Effect of Aging on the Prognostic Significance of Ambulatory Systolic, Diastolic, and Pulse Pressure in Essential Hypertension

Rajdeep S. Khattar, BM, MRCP; John D. Swales, MA, MD, FRCP; Caroline Dore, BSc; Roxy Senior, DM, MRCP; Avijit Lahiri, MB, BS, MSc, MRCP

Background—This study compared the relative prognostic significance of 24 hour intra-arterial ambulatory systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP) parameters in middle-aged versus elderly hypertensives.

Methods and Results—A total of 546 subjects aged <60 years and 142 subjects aged ≥60 years who had undergone baseline pretreatment 24-hour intra-arterial ambulatory blood pressure monitoring were followed for 9.2±4.1 years. Multivariate analysis showed that in younger subjects, 24-hour, daytime, and nighttime DBP, MAP, and SBP, when considered individually, were positively related to morbid events; DBP parameters provided the best predictive values. In the group ≥60 years (elderly group), 24-hour, daytime, and nighttime PP and SBP were the most predictive parameters, whereas ambulatory DBP and MAP measurements failed to provide any prognostic value. When 24-hour values of SBP and DBP were jointly included in the baseline model, DBP (z=2.02, P=0.04) but not SBP (z=−0.43, P=0.67) was related to outcome in younger subjects, whereas in the elderly group, SBP (z=3.33, P=0.001) was positively and DBP (z=−1.75, P=0.07) was negatively related to outcome. Clinic blood pressure measurements failed to provide any independent prognostic value in either age group.

Conclusions—The relative prognostic significance of ambulatory blood pressure components depends on age; DBP parameters provided the best prognostic value in middle-aged individuals, whereas PP parameters were the most predictive in the elderly. This may reflect differing underlying hemodynamic mechanisms of hypertension in these age groups. (Circulation. 2001;104:783-789.)

Key Words: aging ■ blood pressure ■ prognosis

Many observational studies evaluating the changing pattern of blood pressure with the aging process have shown a concomitant increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) until middle adult life.1 Beyond the approximate age of 60 years, SBP continues to increase but DBP reaches a plateau or gradually falls, and this leads to an accelerated rise in PP.1,2 These observations have been made in the normal population using conventional clinic blood pressure measurements. However, 24-hour ambulatory blood pressure monitoring may provide a more representative measure of the daily blood pressure load, and many studies have shown this technique is superior to clinic blood pressure measurements for the prediction of cardiovascular morbidity and mortality.3–7 The intra-arterial technique of ambulatory blood pressure monitoring provides direct beat-by-beat measurements of blood pressure and is considered the reference standard by which noninvasive monitors are validated.8 A 10-year follow-up study of 688 hypertensive patients from our institution showed pretreatment 24-hour intra-arterial ambulatory blood pressure parameters provided independent prognostic information for the prediction of cardiovascular events, whereas clinic blood pressure measurements did not.7

In the present analysis of the same hypertensive cohort, we hypothesized that in view of the age-related changes in blood pressure behavior, the relative prognostic significance of ambulatory SBP, DBP, PP, and mean arterial pressure (MAP) parameters in middle-aged versus elderly subjects may differ. Therefore, the aims of this study were to evaluate the age-related changes in 24-hour intra-arterial ambulatory SBP, DBP, MAP, and PP in our purely hypertensive population and to compare the prognostic significance of ambulatory blood pressure parameters in middle-aged versus elderly subjects.
Methods
During the period from January 1, 1979, to January 1, 1993, 723 patients were subjected to 24-hour intra-arterial ambulatory blood pressure monitoring at our institution. All patients were originally referred for the management of hypertension on the basis of a persistently elevated clinic blood pressure taken over a period of weeks to months in a primary care setting. At each hospital visit, a single blood pressure measurement was taken by a nurse or techni- cian using the conventional auscultatory technique after 5 to 10 minutes of semisupine rest in a warm environment. The point of disappearance of auscultatory sounds was taken as the DBP. Secondary causes of hypertension were excluded, as far as possible, in all patients, as previously described. Baseline clinic blood pressure was taken as the mean of ≥2 untreated readings at separate clinic visits in the 4 weeks before or after the intra-arterial study. Those in whom clinic SBP was ≥140 mm Hg or DBP was ≥90 mm Hg were requested to undergo 24-hour intra-arterial ambulatory blood pressure monitoring within 2 months.

