Cardiovascular Risk Assessment Using Pulse Pressure in the First National Health and Nutrition Examination Survey (NHANES I)

Michael Domanski, James Norman, Michael Wolz, Gary Mitchell, Marc Pfeffer

Abstract—Increased stiffness of the conduit arteries has been associated with increased risk of death and cardiovascular death in a number of populations. None of these populations, however, are fully representative of the US population. The cohort examined in the First National Health and Nutrition Examination Survey (NHANES I) that was free of overt cardiovascular disease was selected to be representative of the US population. We assessed and quantified the increased risk of death associated with elevated pulse pressure in this population. A cohort of 5771 subjects from NHANES I was used to determine the value of adding pulse pressure to standard cardiovascular disease risk factors for assessment of the risk of death during a mean follow-up period of 16.5 years. Analyses were performed by use of the SUDAAN statistical package for performing Cox proportional regression, logistic regression, and other standard methods in complex, weighted samples. Pulse pressure increased with increasing age, body mass index, cholesterol level, and mean arterial pressure. With increasing pulse pressure, the percentage of cigarette smokers decreased and the percentage of diabetics increased. Despite these associations with known risk factors, pulse pressure was independently predictive of an increased risk of death from cardiovascular disease, coronary heart disease, and all-cause mortality. It provides independent prognostic information beyond that provided by known risk factors that were evaluated in this study, including the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure hypertension classification. A 10 mm Hg increase in pulse pressure in persons 25 to 45 of age was associated with a 26% increase in risk of cardiovascular death (95% confidence interval [CI], 5 to 50) and with an 10% increase (95% CI, 2 to 19) in persons 46 to 77 years of age. In a cohort designed to be representative of the US population, elevated pulse pressure has been shown to provide independent prognostic information. This variable may be a marker for the extent of vascular disease and may contribute to the occurrence of clinical events. (Hypertension. 2001;38:793-797.)

Key Words: pulse arteries cardiovascular diseases

Increased arterial stiffness, as indicated by increased pulse pressure, has been associated with an increased risk for adverse cardiovascular events, including stroke, myocardial infarction, heart failure, cardiovascular death, and overall mortality, in a number of populations.1-11 With aging, there is a gradual stiffening of the conduit arteries that results from the loss of elastin and deposition of collagen.12 With stiffening, peak systolic pressure increases for any given flow wave. Additionally, the pulse wave velocity of the pressure pulse is increased. This results in earlier return of reflections from the periphery that, as stiffening progresses, arrive in the central aorta in late systole rather than early diastole. This contributes to an augmentation of peak systolic pressure and a reduction in diastolic pressure (and consequently an increase in pulse pressure). In addition to aging, arterial stiffening appears to be hastened by a number of conditions, including hypertension,12 menopause,13 glucose intolerance,14 elevated homocysteine levels,15 polymorphisms of the angiotensin type I receptor gene,16 and renal failure.17

Although a number of populations have been studied, none of them is fully representative of the US population as a whole. The First National Health and Nutrition Examination Survey (NHANES I) was a complex, stratified probability sample of the noninstitutionalized US population between 1 and 77 years of age.18-20 We examined individuals in this cohort who were ≥25 years to determine and quantify the independent prognostic significance of pulse pressure and to determine whether pulse pressure adds prognostic information beyond that supplied by the classification of the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) on prognosis.21

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Causes of death were coded according to the ninth revision of the International Classification of Diseases between 1982 and 1992 by matching with the National Death Index. Details on study methods are available for our analyses. The mean length of follow-up was 16.5 years (range, 16 days to 22 years). Mortality data were collected between 1982 and 1992 by matching with the National Death Index. Causes of death were coded according to the ninth revision of the International Classification of Diseases.21 If the decedent’s code was between 390 and 459, the cause of death coded was attributed to cardiovascular disease (CVD). Coronary heart disease (CHD) was coded as 410 through 414. Of the original cohort, 96.2% of those 25 to 77 years of age were successfully traced, and death certificates were obtained from 4497 (97.7%) of the 4604 decedents.

