Importance of arterial pulse pressure as a predictor of coronary heart disease risk in PROCAM

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KEYWORDS
Pulse pressure; Blood pressure; Atherosclerosis; Myocardial infarction; Coronary risk

Aims To investigate pulse pressure (PP) as an independent predictor of coronary heart disease (CHD) risk.

Methods and results On the basis of a 10-year follow-up of 5389 men aged 35–65 at recruitment into PROCAM, we used a proportional hazards model to calculate the effect of systolic blood pressure (SBP), diastolic blood pressure (DBP), and PP on CHD risk after correcting for age, high-density lipoprotein cholesterol, LDL cholesterol, triglycerides, smoking, diabetes, and family history of premature CHD. Increases of 10 mmHg in DBP, SBP, and PP were associated with an increased CHD hazard ratio (HR) of ~10%. When the group was divided into the age groups <50, 50–59, and >59 years, this relationship was seen in the age group 50–59 years for DBP, SBP, and PP and in men aged ≥60 for PP only (25% increase in HR). Overall, CHD risk in men with PP >70 mmHg was more three times that of men with PP <50 mmHg. This increased risk was not apparent at age <50 years, was greatest at age >60 years, and was also present in men who were normotensive at recruitment (SBP ≤160 mmHg, DBP ≤95 mmHg).

Conclusion In older European men, increased PP is an important independent determinant of coronary risk, even among those initially considered normotensive.

Introduction

Three variables characterize blood pressure. The mean of the systolic blood pressure (SBP) and diastolic blood pressure (DBP) ensures perfusion of most organs in the body while the left ventricle of the heart is perfused throughout diastole via the coronary arteries. The pulse pressure (PP) is the arithmetic difference between the SBP and DBP. PP reflects stiffness of the aorta and large arteries and pulse wave velocity.1,2 Stiffening of the large arteries is the result of a chronic irreversible age-related process in the media characterized by elastin degeneration and subsequent remodelling with an increase in collagen and deposition of extracellular matrix and calcium.3 Widening of the PP is common after the age of 60 years as a result of increasing SBP and falling DBP.4,5 In cross-sectional studies, PP showed a direct association with carotid atherosclerosis,6–8 peripheral vascular disease,9 left ventricular mass,10 and lesions in the white matter of the brain detected by magnetic resonance imaging.11

In recent years, evidence has accumulated that increased PP predicts cardiovascular and coronary artery disease, myocardial infarction (MI), and congestive heart failure, independent of DBP and SBP, other risk markers, and 'white coat' hypertension.12–23 In addition, PP has been shown to predict all-cause mortality, total cardiovascular mortality, and coronary mortality in normotensive and hypertensive men, although not in women.18,24 PP also predicts long-term mortality after acute stroke.25

SBP shows a consistent linear relationship with cardiovascular morbidity and mortality at all age groups and in both men and women.26,27 Normal levels of DBP, however, may result from an increase in peripheral vascular resistance (which elevates DBP) combined with an increase in arterial stiffening (which lowers DBP). Although both these phenomena indicate increased cardiovascular risk, their effects on DBP may cancel each other out. DBP may be even less of an indicator in older adults, where the prevailing form of high blood pressure is isolated systolic hypertension. As arterial stiffening causes SBP to increase and DBP to decrease, PP may be the best predictor of cardiovascular events for all blood pressure values.28 With increasing age among participants in the Framingham study, there was a gradual shift from DBP to SBP and then to PP as a predictor of coronary risk.5 This has led some commentators to suggest that PP should become part of the Framingham risk algorithm.29

The Prospective Cardiovascular Münster (PROCAM) study is a prospective investigation of cardiovascular risk factors of the working population in the city of Münster and the
northern Ruhr valley in Germany. At present, 10 years of follow-up data are available in the cohort of middle-aged men in PROCAM, a group in which a sufficient number of coronary events occurred to allow valid statistical analysis. The present report examines the value of arterial PP as an independent predictor of coronary risk in this cohort.