Antihypertensive medication had either not been started or had been withdrawn in the 8 weeks preceding intra-arterial blood pressure monitoring. General practitioners were informed of the results of the test, and antihypertensive therapy was generally recommended if 24-hour ambulatory SBP was ≥140 mm Hg or DBP was ≥90 mm Hg. The treatment of lower ambulatory blood pressure readings was more conservative and discretionary. Subsequent assessment of blood pressure control and treatment was largely left to the individual physicians and was based on clinic blood pressure measurements in keeping with standard clinical practice.

Intra-Arterial Blood Pressure Monitoring
The technique of intra-arterial blood pressure recording used in this laboratory has been well documented, as has the method of analysis. Blood pressure was recorded from a fine brachial artery cannula using a specially designed transducer/perfusion unit and an Oxford Medilog Mark I tape recorder. The equipment was designed so that patients were fully ambulant and able to carry out their normal daily activities away from the hospital environment. The 24-hour tape recordings were analyzed on a custom-built hybrid computer using a program that calculated mean hourly blood pressure. Twenty-four hour mean SBP, DBP, MAP, and PP were calculated by averaging the 24-hour mean readings of these parameters. Blood pressure variability was expressed as the SD of mean calculated by averaging the 24-hour mean readings of these parameters. Blood pressure variability was calculated as the SD of mean calculated by averaging the 24-hour mean readings of these param-
eters. Blood pressure variability was expressed as the SD of mean hourly SBP and DBP, respectively. Daytime mean SBP, DBP, MAP, and PP were defined as the average of the hourly blood pressure readings from 6 AM to 10 PM, and the nighttime mean blood pressures were defined as those between 10 PM and 6 AM. The nocturnal falls in SBP and DBP were calculated by subtracting respective nighttime mean from daytime mean blood pressure readings. Nondippers were defined as those who did not exhibit a reduction in mean SBP and DBP by ≥10% from day to night; the remaining subjects were classified as dippers.

Follow-Up Evaluation
The study patients have been intermittently reviewed over the years to record clinic blood pressure, drug therapy, and the occurrence of interim cardiovascular events. Ethical approval for the most recent follow-up, performed during an 18-month period from 1994 to 1996, was gained from the hospital ethics committee before contacting patients or their family practitioners. To obtain complete mortality data, the dates and certified causes of interim deaths were obtained from the National Health Service Central Register, Southport, United Kingdom. The hospital records of all patients were also scrutinized. Survivors were invited to attend a follow-up evaluation for docu-
mantion of events, clinic blood pressure measurement on current treatment, serum creatinine estimation, and fasting cholesterol level. General practitioners of the nonattendees were sent a questionnaire for details on these patients.

Documented events consisted of noncardiovascular death, coronary death (myocardial infarction or ischemia, ventricular fibrilla-
tion, or cardiac failure), cerebrovascular death, peripheral vascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization.

Statistical Analysis
Continuous variables were expressed as mean±SD and categorical variables as proportions. The study population was dichoto-
mized into those aged <60 years (middle-aged) and those ≥60 years (elderly), and between-group comparisons of clinical vari-
ables and blood pressure parameters were made using the 2-sample t test and Fisher’s exact test. Within-group comparisons of those with and without events were made by univariate Cox proportional hazards analysis. Multivariate analyses were performed separately in each of the 2 age groups using a baseline Cox regression model containing age, sex (men versus women), race (South Asians versus whites and blacks versus whites), smoking (smokers versus nonsmokers), diabetes mellitus, previ-
ous cardiovascular disease, and fasting cholesterol level for predicting the time to experiencing a first event.

Separate regression models were then created by individually adding the clinic and ambulatory blood pressure parameters to the clinical variables to assess whether any of these parameters could enhance the predictive value of the model using the likelihood ratio test. Finally, a series of Kaplan-Meier survival curves were constructed for each group of patients to determine the effects of 24-hour mean SBP, DBP, MAP, and PP cut-off points of 160 mm Hg, 90 mm Hg, 110 mm Hg, and 70 mm Hg, respectively, on event-free survival after correction for clinical variables. In addition, the 24-hour mean SBP curves were adjusted for the effects of 24-hour mean DBP and vice versa; similarly, the 24-hour mean PP and 24-hour mean MAP curves were corrected for mutual effects on survival. P<0.05 was considered significant.

