A Decrease in Diastolic Blood Pressure Combined With an Increase in Systolic Blood Pressure Is Associated With a Higher Cardiovascular Mortality in Men

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OBJECTIVES	The study evaluated the risk of cardiovascular mortality according to combined spontaneous (non-treatment-related) changes in both systolic and diastolic blood pressure (BP).
BACKGROUND	Long-term longitudinal changes in blood pressure may be a more accurate determinant of cardiovascular risk since changes in systolic or diastolic blood pressure over a period of time reflect the evolution of arterial and arteriolar alterations.
METHODS	Two independent French male cohorts were studied: the IPC cohort (Investigations Préventives et Cliniques) composed of 15,561 men aged 20 to 82 years who had had two visits spaced four to 10 years apart, and the Paris Prospective Study composed of 6,246 men aged 42 to 53 years, examined annually for a period of four years. None of the subjects were taking antihypertensive medication. Annual changes in BP were estimated, and subjects were divided into groups according to the increase, lack of change, or decrease of systolic or diastolic BP. Nine groups were formed by combining the changes of systolic and diastolic BP. Cardiovascular mortality was assessed for a mean period of 13.5 years for the IPC Study and 17 years for the Paris Prospective Study.
RESULTS	In both cohorts, after adjustment for age and major risk factors, the group with an increase in systolic and a decrease in diastolic BP presented the highest relative risk of cardiovascular mortality compared to the group with no changes in either systolic or diastolic BP (relative risk: 2.07 [1.05 to 4.06] in the IPC Study and 2.16 [1.16 to 4.01] in the Paris Prospective Study).
CONCLUSIONS	Assessment of spontaneous changes of BP over a long period of time can contribute to the evaluation of cardiovascular risk. Subjects whose systolic BP increased while their diastolic BP decreased had the highest cardiovascular risk independently of absolute values of BP or other risk factors. (J Am Coll Cardiol 2000;35:673–80) © 2000 by the American College of Cardiology

In various epidemiological studies a strong positive relationship between cardiovascular disease and blood pressure (BP) has been reported (1,2). It has been shown that both systolic and diastolic BP are associated with cardiovascular disease risk. This is to be expected as these two parameters are closely correlated in most subjects. In 1980, the Framingham Study (3) showed that high systolic BP was the best predictor of both all-cause and cardiovascular mortality, even among individuals with diastolic hypertension. This study, and others as well, have shown that after adjustment for systolic BP, the relationship between diastolic BP and the risk of cardiovascular disease is either absent or negative, especially in subjects over 45 years of age (3,4). This observation suggests that diastolic BP levels, which are the gold standard criterion in most clinical trials, may not be specific or sensitive enough, and may at times even be misleading, in determining cardiovascular disease risk. We believe that this is due to the fact that diastolic BP levels may not reflect the importance of arterial and arteriolar alterations, which are associated with cardiovascular morbidity and mortality.

Thus, although high systolic BP usually reflects an elevation in total peripheral resistance and/or large artery stiffness, diastolic BP levels are influenced by arterial or

Abbreviations and Acronyms

BMI	=	body mass index
BP	=	blood pressure
Dia↑	=	increase in diastolic blood pressure
Dia↓	=	decrease in diastolic blood pressure
Dia↔	=	no change in diastolic blood pressure
INSEE	=	Institute National de Statistiques et d'Etudes Economiques
INSERM	=	National Institute of Health and Medical Research
IPC	=	Investigations Préventives et Cliniques
Sys↑	=	increase in systolic blood pressure
Sys↓	=	decrease in systolic blood pressure
Sys↔	=	no change in systolic blood pressure

arteriolar alterations in opposite ways: an increase in peripheral vascular resistance leads to an elevation in diastolic BP, whereas stiffening of large arteries can induce a decrease in diastolic BP (5,6). Therefore, normal levels of diastolic BP are influenced by the combination of these two vascular alterations, which are both independent risk factors of cardiovascular disease, especially coronary artery disease (7,8). This leads to the conclusion that levels of diastolic BP may not necessarily reflect cardiovascular risk, especially in older subjects among whom arterial stiffness is more frequent.