Methods

The PROCAM study was begun in 1979. The data in this report were obtained between 1979 and 1985. During this time, 20,060 employees of 52 companies and government authorities in the region of the Münster and the northern Ruhr Valley region of Germany were investigated. Because only employed people were included, the results of PROCAM are subject to the ‘healthy worker’ effect and possibly underestimate the true extent of morbidity and mortality in the German population.

The examination at study entry included a case history using standardized questionnaires, measurement of blood pressure and anthropometric data, a resting electrocardiogram (ECG), and collection of a blood sample after a 12-h fast for the determination of more than 20 laboratory parameters. Details of the examination procedure are reported elsewhere. The examination was carried out during paid working hours. Participation was voluntary, and between 40 and 80% (average 60%) of employees participated. There was no charge to the volunteers or to their employers (apart from time lost from work). All findings were reported to the participant’s general practitioner, and the participant was told if the results of the examination were normal or if a checkup by the general practitioner might be advisable. The investigators neither carried out nor arranged for any intervention.

Anthropometric and biochemical measurements

A history of cigarette smoking was obtained during the recruitment examination. Persons who reported smoking cigarettes during the previous 12 months were considered current smokers. The recommendations of the American and British Heart Associations were followed for measuring blood pressure. Systolic and diastolic readings were taken using a mercury sphygmomanometer on the left arm with the participant seated and the arm at heart level. One measurement was taken at the start of the interview and one was taken at the end of the interview. The second measurement was recorded. The same physician performed all measurements. ECGs were taken with the participant lying down using three standard leads, three augmented unipolar lead, and six precordial leads. A participant was considered to suffer from diabetes mellitus if this diagnosis had been previously made or if the fasting concentration of glucose in whole blood was ≥120 mg/dL. Total cholesterol and triglycerides were measured using enzymatic assays, and high-density lipoprotein (HDL) cholesterol was measured using a precipitation method from Boehringer Mannheim on a Hitachi 737 autoanalyzer. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula provided the triglyceride level was <400 mg/dL. Additional methods have been described elsewhere.

Follow-up

After the initial examination, questionnaires were sent to the participants in PROCAM every 2 years to determine the occurrence of MI, stroke, or death. The response rate to these questionnaires was 96% after a maximum of two reminders per participant by mail and telephone. In cases where the participant had died, the death certificate was reviewed. In cases where mortality and morbidity data were obtained from the questionnaire, hospital records, records from the attending physician, and an eyewitness account of death were requested. A Critical Event Committee (Prof. K. Kochsieck, Würzburg; Prof. E. Köhler, Bad Salzuflen; Prof. U. Gleichmann, Bad Oeynhausen) met at regular intervals to verify the diagnosis or cause of death of the participants in PROCAM. The initial examination was repeated after 6–7 years. Non-fatal MI, fatal MI, and sudden cardiac death were defined as ‘major coronary events’ and were considered endpoints. Participants were excluded from follow-up if at the time of recruitment they had a history of either MI or stroke or if the ECG at recruitment showed signs of ischaemic heart disease. Patients with a history of angina pectoris at recruitment, as defined using the Rose questionnaire, were excluded from the present analysis.