Results
The study population consisted of 688 patients (440 men and 248 women) with follow-up data, of whom 528 were white, 106 were South Asian, and 54 were black. A total of 157 first events were recorded during a mean follow-up period of 9.2±4.1 years, including 32 noncardiovascular deaths, 27 coronary deaths, 10 cerebrovascular deaths, 4 peripheral vascular deaths, 46 nonfatal myocardial infarctions, 20 non-
fatal strokes, and 18 coronary revascularization procedures.

Relationship Between Age and Ambulatory Blood Pressure
Figures 1 and 2 show the trends of 24-hour mean SBP, DBP, MAP, and PP in 7 groups divided according to 5-year age strata from <40 years to ≥65 years. Although SBP and PP generally increased with age, DBP and MAP reached a plateau at 50 to 60 years, with a gradual and more apparent fall in DBP thereafter. As a continuous variable, age was strongly correlated with PP (r=0.51; P<0.001) and SBP (r=0.33; P<0.001), weakly correlated with MAP (r=0.14; P=0.008), and bore no relationship with DBP.

Comparison of Demographic Characteristics in Patients
As shown in Table 1, the proportions of men, diabetics, and smokers in the elderly and middle-aged groups were similar, but a higher mean total cholesterol level and greater proportions of white subjects and those with previous cardiovascular disease were noted in the elderly group. Within each age group, the proportions of men, smokers, diabetics, and those with a previous history of cardiovascular disease were significantly greater in the subgroups with events than in those
without events. Higher mean age and total cholesterol levels were observed in those with events compared with those without events in the younger subjects only.

Comparison of Clinic and Ambulatory Blood Pressure Parameters

Clinic SBP, DBP, MAP, and PP levels were higher in those aged ≥60 years compared with those aged <60 years (Table 2). In the younger group, clinic SBP, DBP, and MAP were higher in those with events than in those without events, but there was no significant difference in clinic PP. However, in the elderly group, none of the clinic blood pressure measurements could distinguish between those with and without events.

Consistent with the ambulatory blood pressure trends noted in Figures 1 and 2, the elderly subjects had higher 24-hour mean, daytime mean, and nighttime mean SBP and PP levels but similar MAP and lower DBP levels than those aged <60 years. Within each age group, those with events had higher 24-hour mean, daytime mean, and nighttime mean SBP, PP, and MAP levels than those without events. Whereas in the

**TABLE 1. Comparison of Baseline Demographic Characteristics**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Events (n=95)</th>
<th>No Events (n=451)</th>
<th>Events (n=62)</th>
<th>No Events (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47±9</td>
<td>51±7</td>
<td>47±10†</td>
<td>64±3*</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>64</td>
<td>82</td>
<td>60†</td>
<td>64</td>
</tr>
<tr>
<td>White race, %</td>
<td>73</td>
<td>72</td>
<td>73</td>
<td>91*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27±4</td>
<td>26±4</td>
<td>27±4</td>
<td>27±4</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.8±1.2</td>
<td>6.3±1.1</td>
<td>5.7±1.2†</td>
<td>6.3±1.2*</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>8</td>
<td>13</td>
<td>6†</td>
<td>8</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>40</td>
<td>54</td>
<td>37†</td>
<td>42</td>
</tr>
<tr>
<td>Past CVD, %</td>
<td>5</td>
<td>14</td>
<td>3†</td>
<td>16*</td>
</tr>
</tbody>
</table>

Values are mean±SD or percent. BMI indicates body mass index; CVD, cardiovascular disease.

*P<0.05 compared with all patients (n=546) <60 years; †P<0.05 compared with those with events within the same age group.
younger group, 24-hour mean, daytime mean, and nighttime mean DBP were higher in those with events, in the elderly group, there was a trend toward lower DBP levels in those who experienced an event. Although there was a greater proportion of nondippers and lower nocturnal reductions in SBP and DBP in the elderly compared with the younger group, within-group comparisons of those with and without events did not reveal any significant differences in these variables. Moreover, the SDs of mean hourly SBP and DBP were not able to discriminate between age groups or events.