### Methods

In 1971 to 1975, the National Center for Health Statistics conducted the NHANES I data collection. Data were collected from a complex, stratified probability sample of 23,808 individuals in the civilian noninstitutionalized US population through a variety of questionnaires and a standardized medical examination administered through mobile hospitals. Starting in 1982, the NHANES Epidemiologic Follow-Up Study was conducted to provide a database for studies on the relationship between chronic disease, morbidity and mortality. The study is described in detail elsewhere.22–24 There were 14,407 examinees in NHANES I who were aged 25 to 77 years at the time of the initial examination (1971 to 1975). Direct information on smoking habits at baseline was available from a subsample of 6903 of the original participants of NHANES I. Data were collected from a complex, stratified probability sample of 23,808 individuals in the civilian noninstitutionalized US population through a variety of questionnaires and a standardized medical examination administered from mobile hospitals. Starting in 1982, the NHANES Epidemiologic Follow-Up Study was conducted to provide a database for studies on the relationship between chronic disease, morbidity and mortality. The study is described in detail elsewhere.22–24 There were 14,407 examinees in NHANES I who were aged 25 to 77 years at the time of the initial examination (1971 to 1975). Direct information on smoking habits at baseline was available from a subsample of 6903 of the original participants of NHANES I who were given a detailed examination. After those who were taking blood pressure medication were eliminated, a subsample of 5771 persons with all values of the variables of interest was available for our analyses. The mean length of follow-up was 16.5 years (range, 16 days to 22 years). Mortality data were collected between 1982 and 1992 by matching with the National Death Index. Causes of death were coded according to the ninth revision of the International Classification of Diseases.21 If the decedent’s code was between 390 and 459, the cause of death coded was attributed to cardiovascular disease (CVD). Coronary heart disease (CHD) was coded as 410 through 414. Of the original cohort, 96.2% of those 25 to 77 years of age were successfully traced, and death certificates were obtained from 4497 (97.7%) of the 4604 decedents.

### Statistical Methods

The cohort in this analysis consisted of 5771 adults 25 to 74 years of age who, when appropriately weighted according to the geographic and demographic strata from which they were drawn, accurately represent the US population of the same ages. Analyses were performed with the SUDAAN statistical package,26 which contains procedures for performing Cox proportional-hazards regression, multiple linear regression, logistic regression, and other standard methods applied to complex, weighted samples. Covariates used in these analyses were the following risk factors for CVD measured or observed at baseline: gender, race (specified as black or nonblack on NHANES I data forms), diabetes, and cigarette smoking (each as binary variables), as well as age, body mass index, serum cholesterol, and mean arterial pressure calculated as one third systolic plus two thirds diastolic blood pressure.

### Results

Known risk factors for CVD were assessed as a function of quartile of pulse pressure (Table 1). Increasing pulse pressure is associated with increasing age, body mass index, cholesterol level, and mean arterial pressure; an increasing percentage of diabetics; and fewer cigarette smokers. The percentages of blacks and women display significant U-shaped distributions. A Cox regression analysis, adjusted for the influence of known CVD risk factors, including mean arterial pressure level, assessed the effect of pulse pressure on overall mortality, CVD mortality, and CHD mortality. Tables 2 through 4 display the results of these multivariate analyses. Pulse pressure is significantly associated with total mortality in patients above the median age of 45 years and with CVD and CHD mortality in patients of all ages. Pulse pressure was most strongly associated with the risk of CHD death (Table 4). Mean arterial pressure is associated with total and CVD death in all ages and with CHD death in patients ≥46 years of age. Pulse pressure is not associated with an increase in non-CVD. Compared with persons of other races, blacks are at increased risk for death from all causes and for death as a result of CVD but not of CHD. No evidence was found of an