Definition of endpoints

The endpoint used in PROCAM was a ‘major coronary event’ defined as either sudden cardiac death or non-fatal definite MI. Sudden cardiac death was diagnosed if a previously apparently well participant was observed to have died within 1 h of onset of symptoms, providing the cause of death could not be attributed to violence, trauma, or some other potentially lethal condition other than coronary heart disease (CHD). Fatal MI was diagnosed if a death certificate or hospital record described MI as the cause of death and the participant had been admitted to hospital with definitive or suspected MI using the criteria outlined subsequently or if acute MI was found during autopsy. Definite MI was diagnosed if at least one of the following was present: (i) diagnostic ECG at the time of the event, (ii) presence of ischaemic cardiac pain (severe substernal pain with a deep or visceral quality and lasting for at least 30 min) plus diagnostic enzyme changes, (iii) ischaemic cardiac pain plus equivocal enzyme changes plus equivocal ECG, (iv) an ECG diagnostic of MI if a previous one was not. An ECG at the time of the event was considered diagnostic if either of the following was present: (i) unequivocal Q or QS pattern (Minnesota code 1-1), (ii) Q or QS pattern (codes 1-2-1–1-2-7) plus any T-wave item (codes 5-1–5-3). In the presence of ventricular conduction defects, only condition (i) was used. An ECG at the time of the event was considered equivocal if any of the following was present: (i) Q or QS pattern (codes 1-2-1–1-2-7), (ii) ST junction and segment depression (codes 4-1–4-3), (iii) T-wave item only (codes 5-1 and 5-2), (iv) left bundle branch block (code 7-1). Enzyme levels measured at the time of the event were considered diagnostic if creatine kinase, serum glutamic transaminase, and/or lactic dehydrogenase were at least twice the upper limit of the local laboratory, but less than 15 times that value. Enzyme levels were considered equivocal if at least one of the enzymes was elevated while failing to meet the criteria for diagnostic enzyme levels.

In the cohort of 5389 men aged 35–65 recruited before the end of 1985, 325 major coronary events occurred within 10 years, enough to allow statistically valid longitudinal analysis. Within the 10 years, 230 men were lost to follow-up, 14 suffered suspected coronary death, 218 died from other causes, and 46 non-fatal cases of stroke occurred. In addition, in 63 men who did not suffer an acute coronary event, CHD was diagnosed by angiography. All of these subjects were included in the population at risk until such time as death, loss to follow-up, or censoring occurred. Thus, 4493 middle-aged men survived 10 years without a major coronary event and without an event causing censoring.

Data analysis

CHD rates and mortality rates were evaluated as the cumulative proportion of those surviving without an event by life table analysis. The relations of CHD hazard ratios (HRs) to the blood pressure components SBP, DBP, and PP as continuous variables were evaluated by Cox proportional hazards regression. The Cox model used was that which had previously served to generate the PROCAM risk score. SBP, DBP, and PP were assessed separately in the model. Adjusted HRs and the respective 95% confidence intervals for 10 mmHg
incorporates in each blood pressure component were estimated as the exponent (e) raised to the power of the respective regression coefficient and were derived from models involving all prognostically related non-blood pressure parameters, namely, age, HDL and LDL-cholesterol, triglycerides, smoking, diabetes mellitus, and positive family history. The assumption of proportional hazards over time was verified by adding interaction terms with the logarithm of time to the proportional hazard model before the analyses were performed. This was met by all covariates. The assumption concerning linearity of continuous covariates was also verified before analysis by the use of design variables, that is, by replacing the continuous variables with design variables formed using various cutpoints as described by Hosmer and Lemeshow. Comparisons of HRs between groups were done by Cox proportional hazards regression with a dichotomous variable describing the groups. Cox proportional hazard analyses were performed for the entire group and in subgroups according to age.

To assess the performance of the prognostic tests for the different blood pressure components, the areas under receiver operating characteristic (ROC) curves were calculated taking into account the censored nature of the data and compared using the approach of Hanley and McNeil. SPSS statistical software was used throughout. A value of $P < 0.05$ was considered significant. All tests were two-sided. Because this was an exploratory rather than a confirmatory analysis, no corrections for multiple tests were done.

Results

Of the 5389 men aged 35–65 who were included in the present study, 374 were taking anti-hypertensive medicine at recruitment and 5015 men were not. The incidence of MI among those not on anti-hypertensive treatment was 5.8% (280 events), compared with 12.9% (45 events) of MI among those not on anti-hypertensive treatment. The 10-year risk of CHD was at least doubled. The greatest coronary risk was seen in men with poorly treated hypertension, in whom the risk of a coronary event was 2.7 times that of normotensive men.

