Central Aortic Reservoir-Wave Analysis Improves Prediction of Cardiovascular Events in Elderly Hypertensives

Om Narayan, Justin E. Davies, Alun D. Hughes, Anthony M. Dart, Kim H. Parker, Christopher Reid, James D. Cameron

Abstract—Several morphological parameters based on the central aortic pressure waveform are proposed as cardiovascular risk markers, yet no study has definitively demonstrated the incremental value of any waveform parameter in addition to currently accepted biomarkers in elderly, hypertensive patients. The reservoir-wave concept combines elements of wave transmission and Windkessel models of arterial pressure generation, defining an excess pressure superimposed on a background reservoir pressure. The utility of pressure rate constants derived from reservoir-wave analysis in prediction of cardiovascular events is unknown. Carotid blood pressure waveforms were measured prerandomization in a subset of 838 patients in the Second Australian National Blood Pressure Study. Reservoir-wave analysis was performed and indices of arterial function, including the systolic and diastolic rate constants, were derived. Survival analysis was performed to determine the association between reservoir-wave parameters and cardiovascular events. The incremental utility of reservoir-wave parameters in addition to the Framingham Risk Score was assessed. Baseline values of the systolic rate constant were independently predictive of clinical outcome (hazard ratio, 0.33; 95% confidence interval, 0.13–0.82; P=0.016 for fatal and nonfatal stroke and myocardial infarction and hazard ratio, 0.38; 95% confidence interval, 0.20–0.74; P=0.004 for the composite end point, including all cardiovascular events). Addition of this parameter to the Framingham Risk Score was associated with an improvement in predictive accuracy for cardiovascular events as assessed by the integrated discrimination improvement and net reclassification improvement indices. This analysis demonstrates that baseline values of the systolic rate constant predict clinical outcomes in elderly patients with hypertension and incrementally improve prognostication of cardiovascular events. (Hypertension. 2015;65:00-00. DOI: 10.1161/HYPERTENSIONAHA.114.04824.) • Online Data Supplement

Key Words: aging □ blood pressure □ cardiovascular diseases □ hypertension □ pulse wave analysis □ vascular stiffness

Central aortic blood pressure and morphological parameters derived from central aortic wave analysis have been proposed as potentially better predictors of cardiovascular risk than traditional brachial blood pressure. Two clinical trials in hypertensive patients with independent adjudication of clinical end points—the arterial mechanics substudy of the Second Australian National Blood Pressure Study (ANBP2) and the Conduit Artery Functional Evaluation (CAFE) have reported on associations between central arterial parameters and the subsequent occurrence of cardiovascular events. CAFE assessed on-treatment central aortic blood pressure parameters in a subgroup of the Anglo Scandinavian Cardiac Outcomes Trial and found that derived central aortic pulse pressure was independently associated with a post hoc defined secondary end point. As all measurements were made postrandomization, CAFE could not elucidate the relationship between baseline values of these parameters and outcomes. ANBP2 was a prospective, randomized, open-label, blinded end point study of the effect of angiotensin-converting enzyme inhibitors (ACEi) versus diuretic-based regimens in the treatment of elderly hypertensives. The full protocol and results have been reported. The arterial mechanics substudy of ANBP2 participants examined the influence of baseline central aortic function on treatment responsiveness and cardiovascular outcome. There was no association between any index of central aortic blood pressure or arterial stiffness and outcome, nor was a treatment-related (ACEi-based versus diuretic-based) influence on arterial mechanics demonstrated. ANBP2 remains the only outcome study performed in arterial hypertension that has reported baseline (postrandomization) measurements of central blood pressure parameters.

Reservoir-wave analysis is based on the premise that not all changes in aortic pressure and flow can be ascribed to forward
and backward traveling waves.\textsuperscript{11–14} It attempts to unify wave propagation and 3-element Windkessel models, thereby accounting for the distributed capacitive function of conduit arteries. In reservoir analysis, pressure waveforms are separated into 2 components: a reservoir pressure that relates to arterial compliance and is temporally uniform throughout the large arterial system but shows a time lag that depends on the location and the wave properties of the arteries; and an excess pressure that is the difference between the total pressure waveform and the reservoir pressure waveform (Figure A). The areas under the reservoir and excess pressure curves as well as their amplitudes have been shown to predict survival in a large cohort of patients undergoing coronary angiography\textsuperscript{15} and in a recent analysis from the CAFE study.\textsuperscript{16}

If wave reflections are assumed to be of minimal intensity, the rate constant for reservoir filling ($k_s$) will be inversely related to the product of aortic characteristic impedance and total arterial compliance ($k_s = (Z_C R_C)^{-1}$). Similarly, the rate constant for reservoir emptying ($k_d$) is inversely related to the product of systemic arterial resistance and total arterial compliance ($k_d = (RC)^{-1}$) and is the reciprocal of the diastolic time constant $\tau$ (Figure B; online-only Data Supplement). The utility of these rate constants for predicting benefit from antihypertensive therapy or clinical outcome is unknown. We therefore applied reservoir-wave analysis to the baseline data from the arterial mechanics substudy of ANBP2 to (1) investigate the prognostic value of reservoir pressure model parameters on cardiovascular outcome in elderly hypertensive subjects and (2) examine any drug-class effects between treatment arms in the cohort.