### TABLE 1. CVD Risk Factor Means by Quartiles of Pulse Pressure

<table>
<thead>
<tr>
<th>Pulse Pressure Quartile, mm Hg</th>
<th>≤36</th>
<th>36–44</th>
<th>44–55</th>
<th>&gt;55</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1471</td>
<td>1370</td>
<td>1377</td>
<td>1553</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>31.0±7.7</td>
<td>40.7±3.7</td>
<td>49.4±3.7</td>
<td>68.5±15.8</td>
<td>...</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>92.3±15.3</td>
<td>95.5±14.8</td>
<td>98.6±3.8</td>
<td>108.9±23.6</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>112.9±15.3</td>
<td>122.6±15.5</td>
<td>131.5±17.4</td>
<td>154.5±29.5</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg</td>
<td>82.0±15.3</td>
<td>81.9±14.8</td>
<td>82.1±17.8</td>
<td>86.0±22.8</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Age, y</td>
<td>40.2±11.1</td>
<td>42.0±15.2</td>
<td>45.4±13.7</td>
<td>54.6±16.5</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.8±5.8</td>
<td>25.1±5.9</td>
<td>25.5±5.9</td>
<td>26.5±7.1</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>212.4±61</td>
<td>215.8±59</td>
<td>219.1±56</td>
<td>230.7±63</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Race, % black</td>
<td>10.2</td>
<td>8.5</td>
<td>8.9</td>
<td>11.6</td>
<td>...†</td>
</tr>
<tr>
<td>Gender, % women</td>
<td>54.5</td>
<td>49.3</td>
<td>50.6</td>
<td>54.2</td>
<td>...†</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>1.6</td>
<td>3.0</td>
<td>2.5</td>
<td>6.7</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Cigarette smokers, %</td>
<td>45.3</td>
<td>42.2</td>
<td>40.2</td>
<td>37.6</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate.

*For test of trend.

†Significant curvilinear effect.
interaction between pulse pressure and gender or between pulse pressure and race in the analyses of CVD deaths in the either age group.

Table 5 presents the results of a Cox regression analysis of cardiovascular disease mortality with mean arterial pressure replaced by the JNC VI classification with the 5 levels described above. It shows that pulse pressure retains its prognostic significance for cardiovascular death in persons of all ages. An increase in pulse pressure of 10 mm Hg in persons 45 years of age produces an estimated increase in the risk of CVD death of 24%; the same increase in persons >45 years of age predicts an increase in risk of 12%.

**Discussion**

This analysis assesses the significance of pulse pressure on the risk of death in a cohort of patients that is specifically designed to be representative of the US population. It demonstrates that pulse pressure is associated with an increased risk of all-cause, CVD, and CHD death independent of mean arterial pressure but not with death from noncardiovascular causes. Furthermore, it provides a quantitative estimate of the hazard ratios in the US population. Interestingly, blacks are at greater risk for all-cause mortality than persons of other races, a finding that appears to be based solely on non-CHD deaths. In this cohort, they did not appear to be at increased risk for death from CHD.

By including the JNC VI classification as a covariate in a Cox regression model with pulse pressure and the other CVD risk factors, we have demonstrated that pulse pressure has prognostic significance independent of the JNC VI classification. A general approach to risk assessment in any data set using blood pressure is improved by including both systolic and diastolic pressures. Because of the equivalence of the information conveyed by either mean arterial and pulse pressures or systolic and diastolic blood pressures, the use of either pair in any regression model results in identical values of the statistical measure of fit of the models. Although systolic blood pressure is a major prognostic determinant, the inclusion of information from diastolic or pulse pressure may add prognostic information, depending on the database examined. Systolic pressure includes substantial contributions from both systolic and diastolic blood pressures. Because of the equivalence of the information conveyed by either mean arterial and pulse pressures or systolic and diastolic blood pressures, the use of either pair in any regression model results in identical values of the statistical measure of fit of the models. Although systolic blood pressure is a major prognostic determinant, the inclusion of information from diastolic or pulse pressure may add prognostic information, depending on the database examined. Systolic pressure includes substantial contributions from both systolic and diastolic blood pressures. Because of the equivalence of the information conveyed by either mean arterial and pulse pressures or systolic and diastolic blood pressures, the use of either pair in any regression model results in identical values of the statistical measure of fit of the models. Although systolic blood pressure is a major prognostic determinant, the inclusion of information from diastolic or pulse pressure may add prognostic information, depending on the database examined. Systolic pressure includes substantial contributions from both systolic and diastolic blood pressures. Because of the equivalence of the information conveyed by either mean arterial and pulse pressures or systolic and diastolic blood pressures, the use of either pair in any regression model results in identical values of the statistical measure of fit of the models. Although systolic blood pressure is a major prognostic determinant, the inclusion of information from diastolic or pulse pressure may add prognostic information, depending on the database examined. Systolic pressure includes substantial contributions from both systolic and diastolic blood pressures. Because of the equivalence of the information conveyed by either mean arterial and pulse pressures or systolic and diastolic blood pressures, the use of either pair in any regression model results in identical values of the statistical measure of fit of the models. Although systolic blood pressure is a major prognostic determinant, the inclusion of information from diastolic or pulse pressure may add prognostic information, depending on the database examined. Systolic pressure includes substantial contributions from both systolic and diastolic blood pressures. Because of the equivalence of the information conveyed by either mean arterial and pulse pressures or systolic and diastolic blood pressures, the use of either pair in any regression model results in identical values of the statistical measure of fit of the models. Although systolic blood pressure is a major prognostic determinant, the inclusion of information from diastolic or pulse pressure may add prognostic information, depending on the database examined. Systolic pressure includes substantial contributions from both systolic and diastolic blood pressures. Because of the equivalence of the information conveyed by either mean arterial and pulse pressures or systolic and diastolic blood pressures, the use of either pair in any regression model results in identical values of the statistical measure of fit of the models. Although systolic blood pressure is a major prognostic determinant, the inclusion of information from diastolic or pulse pressure may add prognostic information, depending on the database examined. Systolic pressure includes substantial contributions from both systolic and diastolic blood pressures. Because of the equivalence of the information conveyed by either mean arterial and pulse pressures or systolic and diastolic blood pressures, the use of either pair in any regression model results in identical values of the statistical measure of fit of the models. Although systolic blood pressure is a major prognostic determinant, the inclusion of information from diastolic or pulse pressure may add prognosis.