Table 1

<table>
<thead>
<tr>
<th>Status at recruitment</th>
<th>n</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>PP (mmHg)</th>
<th>Age (years)</th>
<th>10-year CHD rate (%)</th>
<th>10-year mortality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>4074</td>
<td>124.7 ± 13.1</td>
<td>81.4 ± 7.3</td>
<td>43.4 ± 10.2</td>
<td>45.7 ± 7.4</td>
<td>4.9</td>
<td>5.7</td>
</tr>
<tr>
<td>New hypertensive</td>
<td>941</td>
<td>153.0 ± 15.8</td>
<td>100.5 ± 8.3</td>
<td>52.5 ± 14.7</td>
<td>48.7 ± 7.1</td>
<td>10.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Treated to &lt;160/95 mmHg</td>
<td>152</td>
<td>135.1 ± 10.5</td>
<td>86.0 ± 4.7</td>
<td>49.1 ± 9.9</td>
<td>50.7 ± 7.5</td>
<td>11.9</td>
<td>9.4</td>
</tr>
<tr>
<td>Treated to ≥160/95 mmHg</td>
<td>222</td>
<td>160.0 ± 17.6</td>
<td>102.7 ± 9.7</td>
<td>57.2 ± 16.4</td>
<td>51.8 ± 6.3</td>
<td>13.6</td>
<td>11.8</td>
</tr>
<tr>
<td>Total</td>
<td>5389</td>
<td>131.4 ± 18.4</td>
<td>85.7 ± 11.0</td>
<td>45.7 ± 12.2</td>
<td>46.7 ± 7.5</td>
<td>6.3</td>
<td>6.6</td>
</tr>
</tbody>
</table>

All values are those measured at recruitment into PROCAM. Normotensive participants had a blood pressure of $\leq 140/90$ mmHg at recruitment. Patients who were known to be hypertensive at recruitment are divided into those who were receiving adequate therapy (sufficient to lower blood pressure to below 160/95 mmHg) and those who were not (blood pressure $>160/95$). The 10-year cumulative hazard rate of major coronary events was increased about two-fold among participants who were hypertensive at recruitment and was greatest in persons with known hypertension. This increase in 10-year risk may be due, in part, to the greater age of the group with known hypertension. Note that participants with poorly controlled hypertension had the greatest coronary risk. All values are mean ± standard deviation.

In the present study, men with hypertension were older than normotensive men, partially explaining the increase in CHD risk among hypertensives (Table 1). However, hypertension itself was associated with significant excess risk. Thus, major coronary events were at least 50% more common in hypertensive than in normotensive men at all ages (Table 2). Ten-year mortality was also increased in hypertensive men at all ages (Table 2).

When compared with the normotensive men, men with hypertension had a generally unfavourable risk factor profile, with lower levels of HDL cholesterol, higher levels of total and LDL cholesterol and of triglyceride. Diabetes mellitus was about twice as common in the hypertensive men as in the normotensive men (Table 3) as was both fatal and non-fatal stroke (data not shown). In contrast, blood pressure did not show a relationship with other causes of death including cancer (data not shown).

Pulse pressure

To evaluate the predictive power of the various components of blood pressure, ROC curve analysis was performed. In the
overall population of men, the area under the ROC curve was significantly greater for SBP (0.60, \( P = 0.001 \)) and for PP (0.59, \( P = 0.047 \)) than that for DBP (0.54).

To further investigate the effect of blood pressure on coronary risk, a proportional hazards model was used to calculate the increase in HR for major coronary events associated with a 10 mmHg rise in SBP, DBP, and PP after correcting for age, HDL, triglycerides, smoking, diabetes mellitus, and family history of premature CHD (Table 4). For the group as a whole, increases in all three components of blood pressure were associated with an increase in the CHD HR of ~10%. When the group was broken down into men <50 years, men aged 50–59, and those aged >60, this relationship was apparent only in men aged 50–59 for all blood pressure variables and in the older men (>60 years) for PP only (Table 4).

