Implications of Pulse Pressure as a Predictor of Cardiac Risk in Patients With Hypertension

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Abstract—Previously we demonstrated that pulse pressure is a strong risk factor for coronary events in male hypertensive subjects in the MRC Mild Hypertension Trial, whereas stroke is best predicted by mean blood pressure. In this study, we have assessed the implications of this finding in the treatment of mild essential hypertension. We examined the relationship between diastolic blood pressure and both coronary disease risk and stroke when these events were predicted by the above blood pressure measures using an empirical linear model and multivariate logistic regression models that contained data from the MRC trial. Under these circumstances, the predicted stroke risk increased progressively with increasing values of diastolic blood pressure, but in both empirical and formal statistical models, the predicted risk of a coronary event exhibited a J-shaped relationship with diastolic blood pressure. These results suggest that if coronary event risk in mild essential hypertension is predicted by pulse pressure then it may increase at low values of diastolic blood pressure, in contrast to stroke risk, which declines continuously as diastolic blood pressure falls within the physiological range. This raises the possibility that different sequelae of hypertension are best predicted by different measures of blood pressure and that the effect of treatment on stroke and coronary events in some circumstances may be discordant. (Hypertension. 2000;36:907-911.)

Key Words: drug therapy • blood pressure • risk factors • coronary artery disease • MRC Mild Hypertension Trial

Cardiovascular mortality and its various clinical manifestations such as angina, myocardial infarction, stroke, and cardiac failure are increased in the presence of raised blood pressure (BP). Traditionally, this has been measured by oscillographic sphygmomanometry, which returns 2 measures: systolic and diastolic BP. Although these measures correlate significantly with both fatal and nonfatal cardiovascular events, it is becoming increasingly clear that of the 2, systolic BP is more strongly correlated than diastolic BP, which may be negatively correlated with cardiac event rates, and that neither may be as strong as pulse pressure. Recently, we demonstrated that pulse pressure was the strongest predictor of coronary events in untreated males in the MRC Mild Hypertension Trial, a finding that is consistent with several other clinical trials and epidemiological studies. However, it has proven difficult to distinguish independent effects of systolic BP and pulse pressure on cardiac risk, because they correlate so strongly with each other. In this study, we examine some implications for clinical practice if coronary heart disease risk is predicted mainly by pulse pressure.

Methods

We studied the MRC Trial of Treatment of Mild Hypertension with the approval of the management committee. Details of the trial and the role of pulse pressure as a cardiac risk predictor in middle-aged (35 to 64 years) placebo-treated male subjects have been described previously.

To further demonstrate the effect of pulse pressure, we measured stroke and coronary event rates in 3 related analyses in males. The population was subgrouped in (1) quartiles of systolic BP; (2) ascending ranges of entry systolic BP that contained equal numbers of strokes; and (3) corresponding ranges that contained equal numbers of coronary events. The 4 groups defined under each of (2) and (3) are not quartiles because event rate increases with increasing BP. These subgroups were further categorized according to whether diastolic BP was less than or greater than the mean value in each major quartile or subgroup. Stroke and coronary event rates were measured and plotted against the mean value of systolic BP in each subgroup.

We then modelled the effects of pulse pressure or systolic BP on coronary event risk and the effects of mean BP on stroke risk with an empirical approach and by logistic regression analysis. Empirically, we took various arbitrary but clinically realistic BP values in the normal range and in the range of mild hypertension studied in treatment trials (130/60, 130/70, 137/80, 145/90, 160/95, 180/100, 190/105, and 200/110 mm Hg) and modelled stroke or coronary risk with the linear equations

\[ Stroke\ risk = k_3 \times Mean\ BP, \]  
\[ k_3 \] is a proportionality constant.

\[ Coronary\ risk = k_4 \times Pulse\ Pressure, \]  
\[ k_4 \] is a proportionality constant.