**Comparison With Other Studies**

A number of studies in diverse cohorts support the notion that pulse pressure carries important, independent prognostic information. An analysis of data from the Hypertension...
with increased mortality. Across a wide spectrum of diseases from severe hypertension to heart failure with lowered mean arterial pressure, an elevated pulse pressure was found to be an indicator of heightened CVD risk.

Chae et al\textsuperscript{31} followed 1621 healthy elderly subjects with no history of heart failure and a mean age of 77.9 years for an average of 3.8 years. After adjustment for other CVD risk factors, pulse pressure was shown to be independently associated with the risk of developing heart failure.

Data from 50 years of follow-up of participants in the Framingham study demonstrated that pulse pressure, rather than systolic or diastolic pressure, had the strongest association with mortality.\textsuperscript{4} Although Framingham comprises an initially healthy cohort of adults in an eastern Massachusetts city, the design of NHANES I provides a population that is representative of the US population.

Pathophysiology Associated With Increased Conduit Vessel Stiffness

There are a number of potential mechanisms by which increased arterial stiffness could worsen prognosis. The loading caused by increased vascular stiffness has been shown to be associated with increased left ventricular mass.\textsuperscript{28–30} Increased pulse pressure is also associated with increased intimal and medial thickness of the carotid artery.\textsuperscript{31–33} Data from animal studies suggest that the ventricle is more susceptible to ischemia when the aorta is stiff\textsuperscript{34,35} and that coronary occlusion results in greater ventricular damage.\textsuperscript{36}

Although the presence of atherosclerosis may increase arterial stiffness, increased stiffening occurs even in populations in which atherosclerosis is unusual, as demonstrated by the work of Avolio et al\textsuperscript{31} in China. It is possible that aortic stiffening may be atherogenic. In a primate model, atherosclerosis severity was found to increase with an increase in pulsatile strain.\textsuperscript{37} In addition, increased pulse pressure has been associated with reduced NO production by the endothelium,\textsuperscript{38} which has been shown to be atherogenic.\textsuperscript{39} It should be added that pulse pressure changes may occur with changes in stroke volume. Thus, an elevated pulse pressure should be viewed as both a marker of vascular disease and a contributor to disease progression.