Among the entire cohort of men in the present study (with exclusion of those who were receiving anti-hypertensive treatment at recruitment), the risk of CHD in men with a PP of at least 70 mmHg was more than three times that of men with a PP of 60–69 mmHg (16.4 vs. 6.7%, \( P < 0.001 \)) and more than twice that of men with a PP of 60–69 mmHg (16.4 vs. 6.6%, \( P < 0.001 \)). The three-fold increase in coronary risk associated with a PP of ≥70 mmHg was at least as great as, if not greater than, that conferred by conventional hypertension (Table 1). After correction for age, HDL cholesterol, LDL cholesterol, triglycerides, smoking, diabetes mellitus, and family history of premature CHD, the relative risk associated with a PP ≥70 mmHg fell to 1.67 (\( P = 0.012 \)), whereas that associated with conventional hypertension (SBP ≥160 mmHg and DBP ≥95 mmHg) fell to 1.55 (\( P = 0.046 \)). This increase in relative risk associated with a high PP was not present in men <50 years at recruitment, but was clear in those aged 50–59 and greatest in those aged ≥60 (Figure 1).

The 10-year risk of CHD in normotensive men aged 35–65 with a PP of ≥70 mmHg (prevalence of this subgroup 1.4%) was 12.5% compared with 4.7% in men with a PP of <60 mmHg (\( P = 0.006 \)). The increase in coronary risk associated with increased PP was also seen in men aged 36–65 who were newly diagnosed as hypertensive on entry into PROCAM: among these men (16.2% of entire cohort), the 10-year risk of CHD was 18.8% in those with a PP of ≥70 mmHg compared with 6.7% in men with a PP of <60 mmHg (\( P = 0.001 \)).

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**Table 3** Levels of various risk factors according to blood pressure status

<table>
<thead>
<tr>
<th>Status at recruitment</th>
<th>n</th>
<th>HLD-C (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>Trig. (mg/dL)</th>
<th>TC (mg/dL)</th>
<th>BMI (kg/m²)</th>
<th>Smoking (%)</th>
<th>Diabetes (%)</th>
<th>Family hist. prem. MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>4074</td>
<td>46 ± 12</td>
<td>147 ± 38</td>
<td>138 ± 70</td>
<td>220 ± 41</td>
<td>26 ± 3</td>
<td>35</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>New hypertensive</td>
<td>941</td>
<td>45 ± 12</td>
<td>154 ± 37</td>
<td>163 ± 78</td>
<td>232 ± 40</td>
<td>28 ± 3</td>
<td>32</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Treated to &lt;160/95</td>
<td>152</td>
<td>44 ± 11</td>
<td>152 ± 38</td>
<td>159 ± 76</td>
<td>228 ± 41</td>
<td>28 ± 3</td>
<td>20</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Treated to ≥160/95</td>
<td>222</td>
<td>45 ± 11</td>
<td>154 ± 37</td>
<td>182 ± 88</td>
<td>234 ± 42</td>
<td>28 ± 3</td>
<td>20</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>5389</td>
<td>46 ± 12</td>
<td>149 ± 38</td>
<td>145 ± 74</td>
<td>223 ± 41</td>
<td>26 ± 3</td>
<td>33</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

All values are those measured at recruitment into PROCAM. Normotensive participants had a blood pressure of <140/90 mmHg at recruitment. Patients who were known to be hypertensive at recruitment are divided into those who were receiving adequate therapy (sufficient to lower blood pressure to <160/95 mmHg) and those who were not (blood pressure ≥160/95). Trig., triglycerides; TC, total cholesterol; BMI, body mass index; Family hist. prem. MI, history of myocardial infarction in a first-degree family member before the age of 60 years. All values are mean + SD.