Long-term longitudinal changes in BP may be a more accurate determinant of BP-related risk; this is because changes in systolic BP or diastolic BP over a period of time reflect the evolution of arterial and arteriolar alterations. Witteman et al. (9) showed that, in women, a decrease in diastolic BP during a nine-year follow-up was associated with a progression of atherosclerotic lesions of the aorta. The investigators suggested that the decrease of diastolic BP could be a marker of atherosclerosis.

To our knowledge, there are no epidemiological data showing the effect of spontaneous (non-treatment-related) changes of systolic and diastolic BP over an extended period of time, on cardiovascular mortality. The present analysis was performed in two independent French male cohorts: the IPC (Investigations Préventives et Cliniques) cohort, consisting of 15,561 males who had had two visits spaced four to 10 years apart at the "IPC" Centre, and the Paris Prospective Study I, consisting of 6,246 men who had had an annual medical exam over a four-year period. The associations between combined changes in systolic BP and diastolic BP over this period were studied, and subsequent cardiovascular mortality was also assessed (a mean period of 13.5 years for the IPC Study and 17 years for the Paris Prospective Study, beginning after the last visit).

METHODS

Population and Mortality Data

The IPC Study. The French national health care system (Securité Sociale–CNAM) provides all working and retired persons and their families with a free medical examination. The IPC Center is one of the largest medical centers of this kind in France, having carried out approximately 20,000 examinations annually since 1970 for people living in the Paris area. Approximately 20% of those examined voluntarily come back four to 10 years later for another checkup (a minimum of four years between two visits is required to qualify for a free examination). In the IPC database, 17,439 male subjects had the first examination between 1973 and 1987 and a second one between 1978 and 1991. When subjects had more than two examinations, the first two were used for the analysis. Subjects with antihypertensive treatment at the time of the first or second visit, or those who had taken antihypertensive medication between the two visits, were excluded from the analysis (n = 1,568). Three hundred and ten additional subjects were eliminated because of missing clinical or mortality data. All other male subjects were included in this analysis. Thus, in the present study, data describe a population composed of 15,561 men aged 20 to 82 years (mean 42 ± 10 years).

Supine BP was measured in the right arm by a nurse, using a manual sphygmomanometer. After a 10-min rest period, BP was measured three times and the mean of the last two measurements was calculated. Family medical history (diabetes, hypertension, cardiovascular disease and sudden death before 60 years), personal drug regimen and tobacco consumption were assessed using a self-administered questionnaire. Blood samples for biological tests were drawn under fasting conditions.

The follow-up study period ended in December 1996. The minimum follow-up period after the second visit was 5 years, the maximum was 17 years, and the mean follow-up period was 13.5 years. Deceased subjects were identified from the mortality records at the Institut National de Statistiques et d'Etudes Economiques (INSEE). A patient from our cohort was classified as deceased when he had the same first name, last name, gender and date of birth as a person recorded in the INSEE mortality records during the period of the follow-up. By using this matching procedure, the identification error was less than 1%. Only subjects meeting all four of these criteria were classified as deceased. All other subjects were considered to be alive at the end of the follow-up period. Following this procedure, 874 subjects from our cohort were classified as having died during the follow-up period. Causes of mortality were taken from the death certificates. These data were provided by the Department of Mortality (SC 8) at the National Institute of Health and Medical Research (INSERM). Causes of death were codified according to the International Classification of Disease (8th revision until 1978, 9th revision thereafter).

Paris Prospective Study I. Details pertaining to recruitment, design, and procedures of the Paris Prospective Study I have been described elsewhere (10). Briefly, the first examination (baseline) for 7,746 French policemen aged 43 to 52 years was carried out between 1967 and 1972. Subjects

had a physical examination, provided blood samples for laboratory tests and answered questionnaires administered by trained interviewers, regarding sociodemographic factors, medical history and smoking habits. Each year following the baseline examination and up to four years after, all subjects were invited to undergo a similar follow-up examination. The number of participants per cohort who had one, two, three, four, or five examinations was 614, 604, 601, 1,671 and 4,456, respectively. During each examination, BP was measured in the sitting position after at least a 5-min rest, and the mean of two measurements was used for the analysis. Through inquiries made to hospitals, family physicians and medical services at work, men were followed up until January 1, 1994. Date and place of death were also noted, and the medical causes of death were obtained from death certificates from INSERM, in the same manner as for the IPC cohort. Of the 7,332 subjects who had at least two examinations, the vital status after an average follow-up of 17 years after the last examination was obtained for 6,892 subjects (94%). In the present study, we included all subjects of this cohort who did not receive antihypertensive treatment and for whom complete clinical and mortality data were obtained.