**Multivariate Analysis**

As summarized in Table 3, multivariate analysis in those aged <60 years showed that the addition of ambulatory DBP or
MAP parameters, whether 24-hour mean, daytime mean, or nighttime mean, to the baseline model provided the best predictive value. The inclusion of ambulatory SBP values also significantly improved the fit of the model, but PP measurements did not exhibit any predictive value. In the older subjects, ambulatory PP followed by SBP parameters were the most predictive blood pressure variables, whereas DBP or MAP values failed to provide any significant prognostic information. When 24-hour mean values of SBP and DBP were jointly included in the baseline model, DBP ($z=2.02$, $P=0.04$) but not SBP ($z=-0.43$, $P=0.67$) was related to outcome in younger subjects. However, in the elderly group, SBP ($z=3.33$, $P=0.001$) was positively and DBP ($z=-1.75$, $P=0.07$) was negatively related to outcome. Notably, neither the measures of blood pressure variability (including hourly standard deviations of blood pressure, nocturnal falls in blood pressure, and nondipper status) nor the clinic blood pressure measurements were able to provide any independent prognostic information in either age group.

Kaplan-Meier Survival Curve Analysis

Figures 3 and 4 illustrate the findings of Kaplan-Meier survival curve analysis in the 2 age groups using 24-hour mean SBP, DBP, MAP, and PP cut-off points of 160 mm Hg, 90 mm Hg, 110 mm Hg, and 70 mm Hg, respectively. The effects of age and PP on event-free survival were additive. Survival rates were highest in those aged <60 years with a PP <70 mm Hg and lowest in those aged ≥60 years with a PP ≥70 mm Hg; survival in the other 2 groups was intermediate. In those aged <60 years, survival outcome was similar whether the SBP was above or below 160 mm Hg or DBP above or below 90 mm Hg. However, in the older age group, there was a trend toward reduced survival in those with an SBP ≥160 mm Hg (compared with those with an SBP <160 mm Hg; hazard ratio, 1.6; 95% CI, 0.9 to 2.9; $P=0.11$) and in those with a DBP <90 mm Hg (compared with those with a DBP ≥90 mm Hg; hazard ratio, 1.3; 95% CI, 0.7 to 2.2; $P=NS$).

Discussion

The present study evaluated the prognostic effects of intraarterial ambulatory blood pressure parameters in the context of the observed age-related changes in blood pressure in a hypertensive population. Although 24-hour mean values of SBP and PP progressively increased with age, a plateau effect of DBP was observed between 50 and 60 years, followed by a gradual reduction in DBP beyond the age of 60 years. This differing pattern of blood pressure from middle adult life to advanced age confirms the findings of other population studies and formed the basis for dividing our study population into those older than and younger than 60 years. In those aged <60 years, ambulatory DBP followed by MAP parameters, whether 24-hour mean, daytime mean, or nighttime mean, provided the most incremental value for the prediction of morbid events in conjunction with clinical variables; ambulatory SBP parameters also improved the prediction of events, but to a lesser extent than DBP or MAP readings. In contrast, in those aged ≥60 years, ambulatory PP followed by SBP parameters were the best predictors of events, whereas DBP and MAP values failed to provide any additional prognostic information over and above clinical variables.
In this elderly group, the inclusion of both 24-hour mean SBP and DBP in the multivariate model suggested that the direct association of PP with subsequent morbidity and mortality was due to the independent effects of both elevated SBP and reduced DBP. This was further supported by the Kaplan-Meier survival curve analysis showing 24-hour mean values of SBP ≥160 mm Hg and DBP <90 mm Hg were associated with an adverse outcome in those aged ≥60 years. These findings suggest that the prognostic significance of ambulatory SBP, DBP, MAP, and PP measurements depend on the age group evaluated. In both age groups, clinic blood pressure measurements and markers of blood pressure variability failed to provide any independent prognostic information in conjunction with clinical variables.

Although an elevated clinic DBP has historically been associated with increased cardiovascular risk, studies from which this relationship was described often consisted of relatively younger subjects in whom systolic and pulsatile components of blood pressure were not adequately appraised. The emphasis on DBP was subsequently strengthened by a number of therapeutic trials showing the benefits of treating hypertension defined on the basis of an elevated DBP. However, recent studies evaluating the relative prognostic effects of SBP, DBP, MAP, and PP in older age groups have results that are consistent with our findings of a negative association of DBP with subsequent outcome, suggesting that the use of a threshold level of DBP as a criterion for antihypertensive treatment may not be appropriate in the elderly.