We also standardized the values obtained to the value at DBP=90 mm Hg. This approach does not measure absolute or relative stroke or coronary risk per se but merely indicates the potential effect of changes in BP on the contribution of each specified measure to risk in the absence of any other risk factors. It also assumes that the relationships are linear.
We then formally estimated the above risks with multivariate logistic regression models and data for placebo-treated male subjects in the MRC Mild Hypertension Trial. The regression models included the specified measure of BP for fatal and nonfatal stroke (mean BP) and coronary events (pulse pressure or systolic BP), plus the other independent variables on entry that were shown to be significant predictors of each risk: for stroke, these were age and cigarette smoking, and for coronary events age and smoking, plasma cholesterol and plasma sodium (inversely). The models for dichotomous end points have the form

\[
\text{Event risk} = \frac{1}{1 + e^{-Z}}
\]

where \(Z = B_0 + B_{\text{age}} \times \text{age} + B_{\text{cigs}} \times \text{cigs} + B_{\text{meanBP}} \times \left(\frac{\text{SBP}}{3} - \frac{\text{DBP}}{3}\right) + 2 \times \text{DBP}
\)

for independent variables \(X_i\) and partial regression coefficients \(B_i\). Hence for stroke,

\[
Z_{\text{stroke}} = B_0 + B_{\text{age}} \times \text{age} + B_{\text{cigs}} \times \text{cigs} + B_{\text{meanBP}} \times \left(\frac{\text{SBP}}{3} + \frac{2 \times \text{DBP}}{3}\right)
\]

(1)

and for coronary events (MI),

\[
Z_{\text{MI}} = B_0 + B_{\text{age}} \times \text{age} + B_{\text{cigs}} \times \text{cigs} + B_{\text{meanBP}} \times \text{meanBP} + B_{\text{cholesterol}} \times \text{cholesterol} + B_{\text{Na}} \times \text{Na}
\]

(2)

where \(C_{\text{stroke}}\) and \(C_{\text{MI}}\) are composite variables containing all non-BP independent variables on entry and the constant term. \(\text{Cigs}\) is the number of cigarettes per day and \(\text{Chol}\) is the plasma cholesterol. The partial regression coefficients for these models were determined by logistic regression analysis with data from placebo-treated male subjects. Values of \(Z\) from equations 1 and 2 above and hence values of stroke and coronary risk for each arbitrary level of BP as above were then calculated. To solve the equations, non-BP variables were entered as the mean value, except for cigarette smoking for which the median value was used.

“Risk” in this context is the probability \((P)\) of an event in an individual trial subject or population of trial subjects with specified values for dependent variables during 5 years of follow-up, thus

\[
\sum_{i=1}^{N} \text{Risk} = \text{Total event numbers}
\]

where \(N\) = population size. For an individual with mean values for all independent variables, \(P = \text{average risk} = \text{number of events}/N\). For the male placebo group, \(N = 4525\). For a trial with a 5-year follow-up, risk may be expressed as event rates per 1000 patient-years using the formula \(\text{Event Rate} = P \times 200\). Event rates so obtained were plotted against diastolic BP.

We performed a sensitivity analysis to determine the extent to which the effect of pulse pressure seen in formal modelling was preserved during changes in the continuous non-BP variables (age, cholesterol, and plasma sodium) by entering values equivalent to \((\text{mean} - 2 \text{SD})\), \((\text{mean} - \text{SD})\), \((\text{mean} + \text{SD})\), and \((\text{mean} + 2 \text{SD})\) as well as the mean values into the logistic regression equations. For cigarette smoking, which was not normally distributed, we inserted zero, one half, double, or triple the average daily cigarette intake on entry (6.9 per day), respectively, to include the effect of changes in smoking.