BP Change Calculation

The IPC Study. Individual annual changes in systolic BP and in diastolic BP were calculated as the difference between the second and the baseline value, divided by the time between the two visits. Mean time delay between the first and the second visit was 6.1 ± 1.7 years. Blood pressure increased significantly over time in the entire population (0.2 ± 2.5 and 0.2 ± 2.0 mm Hg per year for systolic BP and diastolic BP, respectively, p < 0.001 for each). Annual changes in systolic BP and in diastolic BP were regressed on baseline values, and residuals were divided into tertiles. For systolic BP, the lowest tertile (i.e., a decrease [↓] in systolic BP) included men whose systolic BP fell by >5.4 mm Hg per five years; the highest tertile (i.e., an increase [↑] in systolic BP) included those whose systolic BP increased by >3 mm Hg per five years; and the intermediate tertile was considered as a lack of change (↔) in systolic BP. The respective cutoff points for tertiles for diastolic BP changes were −2 mm Hg and +3 mm Hg per five years. Nine groups of subjects were formed by combining the changes of systolic BP and diastolic BP between the two visits.

Paris Prospective Study I. Changes in systolic BP and in diastolic BP from the first through the last (fifth or less) examination were estimated using a within-person linear regression method. Systolic BP and diastolic BP were regressed onto calendar time. On the average, systolic BP increased and diastolic BP significantly decreased over time in the entire population (0.2 ± 5.2 mm Hg per year; p = 0.004 and −0.5 ± 4.0 mm Hg per year; p < 0.001, respectively). The resulting annual average systolic BP and diastolic BP changes (regression slopes) were then regressed

Table 1. Patient Characteristics for the Two French Cohorts Recorded During the First Visit and Number of Cardiovascular Deaths During Follow-up

	IPC Study	Paris Prospective Study I
Number of subjects	15,561	6,246
Number of CV deaths	207	475
Age (yrs)	41.9 (9.8)	47.1 (2.0)
BMI (kg/m^2)	24.4 (2.8)	25.8 (3.2)
Systolic BP (mm Hg)	132.6 (13.4)	137.9 (19.1)
Diastolic BP (mm Hg)	81.6 (9.9)	81.9 (14.6)
Cholesterol (mmol/liter)	5.55 (0.98)	5.70 (1.1)
Triglycerides (mmol/liter)	1.09 (0.86)	1.53 (1.24)
Glycemia (mmol/liter)	5.70 (0.81)	5.69 (0.85)
Current smokers (%)	27.9	73.4
Ex-smokers (%)	40.3	10.5

on baseline values, and residuals were divided into tertiles. The cutoff points for tertiles were −10.6 and +5.9 mm Hg per five years for changes in systolic BP and −6.7 and +5.4 mm Hg per five years for changes in diastolic BP. The final sample consisted of 6,246 subjects who were not treated for hypertension and for whom complete data were available.

Statistical analysis. Data from each cohort were analyzed separately. Death rates for the different causes of mortality, according to the systolic BP/diastolic BP-change groups, were compared using a χ^2 test, and differences in survival probability were tested using log-rank test. A Cox multivariate analysis evaluated risks of cardiovascular mortality adjusted for baseline age, total cholesterol, tobacco consumption, diabetes and body mass index (BMI). Because initial BP levels were taken into account in the calculation of BP changes and the formation of the different groups, adjustment for BP was not necessary. The group Sys$\leftrightarrow$Dia$\leftrightarrow$ (lack of change in both systolic BP and diastolic BP between the two visits) was considered as the reference group. All statistical analyses were performed using SAS software.

RESULTS

Table 1 shows the primary patient characteristics of the two cohorts, recorded during the first visit. Subjects from the Paris Prospective Study were older by five years, presented higher values of systolic BP, BMI and serum triglycerides, and the percentage of tobacco consumption was very high. There were 1,674 deaths (26.8%) among the study participants during the 17-year follow-up period, 475 (28.4% of deaths) of which were from cardiovascular disease. In the IPC cohort, 874 (5.6%) subjects died. Among them, 207 (23.6% of deaths) died from cardiovascular causes.