**Table 4** Incidence of CHD by blood pressure and age group in participants not receiving anti-hypertensive treatment (n = 5015)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Blood pressure class</th>
<th>Increase in HR for major coronary event for each 10 mmHg rise in blood pressure (%)</th>
<th>95% Confidence interval</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–65 (280 events in 5015 men)</td>
<td>Systolic</td>
<td>9.8</td>
<td>3.1–16.9</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>11.2</td>
<td>0.0–23.6</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>Pulse</td>
<td>12.8</td>
<td>3.0–23.6</td>
<td>0.009</td>
</tr>
<tr>
<td>&lt;50 (97 events in 3295 men)</td>
<td>Systolic</td>
<td>7.1</td>
<td>−4.2–19.6</td>
<td>0.227</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>6.2</td>
<td>−12.1–28.5</td>
<td>0.532</td>
</tr>
<tr>
<td></td>
<td>Pulse</td>
<td>10.9</td>
<td>−5.9–30.6</td>
<td>0.217</td>
</tr>
<tr>
<td>50–59 (142 events in 1524 men)</td>
<td>Systolic</td>
<td>11.3</td>
<td>2.0–21.4</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>16.9</td>
<td>1.1–35.2</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>Pulse</td>
<td>12.1</td>
<td>0.1–24.7</td>
<td>0.048</td>
</tr>
<tr>
<td>≥60 (41 cases in 196 men)</td>
<td>Systolic</td>
<td>11.5</td>
<td>−4.4–29.9</td>
<td>0.165</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>−2.4</td>
<td>−27.0–30.5</td>
<td>0.869</td>
</tr>
<tr>
<td></td>
<td>Pulse</td>
<td>25.4</td>
<td>1.3–55.2</td>
<td>0.038</td>
</tr>
</tbody>
</table>

This table shows the increase in risk of MI for each 10 mmHg increase in blood pressure in each age group. Corrected for age, HLD- and LDL-cholesterol, triglycerides, smoking, diabetes mellitus, and positive family history using a proportional hazard regression model.
PP in men aged at least 60

In the highest age group (≥60 years of age), the risk of CHD in men with a PP of at least 70 mmHg was nearly three times that of men with a PP <60 mmHg (46.8 vs. 16.9%, P < 0.001). Of particular note is the observation that the increased coronary risk associated with increased PP was also present in subgroups of older men with hypertension and among men whose initial blood pressures complied with the general definition of normal (i.e. SBP < 160 mmHg and DBP < 95 mmHg) (Figure 1). The 10-year risk of CHD in normotensive older men with a PP of at least 70 mmHg (prevalence 5.5%) was 41.7% compared with a 10-year CHD risk of 17.6% in men with a PP of < 60 mmHg (P = 0.041). The increase in coronary risk associated with increased PP was also seen in men >60 years who were newly diagnosed as hypertensive on entry into PROCAM (Figure 1). In such hypertensive older men with a PP of at least 70 mmHg, the 10-year CHD risk was 48.8% compared with a 10-year CHD risk of 12.3% in hypertensive older men with a PP of <60 mmHg (P = 0.022).

Discussion

The main results of the present study are as follows: (i) in middle-aged men in PROCAM, PP was about as powerful as SBP in predicting risk of CHD, and both were much better predictors of risk than the DBP; (ii) the risk associated with increased PP increased with age and, in elderly men, may be greater than that associated with systolic hypertension; (iii) a small proportion of older men who were initially considered normotensive were at increased coronary risk due to raised PP; (iv) increased PP additionally increased risk of CHD in older men with conventional hypertension.