**Results**

Plots of stroke and coronary event risk as a function of subgroups, which were defined by bands of systolic BP on entry containing equal number of strokes during follow-up, showed opposite trends when these subgroups were further subdivided based on diastolic BP. Stroke events rates were directly related to diastolic BP but the opposite was found for coronary events (Figure 1). Hence, those with the greatest pulse pressure were at higher risk of coronary events across the range of systolic BP, but the effect was most notable when systolic BP was high. Similar findings were obtained when the subgroups were defined by quartiles of systolic BP or by ranges of systolic BP that contained equal numbers of coronary events (not shown).

The empirical model suggested that if pulse pressure is the strongest risk predictor for coronary events, the curve relating event probability and diastolic BP does not slope upwards progressively with increasing values of pressure but has a “J” shape (Figure 2). This can be explained by the effect of low diastolic BPs increasing pulse pressure and hence risk, as implied by the negative sign in the expression \(PP = \text{SBP} - \text{DBP}\). This suggestion was confirmed by the solutions to the best-fit logistic regression equations derived from the MRC trial data. The curve relating absolute coronary risk (events/1000 per year) and diastolic BP also had a J shape (Figure 3). However, the corresponding curve obtained for stroke, in which mean BP was the strongest risk predictor, increased progressively with increasing values of diastolic BP. The curves shown as Figure 3 take account of the effect of non-BP variables, which were included in the logistic
regression models at their respective mean values in the terms $C_{\text{Stroke}}$ and $C_{\text{MI}}$ in equations (1) and (2) (see Methods). When systolic BP was the predicting BP variable for coronary events in the logistic regression models, the shape of the curve was progressively upward, with no point of inflection at lower values of diastolic pressure.

In the sensitivity analysis (Figure 4), the J-shaped relation between coronary risk and diastolic BP predicted by pulse pressure was preserved when the values of non-BP variables ranged from (mean $-2\sigma$) to (mean $+2\sigma$). In other words, high values of positively predicting variables (age, cigarettes smoking, and plasma cholesterol) and low values of a negatively predicting variable (plasma sodium) did not overcome the influence of pulse pressure in predicting a J-shaped relationship with overall risk, according to the logistic regression model.

**Discussion**

Superiority of pulse pressure as a cardiac risk predictor in hypertension is supported by 3 strands of evidence: (1) Pulse pressure has been shown to be a risk factor for coronary events (myocardial infarction, angina, heart failure, and cardiac death) in several large population-based studies and clinical trials.5–11 (2) Pulse pressure is strongly associated with, and a potential determinant of, several surrogate markers of cardiac risk such as echocardiographically-determined left atrial12 and ventricular mass, 13 electrocardiographic indicators of ischemia and cardiac size, 14 and carotid wall thickness.15,16 (3) There is an experimentally well-defined and physiologically plausible mechanism linking increased conduit artery stiffness to cardiac risk via raised pulse pressure. In this schema, increased arterial wall stiffness, which itself is a well-recognized index of cardiovascular mortality,17 causes increased systolic BP during systole, increased pulse wave velocity, and early return of the reflected pressure wave during late systole rather than during diastole. These effects increase left ventricular work and oxygen requirements and simultaneously tend to diminish coronary perfusion.18,19 On the other hand, cerebral blood flow occurs throughout the cardiac cycle and the relationship between pulse pressure and stroke is weak.

Certain implications arise if pulse pressure is the main determinant of coronary heart disease risk in hypertensive patients.