Analysis by Subgroups According to the Changes in BP

The IPC Study. Table 2 shows the nine groups of subjects according to the changes in systolic and diastolic BP. No

Table 2. Characteristics of the Nine Groups According to Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) Changes Over Time in the IPC Study

Groups	Sys↓Dia↓	Sys↓Dia↔	Sys↓Dia↑	Sys↔Dia↓	Sys↔Dia↔	Sys↔Dia↑	Sys↑Dia↓	Sys↑Dia↔	Sys↑Dia↑
Number of subjects	3,198	1,629	400	1,435	2,369	1,284	469	1,267	3,510
Number of CV deaths	34	12	5	18	19	14	15	16	74
CVD deaths/10,000 person-years	7.6	5.4	8.9	9.6	6.3	8.2	24.4	9.9	16.3
Age	40.4 (9.6*)	40.3 (9.1)	41.5 (9.7)	40.8 (9.8)	40.6 (9.0)	42.5 (9.1)	44.0 (12.3)	42.7 (10.4)	44.6 (9.9)
SBP (mm Hg)	133.6 (14.8)	131.5 (11.7)	136.6 (13.4)	131.1 (12.9)	129.6 (10.7)	135.8 (11.7)	131.1 (15.3)	127.1 (12.4)	135.2 (13.9)
Δ SBP (mm Hg/5 years)	−11.8 (11.0)	−7.3 (7.7)	−9.5 (8.5)	0.55 (6.5)	1.7 (5.7)	−0.4 (5.9)	9.3 (8.1)	11.2 (7.2)	12.5 (10.7)
DBP (mm Hg)	83.0 (11.2)	79.1 (7.5)	80.1 (10.1)	82.3 (11.0)	79.2 (7.9)	82.5 (8.9)	83.6 (11.2)	78.9 (9.0)	83.3 (9.7)
Δ DBP (mm Hg/5 years)	−9.2 (8.8)	1.5 (4.8)	7.5 (6.9)	−6.0 (7.3)	1.7 (5.0)	6.4 (6.7)	−6.5 (7.2)	2.3 (5.7)	9.7 (8.3)

Groups were determined according to the decrease ↓, lack of change ↔ or increase ↑ in systolic (Sys) or diastolic (Dia) blood pressure.
Δ: Mean changes; CVD: cardiovascular disease.
*Mean ± SD.

large differences among the groups were found for age and baseline BP. Mean values for total cholesterol, triglycerides, glycemia, percentage of smokers, and physical activity were not statistically significant in the nine groups (data not shown).

Cardiovascular mortality rates according to the systolic BP changes were 7.1 deaths per 10,000 person-years in the Sys↓ (decrease in systolic BP), 7.7 per 10,000 person-years in the Sys↔ (no change in systolic BP) and 15.5 per 10,000 person-years in the Sys↑ (increase in systolic BP). According to the diastolic BP changes, mortality rates were 9.6, 6.8 and 13.7 deaths per 10,000 person-years, respectively.

According to the combined changes of both systolic BP and diastolic BP, the analysis in all nine groups showed that the Sys↑Dia↓ (increase in systolic and decrease in diastolic BP) group presented the highest rates for total cardiovascular mortality (24.4 deaths per 10,000 person-years) (Table 2). The Cox regression showed that after adjustment for age alone or age and other risk factors, the Sys↑Dia↓ group was the only group to present a significantly higher risk of cardiovascular mortality compared to the reference group (Sys↔Dia↔ [no change in systolic and no change in diastolic BP]) (Table 3). Analyses performed separately (according to the mean value of age,—that is, 42 years) showed that the higher risk in the Sys↑Dia↓ group was observed in both younger and older subjects. Change in pulse pressure was also a significant determinant of cardiovascular mortality in this cohort. After adjustment for age and other risk factors, the risk ratio related to a 10 mm Hg increase in pulse pressure was 1.9 (1.0 to 3.5) ($p < 0.05$).

The study of the survival curves for cardiovascular mortality clearly indicates that increased mortality in the Sys↑Dia↓ group was not related to an early mortality. This analysis showed that the increased mortality in the Sys↑Dia↓ group, compared to the reference group (Sys↔Dia↔), clearly appeared after the fourth year of the follow-up period and persisted up to the end of follow-up (p = 0.012) (Fig. 1, upper panel). Figure 1 also shows that in the groups with a decrease in diastolic BP, without an increase in systolic BP, the survival curve was not different from the reference group. Finally, in groups with an increase in systolic BP and without a decrease in diastolic BP, the survival curve showed intermediate values between the reference group and the Sys↑Dia↓ group.