Study Limitations

Caution must be exercised in the interpretation of models of mortality in survey data based on death certificates. The causes of death listed on death certificates are not always accurate.\textsuperscript{40} However, they are useful in establishing trends and have been shown to track well with studies of mortality that used more accurate methods of ascertainment.\textsuperscript{41}

Because the white-coat effect may raise initial blood pressures measured in the office setting,\textsuperscript{42} a single measurement can overestimate blood pressure levels. Multiple measurements reduce the variability of the measurements.\textsuperscript{43}

Clinical Implications and Conclusions

This study demonstrates and quantifies the prognostic importance of pulse pressure in a cohort that is representative of the US population. Because there is a functional component of

\begin{table}
\centering
\caption{Survival Analysis: Hazard Ratios for CVD Deaths by CVD Risk Factor and Age Group with JNC VI Classification of Blood Pressure for Adults}
\begin{tabular}{lcc}
\hline
CVD Risk Factor & Age Group & \\
& 25–45 y & 46–77 y \\
\hline
People, n & 2566 & 3205 \\
Deaths, n & 60 & 613 \\
CVD risk factor & & \\
Age (per 10 y) & 1.16 (1.09–1.23) & 1.11 (1.09–1.12) \\
Race (black vs nonblack) & 1.71 (0.87–3.37) & 1.16 (0.87–1.55) \\
Gender (women vs men) & 0.37 (0.20–0.71) & 0.60 (0.47–0.78) \\
Diabetes & 5.76 (2.00–16.61) & 1.65 (1.07–2.56) \\
Cigarette smoking & 1.49 (1.02–2.17) & 1.44 (1.24–1.66) \\
BMI (per kg/m\textsuperscript{2}) & 1.04 (0.98–1.10) & 1.03 (1.01–1.05) \\
Cholesterol (per 10 mg/dL) & 1.12 (1.04–1.20) & 1.02 (1.00–1.05) \\
JNC VI (per unit increase in scale) & 1.61 (1.15–2.26) & 1.22 (1.08–1.38) \\
Pulse pressure (per 10 mm Hg) & 1.24 (1.06–1.46) & 1.12 (1.03–1.21) \\
\hline
\end{tabular}
\end{table}

\footnotesize{Abbreviations as in Table 2. Values in parentheses are 95% CIs. The JNC VI ordinal scale is as follows: 1 = optimal; 2 = normal, not optimal; 3 = high normal; 4 = stage 1 hypertension; and 5 = stage 2 or higher hypertension.

Detection Follow-Up Program reported by Abernathy et al\textsuperscript{27} incorporated other available cardiovascular risk factors into a logistic regression model, demonstrating that pulse pressure is a significant predictor of mortality in that cohort. In 1989, Darne et al\textsuperscript{8} reported their study of 27 000 French subjects in whom pulse pressure was associated with cardiovascular death independent of other known risk factors, including diastolic and mean arterial pressures. Madhavan et al\textsuperscript{6} studied 2207 hypertensive patients in a union-sponsored hypertension control program. In this study, an elevated pretreatment pulse pressure was associated with adverse cardiovascular events. Fang et al\textsuperscript{7} examined data on 5730 participants who entered a hypertension control program between 1973 and 1992. After 5.4 years of follow-up, an elevated pulse pressure was identified as the most important predictor of a subsequent myocardial infarction. Domanski et al\textsuperscript{8} showed an association between pulse pressure and the risk of stroke in patients entered in the Systolic Hypertension in the Elderly Program (SHEP). Using a proportional-hazards model, they demonstrated an 11% increase in the risk of stroke and a 16% increase in total mortality for each 10 mm Hg increase in pulse pressure.

Patients entered in the Survival and Ventricular Enlargement (SAVE) trial were also studied.\textsuperscript{2} For the 2231 post–myocardial infarction patients in the trial (left ventricular ejection fraction ≤0.40), multivariate analysis showed pulse pressure to be an independent predictor of all-cause mortality and myocardial infarction.

Patients entered in the Studies of Left Ventricular Dysfunction (SOLVD) study, who had left ventricular ejection fraction ≤0.35, were shown on multivariate analysis to have a strong association of all-cause mortality and cardiovascular death with pulse pressure.\textsuperscript{1} In fact, in this study, an increase in mean arterial pressure was associated with reduced mortality, whereas an increase in pulse pressure was associated
arterial stiffening, conduit vessel stiffening is a potential therapeutic target. The demonstration that pulse pressure adds prognostic information beyond that of known CVD risk factors, including the JNC VI classification, suggests that it may be useful as an additional factor in risk assessment for future therapeutic decision making.

References
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