Only 4 studies have previously attempted to determine the contribution of the different blood pressure components to cardiovascular risk in different age groups. As early as 1971, data from the Framingham study showed that DBP was the best discriminator of coronary heart disease risk in men younger than 45 years. Beyond this age, a trend of declining relative importance of DBP and a corresponding increase in the importance of SBP was noted in both sexes. Recent reanalysis of the Framingham data restricted to those older than 50 years showed that the inclusion of PP with clinical variables provided the best model for the prediction of events. Darne et al showed that the steady component of blood pressure was a strong risk factor for cardiovascular death in both sexes, but in women older than 55 years, the pulsatile component seemed to predict risk independently of the steady component. However, the number of cardiovascular deaths observed in women was small, raising uncertainty regarding the true significance of this finding. A study conducted by the Veterans Administration showed that when SBP and DBP were considered jointly in a multivariate model containing clinical variables, SBP but not DBP was related to cardiovascular death in men aged <60 years, whereas in older men, SBP was positively and DBP negatively related to outcome, suggesting that PP was the best hemodynamic predictor of outcome in the elderly. Benetos et al showed that MAP and PP were independent predictors of all-cause, noncardiovascular, total cardiovascular, and coronary mortality in normotensive and hypertensive men older and younger than 55 years.

The prognostic importance of DBP and MAP in middle-aged individuals and SBP and PP in the elderly may be attributed, at least in part, to the interaction between peripheral vascular resistance and arterial stiffness at these different stages of adult life. Peripheral resistance increases with age and, at a given cardiac output, this causes an increase in MAP, DBP, and SBP; increased arterial stiffness manifests in the later stages of life and leads to an increase in SBP, a decrease in DBP, and a consequent rise in PP. The progressive rise of both SBP and DBP in middle-aged individuals relates to the predominance of increased peripheral resistance, whereas the plateau or fall in DBP, continued rise in SBP, and the increased slope of PP beyond the sixth decade signifies the preponderance of arterial stiffness in the elderly, albeit associated with an increased peripheral resistance. Therefore, the importance of DBP as a predictor of events in middle-aged individuals may reflect the dominant role of increased peripheral resistance in determining blood pressure behavior in this age group.

The prognostic significance of PP in the elderly may be assigned mainly to blood pressure changes induced by an increase in arterial stiffness, as implied by the independent contributions of both an elevated SBP and reduced DBP. The elevation in SBP caused by an increase in both peripheral resistance and arterial stiffness leads to a disproportionate increase in end-systolic stress, which in turn increases myocardial oxygen consumption, promotes left ventricular hypertrophy, and can compromise coronary perfusion. Because perfusion to the coronary circulation occurs predominantly in diastole, a concomitant reduction in DBP due to increased arterial stiffening may further impair myocardial blood flow and promote ischemia, particularly in the presence of existing atherosclerotic disease. Indeed, it has previously been shown that an increase in arterial stiffness accompanied by a decline in DBP is associated with a progression of atherosclerotic disease with advancing age.

Limitations
The majority of the prognostically important baseline demographic parameters were assessed in this study, but family history of cardiovascular disease was inadequately documented and, hence, not taken into account. Although the much-quoted New Zealand chart for the assessment of cardiovascular risk does not include an evaluation of family history, data from the Framingham study suggest that this variable is an independent risk factor for coronary heart disease. Therefore, it is possible that an evaluation of family history of cardiovascular disease may have altered the findings of multivariate analysis, but the inclusion of noncardiovascular death as an end point in our study may have dampened its effects. In addition, the limited sample size of our study with dichotomization of patients on the basis of age prohibited further subgroup analysis on the basis of sex or event type.

Finally, the assessment of blood pressure control and the administration of antihypertensive drug therapy did not follow a formalized protocol; they were left entirely to the discretion of the attending physician of the hypertension clinic or the family practitioner. Therefore, it was not possible...
to evaluate the relationship between achieved blood pressure and event rate. Blood pressure control was based on clinic blood pressure measurements as part of standard clinical practice because it was not considered justifiable on ethical grounds to repeat intra-arterial blood pressure monitoring.

Acknowledgments
This study was supported by an educational grant from the Northwick Park Hospital Cardiac Research Fund. This study was performed under the invaluable guidance and support of the late Dr E.B. Raftery. We would like to thank Ann Banfield, Christopher Kinsey, and the staff at the NHS Central Register, Southport, UK for their assistance with data collection.

References
Effect of Aging on the Prognostic Significance of Ambulatory Systolic, Diastolic, and Pulse Pressure in Essential Hypertension
Rajdeep S. Khattar, John D. Swales, Caroline Dore, Roxy Senior and Avijit Lahiri

Circulation. 2001;104:783-789
doi: 10.1161/hc3201.094227
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/7/783

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/