Paris Prospective Study I. The characteristics of subjects according to the changes in systolic and diastolic BP are shown in Table 4. Mean age and baseline BP values were not significantly different among the nine groups. Cardiovascular mortality rates according to the systolic BP changes were 39.9 per 10,000 person-years in the Sys↓, 37.4 per 10,000 person-years in the Sys↔, and 57.1 per 10,000 person-years in the Sys↑. According to the diastolic BP changes, these rates were 41.8, 38.5 and 53.5, respectively.

The analysis in nine groups according to the combined changes of both systolic BP and diastolic BP showed that the highest cardiovascular mortality rates were observed in
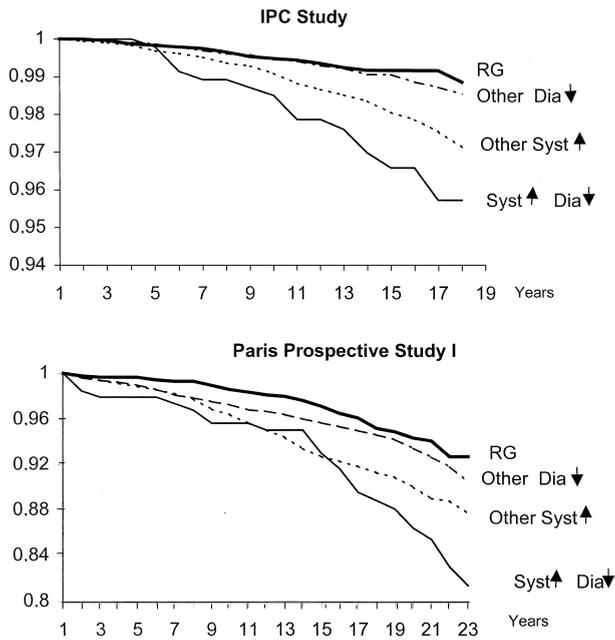
Figure 1. Survival probability curves for cardiovascular mortality in different subgroups of subjects according to the changes in systolic and diastolic blood pressure, in the IPC Study **(upper panel)** and in the Paris Prospective Study I **(lower panel)**. Reference group (RG; Sys↔Dia↔) included men whose systolic blood pressure and diastolic blood pressure did not change over time. The Sys↑Dia↓ group included men whose systolic blood pressure increased and diastolic blood pressure decreased. Other Sys↑ included those whose systolic blood pressure increased, whereas diastolic blood pressure did not change or else increased (groups Sys↑Dia↔ and Sys↑Dia↑). Other Dia↓ included those whose diastolic blood pressure decreased, whereas systolic blood pressure did not change or else decreased (groups Sys↔Dia↓ and Sys↓Dia↓). In both cohorts the Sys↑Dia↓ group showed higher cardiovascular mortality versus the RG (p < 0.05 in both cohorts). Other Dia↓ groups showed similar cardiovascular mortality versus the RG, whereas other Sys↑ groups presented intermediate cardiovascular mortality rates.

the Sys↑Dia↓ group (65.4 deaths per 10,000 person-years, Table 4).

The relative risks for death from cardiovascular disease are shown in Table 3. The age-adjusted relative risk for

subjects in the Sys↑Dia↓ group, compared with those in the Sys↔Dia↔ group, was 2.14 [95% CI 1.15–3.96]. Multivariate adjustment for baseline risk factor levels did not alter these findings. These results were very similar to those observed in the IPC Study (Table 3). As for the IPC cohort, analyses performed according to the mean value of age (47 years) showed that a higher risk of cardiovascular mortality in the Sys↑Dia↓ group was observed in both younger and older subjects. Subjects in the Sys↑Dia↑ (increase in systolic and increase in diastolic BP) group were also at higher risk compared with those in the Sys↔Dia↔ group.

As also observed for the IPC study, change in pulse pressure was a significant determinant of cardiovascular mortality in this cohort. After adjustment for age and other risk factors, the risk ratio (95% CI) related to a 10 mm Hg increase in pulse pressure was 1.7 (1.4–2.1) (p < 0.001.).

The study of the survival curves for cardiovascular mortality in the Paris Prospective Study indicated similar trends to those observed in the IPC Study (Fig. 1, lower panel).