These results essentially confirm those of the Framingham study41 in an independent, European population. In Framingham, DBP and SBP both predicted CHD in those <50 years, whereas in the present study, no component of blood pressure was associated with a significant increase in CHD HR in this age group after correction for the other major CHD risk factors (Table 4). This may be related to the fact that the mean age of the group aged <50 in Framingham (35 ± 8 years) was about 7 years less than the equivalent group in PROCAM (42 ± 4 years). The data from Framingham clearly showed that DBP was the greatest predictor of risk in the young, whereas after the age of 60 years, DBP was negatively related to CHD risk, so that in this age group PP was the most important risk predictor, surpassing even SBP.41

In contrast to the results of the Framingham analysis, several reports have more recently cast doubt on the notion that PP is the most important blood pressure index of risk in the elderly.42–44 In the Chicago Heart Association Detection Project in Industry Study, PP was less strongly related to cardiovascular and cerebrovascular death over a wide range of ages and in both men and women following adjustment for age, race, education, cholesterol, smoking, body mass index, and ECG abnormalities.42 Equally, in a population-based study of older adults throughout the United States SBP, DP, and PP were all strongly and independently related to risk of CHD and stroke but SBP was the best single predictor of cardiovascular events.43 Finally, in the Prospective Studies Collaboration, which included data on 12.1 million patient-years of follow-up in 61 studies—including PROCAM—the most informative predictor of vascular mortality from a single blood pressure measurement at all ages was the average of SBP and DBP, followed by either SBP or DBP alone.44 PP was much less informative at all ages, including in the elderly.

The reason for the discrepancy between the results of the earlier mentioned studies42,43 including, in particular, the Prospective Studies Collaboration44 and both our results and those from the Framingham study4 is not entirely clear, although part of the explanation may lie in the fact that the Prospective Studies Collaboration considered only vascular mortality as an endpoint, whereas Framingham and PROCAM both considered morbidity.

The results of both the present study and the Framingham analysis by Franklin et al.4 are consistent with an age-related shift in the risky component of blood pressure from DBP to SBP to PP. The reason for this shift is not entirely known but may be related to the haemodynamics of blood pressure. The pressure waveform recorded at any site in the arterial tree is the sum of the forward waveform and its echo reflected from the periphery. In peripheral arteries, the reflected wave augments only the systolic part of the incident wave due to the short distance between the site of measurement and the site of reflection. In central arteries, however, the reflected wave can augment either systole or diastole depending on the stiffness of the large
arteries. In young persons with compliant aortas, the pulse wave travels slowly down the arterial tree and back, arriving in the ascending aorta late in the cycle to augment diastole. In older persons, the velocity of the pulse wave is increased so that the reflected wave arrives early and augments systole. In addition to these augmentation effects, the amplitude of the pulse waveform is progressively amplified from the central to the peripheral arteries. In young adults with hypertension, increased vascular resistance leads to a functional increase in the stiffness of large arteries, which in turn reduces amplification of the pulse wave in the brachial artery. This may offset the peripheral increase in SBP without affecting the rise in DBP, which is augmented by increased reflection of the pulse wave. The net result is that peripheral PP tends not to reflect central PP in younger persons. In older persons, in contrast, peripheral PP tends not to reflect central PP in younger persons. In older persons, in contrast, peripheral PP and central PP tend to change in parallel. This difference may explain why PP is a better risk predictor in older persons.

The results of the present study and other investigations have important implications for therapy of hypertension. In particular, the finding that increased PP is an important predictor of CHD risk in older normotensive individuals requires a reappraisal of current therapeutic approaches. Historically, treatment of hypertension has been directed to controlling DBP, although it is now clear that control of SBP is the key to controlling DBP, and that control of SBP is necessary to controlling DBP, and that control of SBP reduces total and cardiovascular mortality, stroke, and heart failure. Poor control of SBP is largely responsible for overall levels of poor blood pressure control.

At any given value of SBP, cardiovascular mortality is higher when the DBP is lower. In fact, the predictive power of PP might arise from two different mechanisms. Increased SBP increases end-systolic stress and promotes cardiac hypertrophy, whereas reduced DBP reduces coronary perfusion promoting myocardial ischaemia and is associated with increased cardiovascular risk. Thus, particular consideration should be given to medications that lower PP such as a combination of a diuretic and angiotensin-converting enzyme inhibitor or angiotensin-receptor antagonists as monotherapy.

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References