First, the association implies that conduit artery stiffness rather than the precapillary arteriolar resistance is an important pathophysiological factor for coronary heart disease in hypertension. This challenges the traditional view of hyper-
tension as a disease in which the anatomical or functional abnormality resides entirely within the precapillary arterioles. Second, pulse pressure is unlikely to be a stronger prognostic factor than systolic BP unless there is a negative relationship between diastolic BP and cardiac risk. Such a situation has been found in several epidemiological studies and is a marker of increasing arterial stiffness that occurs with aging or as a sequel to atherosclerosis, as described above. This conclusion apparently conflicts with epidemiological and clinical studies that show a direct relationship between cardiovascular risk and diastolic BP and the positive correlation that exists in individuals and cross-sectional studies between systolic and diastolic BP. For example, our study of the 2 MRC trials in middle-aged and elderly subjects shows the Pearson correlation coefficients between systolic and diastolic BPs on entry of 0.38 (n = 17 354, P < 0.001) and 0.27 (n = 4387, P < 0.001), respectively (previously unpublished). The apparent inconsistency in the relationships for diastolic BP and risk may be due in part to the lack of distinction in reports of clinical trials between 2 major sequelae of hypertension (stroke and coronary events) that in fact differ qualitatively or quantitatively in their risk factors.

For coronary events, the 2 conflicting influences of diastolic BP presumably balance at some value. In other words, if pulse pressure is the most powerful BP risk factor obtained by sphygmomanometry, an optimum value of diastolic BP below which cardiac risk tends to increase (ie, a J-shaped relationship) is implied. Thus, reduction of diastolic pressure during treatment below some point still to be determined could increase coronary risk. Systolic BP is usually decreased by treatment more than diastolic, and hence treatment will generally diminish pulse pressure. This effect would be expected to offset any primary action of diastolic pressure. However, the interactions between risk, systolic and diastolic BP, and pulse pressure across the full range of pressure seen in treated and untreated hypertensive patients remain to be fully elucidated. J-shaped relationships between cardiac risk and diastolic BP have been reported, but not found by some authors. Reanalysis of the SHEP study has shown that actively treated patients with an event had lower diastolic but not systolic BP and that CHD event rates increased as diastolic BP declined below 65 mm Hg. The HOT study, designed to assess prospectively the effect of variation in target diastolic BP, did not demonstrate increased risk with lower values but the intended diastolic BP targets were not fully met and the mean difference between the groups was small, of the order of 2 mm Hg. More recently, pulse pressure has been shown to be a more powerful predictor of cardiovascular disease than either systolic or diastolic pressures in the Framingham population. That study also demonstrated a negative relationship between cardiovascular risk and diastolic BP. Our models are consistent with these and other studies and suggest that the point of inflection of the J-curve for diastolic BP is between 70 and 90 mm Hg.

Third, the existence of different risk predictors for different sequelae raises the possibility that the clinical benefit of treatment in one area might be accompanied by detriment in another. For example, it appears possible that treatment benefit for stroke, predicted by reduction of mean BP, might be accompanied by reduced benefit for coronary heart disease if the latter is predicted mainly by pulse pressure and if diastolic BP is decreased during treatment beyond the point on the J-curve at which coronary risk begins to increase. Such an effect might explain why most trials in hypertension have shown a greater benefit of treatment on stroke than on coronary events or significant effects on stroke but not on coronary event rates.

Finally, our results suggest that improved reversal of coronary risk would be obtained by antihypertensive drugs that decrease pulse pressure or that have a relatively selective effect on systolic BP by decreasing arterial stiffness. Of the agents that are currently available, ACE inhibitors, diuretics, and nitric oxide (NO) donors appear the most likely candidates, but there is a paucity of data on this important point.

In summary, of the BP measures available from clinical sphygmomanometry, pulse pressure is a strong cardiac risk factor but is difficult to distinguish in this respect from systolic BP. BP indices from more sophisticated methods of BP measurement such as 24-hour ambulatory techniques or more direct indices of arterial stiffness such as pulse wave velocity may be even better risk factors, but less applicable to everyday clinical practice. Pulse wave velocity correlates strongly with the extent of atherosclerosis and cardiovascular mortality. The main consequence if pulse pressure is a stronger risk factor than systolic BP is that one expects a J-shaped relationship between diastolic BP and coronary risk. Precedence for pulse pressure also implies that treatment benefits for different pathological end points, in particular stroke and cardiac events, may be discordant.

References
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