DISCUSSION

The main result of this analysis performed in two independent French male cohorts is that an increase over an extended period of time in systolic BP combined with a decrease in diastolic BP is associated with higher cardiovascular risk, independently of age, initial BP levels and other risk factors. In both cohorts, this BP-evolution profile was associated with a twofold increase in cardiovascular mortality compared to subjects without changes in both systolic BP and diastolic BP, despite similar BP levels. We suggest that the assessment of BP changes over an extended period of time can contribute to better identifying high-risk subjects.

Cardiovascular mortality according to systolic and diastolic BP changes in two French cohorts. In the present report, two independent French cohorts were analyzed separately. As is shown in the Results section, subjects enrolled in the Paris Prospective Study had much higher mortality rates

Table 3. Relative Risk and 95% CI for Cardiovascular Mortality in the Nine Groups

	IPC Study		Paris Prospective Study I	
	Age Adjusted	Multivariate Adjusted*	Age Adjusted	Multivariate Adjusted*
Sys↓Dia↓	0.96 (0.54–1.71)	0.96 (0.55–1.71)	1.04 (0.74–1.46)	1.03 (0.73–1.44)
Sys↓Dia↔	0.89 (0.43–1.83)	0.91 (0.44–1.87)	0.92 (0.61–1.38)	0.93 (0.62–1.40)
Sys↓Dia↑	0.97 (0.33–2.86)	0.98 (0.33–2.89)	1.43 (0.72–2.75)	1.55 (0.86–2.84)
Sys↔Dia↓	1.28 (0.67–2.43)	1.28 (0.67–2.44)	1.06 (0.69–1.63)	1.06 (0.69–1.63)
Sys↔Dia↔	1.00 (Reference Group)	1.00 (Reference Group)	1.00 (Reference Group)	1.00 (Reference Group)
Sys↔Dia↑	1.07 (0.54–2.14)	1.05 (0.53–2.10)	1.27 (0.87–1.86)	1.23 (0.84–1.80)
Sys↑Dia↓	2.07 (1.05–4.06)†	2.03 (1.03–3.99)†	2.14 (1.15–3.96)†	2.16 (1.16–4.01)†
Sys↑Dia↔	1.10 (0.56–2.18)	1.09 (0.55–2.15)	1.53 (1.03–2.26)†	1.46 (0.99–2.17)
Sys↑Dia↑	1.58 (0.95–2.63)	1.55 (0.93–2.58)	1.89 (1.40–2.54)‡	1.77 (1.31–2.38)‡

*Adjusted for age, total cholesterol, tobacco consumption, diabetes and body mass index. †p < 0.05 and ‡p < 0.001 vs. reference group.
For abbreviations, see Table 1 and Methods section.

Table 4. Characteristics of the Nine Groups According to Systolic and Diastolic Blood Pressure Changes Over Time in the Paris Prospective Study I

Groups	Sys↓Dia↓	Sys↓Dia↔	Sys↓Dia↑	Sys↔Dia↓	Sys↔Dia↔	Sys↔Dia↑	Sys↑Dia↓	Sys↑Dia↔	Sys↑Dia↑
Number of subjects	1,366	574	140	599	885	572	174	503	1,433
Number of CV deaths	96	38	8	41	48	44	19	41	140
CVD deaths/10,000 person-years	39.7	38.0	35.0	40.1	34.2	44.5	65.4	48.6	59.1
Age	47.4 (1.9)*	47.2 (2.0)	47.4 (2.0)	47.0 (2.0)	46.9 (2.0)	47.0 (1.9)	47.4 (1.8)	47.1 (1.9)	46.9 (1.9)
Systolic BP (mm Hg)	138.8 (18.3)	140.6 (19.5)	142.4 (21.2)	132.4 (16.4)	135.8 (17.8)	139.6 (19.2)	139.6 (20.9)	136.1 (18.8)	139.6 (20.8)
Δ SBP (mm Hg/5 years)	−26.4 (13.0)	−20.1 (9.0)	−19.7 (10.0)	−1.2 (4.4)	1.1 (4.7)	0.5 (4.4)	21.9 (19.7)	16.3 (12.5)	26.0 (17.7)
Diastolic BP (mm Hg)	82.7 (14.3)	83.3 (14.3)	81.6 (15.8)	79.7 (13.0)	81.0 (14.2)	82.2 (14.7)	81.1 (13.7)	81.0 (14.6)	82.4 (15.5)
Δ DBP (mm Hg/5 years)	−19.7 (8.8)	−3.2 (3.0)	8.6 (7.6)	−15.4 (6.9)	−3.5 (3.1)	8.8 (6.7)	−19.6 (12.7)	−2.6 (2.9)	15.3 (10.0)

