1.03–1.14)	1.07 (0.98–1.14)	1.05 (0.94–1.18)

NT indicates normotensive; HT, hypertensive. Values are relative risk (95% confidence limit).

were similar in normotensive men with a PP >50 mm Hg and in hypertensive men with PP <45 mm Hg. This result was unchanged using a multivariate Cox regression analysis after adjustment for age and other risk factors.

Thus, according to our results, normotensive men that are in the higher PP group (mean values of SBP, 131 mm Hg; DBP, 73 mm Hg; MBP, 92 mm Hg; PP, 58 mm Hg) have (1) an increased relative cardiovascular risk of 40% compared with normotensives who belong in the lower PP group (SBP, 120 mm Hg; DBP, 78 mm Hg; MBP, 92 mm Hg; PP, 42 mm Hg), and (2) a similar cardiovascular risk as hypertensive subjects who belong in the lower PP group (SBP, 145 mm Hg; DBP, 105 mm Hg; MBP, 118 mm Hg; PP, 40 mm Hg).

Interestingly, increased PP was a predictor of coronary heart disease mortality, whereas its predictive value was not significant for cerebrovascular mortality. Physiologically, PP describes the oscillation around the mean arterial pressure (calculated as DBP plus one third PP) and is influenced by hemodynamic mechanisms that differ from those controlling mean arterial pressure. MBP is the pressure that would be present in the aorta and its major arteries during a given cardiac cycle if the cardiac output was nonpulsatile.[1,2] While mean arterial pressure remains nearly constant along the arterial tree, PP increases markedly from central to peripheral arteries as a consequence of a substantial increase in SBP and a small lowering of DBP. At a given stroke volume and velocity of ventricular ejection, the mechanisms influencing PP are related to the status of conduit arteries, ie, the viscoelastic properties of the arterial wall and the timing of the reflected waves. Increased stiffness and earlier wave reflections within the thoracic aorta increase the PP because of an increase in SBP and a decrease in DBP.[1,8] Alternatively, increased stroke volume or ventricular ejection rate may be responsible for an increase in SBP with no change in DBP. In the present study, we found that the highest PPs were due both to higher SBP and lower DBP. Thus, the changes in PP may be considered as markers of increased arterial stiffness, with consequences for cardiovascular mortality, especially coronary mortality.[9,10] The elevation in SBP causes a disproportionate increase in end-systolic stress, which is the principal hemodynamic factor that promotes the development of cardiac hypertrophy, increased ventricular oxygen consumption, and left ventricular hypertrophy,[11] and can compromise capacity for coronary perfusion.[10] These hemodynamic changes could explain why arterial stiffness and PP are related mainly to coronary and not cerebrovascular circulation. In our cohort, MBP was the most significant predictor of cerebrovascular mortality, and mean arterial pressure (but not PP) is the perfusion pressure of cerebral circulation.



Relative risk and 95% confidence limits for total cardiovascular mortality in subjects with PP >50 mm Hg compared with subjects with PP ≤50 mm Hg in the 4 groups of subjects according to gender and presence of hypertension.

In conclusion, this study showed that in both normotensive and hypertensive males, increased PP is an independent predictor of cardiovascular mortality. The lack of such an association in women could be partially explained by the lower cardiovascular mortality rates in this population.

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