Groups were determined according to the decrease ↓, lack of change↔, or increase ↑ in systolic (Sys) or diastolic (Dia) blood pressure.
Δ: Mean changes; CVD: cardiovascular disease.
*Mean ± SD.

compared to subjects in the IPC Study. The differences in mortality can be explained in part by the fact that the subjects from the Paris Prospective Study were older (mean age 47.1 vs. 41.9 years old) and that the follow-up period was longer (17 vs. 13.5 years). However, the main reason for this difference could be that the prevalence of risk factors, especially tobacco consumption, was much higher in the Paris Prospective Study (see Table 1). This cohort was composed of policemen, enrolled in the study between 1967 and 1972, and constituted a population that was very exposed to risk factors. The fact remains that despite these major differences, the following noteworthy result was found in both cohorts: subjects with the Sys↑Dia↓ profile presented a higher cardiovascular risk, a risk that was twice as high as for the reference population (Sys↔Dia↔).

Following the classification in tertiles according to the progression of systolic BP and diastolic BP, the higher cardiovascular death rates were observed in the Sys↑ tertile. This is not really surprising as this tertile had the higher systolic BP levels during the second visit (i.e., at the beginning of the follow-up period). Inside this tertile, one would expect higher mortality rates in the subgroup, which had the higher systolic BP and diastolic BP levels at the time of the last visit. If we consider the subjects from the IPC study, average BP values in the Sys↑Dia↓ group were 141/76 mm Hg during the last visit. In the Sys↔Dia↔ and Sys↑Dia↑ groups the corresponding levels of BP were 141/82 mm Hg and 149/94 mm Hg, respectively. Based on this logic, patients in the Sys↑Dia↑ group should present the highest cardiovascular mortality compared to the other groups. However, in the present study, the higher cardiovascular mortality rates were observed among subjects in the Sys↑Dia↓ group. This excess risk is independent of absolute BP levels measured during single visits, and therefore can be determined only if the evolution of BP over an extended period of time is taken into consideration.

Diastolic BP and cardiovascular risk.

Concerns regarding low levels of diastolic BP and cardiovascular morbidity and mortality have been published for over 10 years (11,12). In 1987, Cruickshank et al. (13) observed that the mortality rates from myocardial infarction among treated patients with hypertension was lowest when diastolic BP was 85 mm Hg. Above and below this value the death rate was higher, suggesting that a J-shaped curve best described the relationship between diastolic BP and myocardial infarction mortality. This finding was restricted to subjects with coronary heart disease. No such relationship was apparent for systolic BP. The J-curve could be explained by a lowered diastolic BP, which is not sufficient enough to drive the diastolic coronary flow, especially in patients with established coronary artery disease.

In addition, Cox et al. (14) pointed out that this relationship has been found in both normotensive individuals and in hypertensive patients receiving placebos. In a detailed review of the subject, Fletcher and Bulpitt (15) raised the

question of whether or not low diastolic BP in patients with isolated systolic hypertension predisposes that group to the risk because of the increased myocardial needs due to associated high systolic BP levels. The results of the present analysis concur with this hypothesis, showing that a decrease in diastolic BP (non–drug-related in this case) was harmful only when it was combined with an elevation in systolic BP. On the contrary, when a decrease in diastolic BP was accompanied with a concomitant decrease or lack of change in systolic BP, cardiovascular risk did not increase (Fig. 1).

Pulse pressure and cardiovascular risk. It has recently been shown that increased pulse pressure was a strong predictor of cardiovascular mortality, especially coronary mortality, independently of mean BP levels (16–18). The present results point out that the increase of systolic and pulse pressure over time is probably due to an increase in aortic stiffness and pulse-wave velocity and to accentuation of the amplitude of the reflected pressure waves (5). We believe that the present study helps clarify the role played by arterial stiffening in cardiovascular complications. The present results demonstrate the risk related to the increase in pulse pressure due to both an increase in systolic BP and a decrease in diastolic BP, which is the classic pattern of large arteries stiffening. We can therefore suggest that other causes leading to elevated pulse pressure, such as increased stroke volume, may be considered less harmful. The study emphasizes that the impact of systolic and pulse pressure is not only observed in the elderly but also in a middle-aged population sample.

Clinical applications. Therapeutic decision-making and management in patients with mild to moderate hypertension are based on the evaluation of cardiovascular risk. Clinicians therefore have sought more precise ways of describing individual patient outlooks. One of the problems when treating for hypertension is that very large numbers of subjects have to be treated to prevent a small number of cardiovascular complications (19). This suggests that the standard criteria, systolic BP or diastolic BP, even if they are generally correlated to cardiovascular risk, may not be specific or sensitive enough to identify groups of subjects that are at high risk owing to BP values. In the present analysis we identified a subgroup of subjects, representing approximately 3% of the total population, whose excess in risk was independent of BP recorded during single visits, age and other risk factors.

In the present study the same hypothesis was tested separately in two independent French cohorts. Because the Paris Prospective Study was composed only of men, only the male population in the IPC cohort was analyzed. Results of the present study may be of interest to clinicians for several reasons. In the case of normal or slightly increased BP levels, when treatment does not need to be proposed, long-term follow-up of BP levels may help estimate an individual's

cardiovascular risk and contribute to therapeutic decision making. In subjects with high BP, for whom physicians should propose a first treatment, comparison with older BP readings when available could contribute to a better estimation of cardiovascular risk.

In conclusion, assessment of spontaneous BP changes over a long period of time may contribute to the evaluation of cardiovascular risk. Subjects who present a combined increase in systolic BP and a decrease in diastolic BP have the highest risk, independently of absolute BP values and other risk factors.

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REFERENCES

1. Kannel WB, Gordon T, Schwartz MJ. Systolic versus diastolic blood pressure and risk of coronary heart disease: the Framingham study. Am J Cardiol 1971;27:335–46.
2. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease: (part 2). Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827–38.
3. Kannel WB, Dawber TR, McGee DL. Perspectives on systolic hypertension. The Framingham Study. Circulation 1980;61:1179–82.
4. Darne B, Girerd X, Safar M, et al. Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. Hypertension 1989;13:392–400.
5. Nichols WV, O'Rourke MF. McDonald's blood flow in arteries; theoretic, experimental, and clinical principles. In: Arnold E, editor. London, Melbourne: Edward Arnold,, 1990:77, 142, 216–69, 398–411.
6. Fang J, Madhavan S, Cohen H, Alderman MH. Measures of blood pressure and myocardial infarction in treated hypertensive patients. J Hypertens 1995;13:413–9.
7. Sleight P. Blood pressures, hearts, and U-shaped curves (letter). Lancet 1988;1:235.
8. Safar ME. Pulse pressure in essential hypertension: clinical and therapeutical implications. J Hypertens 1989;7:769–76.
9. Witteman JCM, Grobbee DE, Valkenburg HA, et al. J-shape relation between change in diastolic blood pressure and progression of aortic atherosclerosis. Lancet 1994;343:504–7.
10. Zureik M, Courbon D, Ducimetière P. Decline in serum total cholesterol and the risk of death from cancer. Paris Prospective Study I. Epidemiology 1997;8:137–43.
11. Anderson TW. Re-examination of the Framingham blood-pressure data. Lancet 1978;2:1139–41.
12. Stewart IM. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. Lancet 1979;1:861–5.
13. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. Lancet 1987;1:581–4.
14. Cox JP, O'Brien E, O'Malley K. The J-shaped curve in elderly hypertensives. J Hypertens 1992;10 Suppl 2:S17–23.

15. Fletcher AE, Bulpitt CJ. How far should blood pressure be lowered? N Engl J Med 1992;326:251–4.
16. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. Hypertension 1994;23:395–401.
17. Benetos A, Safar M, Rudnichi A, et al. Pulse pressure; a predictor of long-term mortality in a French male population. Hypertension 1997;30:1410–5.
18. Mitchell GF, Moye LA, Braunwald E, et al. for the SAVE Investigators. Sphygmomanometric determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. Circulation 1997;96:4254–60.
19. Menard J, Chatellier G. Integration of trial, meta-analysis and cohort results with treatment guidelines. J Hypertens 1996;14:S129–33.