**Methods**

The study design and patient recruitment methodology used in ANBP2 have been published previously.\textsuperscript{3} Briefly, ANBP2 used a prospective, randomized, open label design with adjudicated and blinded assessment of end points to determine whether an ACEi-based regimen was superior to a diuretic-based regimen in 65 to 84-year-old hypertensive patients. A detailed description of inclusion and exclusion criteria may be found in the online-only Data Supplement. After confirmation of eligibility and before randomization, patients were invited to participate in the arterial mechanics substudy. This substudy comprised participants recruited from the Melbourne sites of the left ventricular hypertrophy substudy cohort of ANBP2. All studies were approved by the Royal Australian College of General Practitioners Ethics Committee, the institutional review committees of participating centers, and conformed to the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Data acquisition in the arterial mechanics substudy has been described previously and is detailed in the online-only Data Supplement. Briefly, carotid arterial waveforms were acquired by applanation tonometry of the proximal right carotid artery with a pencil-type tonometer (Millar Micro-tip SPT-301 transducer, 200 Hz sampling rate) calibrated to brachial mean and diastolic blood pressures. Patients were followed for a mean of 4.4 years (range 1.3–5.4 years). End points and adjudication processes have been previously described— the composite end point of the ANBP2 study included fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, sudden or rapid death from cardiac causes, other deaths from coronary causes or coronary events associated with coronary intervention, incident heart failure, acute occlusion of a major feeding artery in any vascular bed other than cerebral or coronary, death from noncoronary cardiac causes, dissecting or ruptured aortic aneurysm, or death from vascular causes.\textsuperscript{1} The primary end point for the current analysis comprised hard cardiovascular events (fatal and nonfatal myocardial infarction and stroke), whereas the combined cardiovascular event end point included all events as defined in the ANBP2 study.

**Statistics**

Group data are presented as means (±SD) or medians (and interquartile range) for non-normally distributed data. Normality was investigated by visual inspection of histograms and confirmed with the Shapiro–Wilk test. Nonparametrically distributed continuous variables were natural log transformed for multivariate analysis. Chi-square and $t$ tests for independent samples were used with categorical and continuous variables, respectively. IBM SPSS Statistics version 22 was used for statistical analyses.

Cox Proportional hazards modeling was applied with the simultaneous entry of covariates using the ENTER function. First, the independent association of reservoir-wave and central blood pressure morphological parameters with the primary and combined cardiovascular outcomes after adjustment for age and sex was assessed (Model 1). Parameters found to significantly predict outcomes were subsequently entered in a more comprehensive model adjusted for recognized cardiovascular risk predictors in addition to age and sex, including brachial systolic blood pressure (SBP), total cholesterol, high-density lipoprotein cholesterol, heart rate, smoking status, presence of diabetes mellitus, treatment randomization, and presence of left ventricular hypertrophy according to electrocardiographic criteria (Model 2). Pulse pressure amplification (PPA), defined as brachial pulse pressure (PP)/central PP, was also tested in this model. The proportional hazards assumption was tested by inspection of Schoenfeld residuals. Subgroup analyses were performed to determine whether associations between reservoir wave parameters and outcomes were altered by sex, treatment allocation, or age. The incremental utility of reservoir-wave parameters when added to the Framingham Risk Score (FRS) was assessed with the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices. Data for patients who were lost to follow-up were censored at the time of the last contact.

**Results**

Baseline, prerandomization demographic characteristics are shown in Table 1. Patients who subsequently experienced events were older, more commonly male, with higher brachial systolic blood pressures, elevated plasma creatinine with a greater prevalence of previous angina, or myocardial infarction (all $P<0.05$). There were no relevant differences between the patients recruited in the substudy compared with those in the ANBP2 cohort.\textsuperscript{1} Recorded waveforms were not suitable for reservoir-wave analysis in 33 patients (3.8% of the initial 871 patient cohort) leaving 838 includable for further analysis. Baseline reservoir pressure parameters are shown in Table 1. Mean peak reservoir pressure, $k_s$, and $k_d$ values were lower in the group experiencing subsequent cardiovascular events compared with those who did not ($P<0.05$ for all comparisons).

**Relationship Between Reservoir Parameters and Central/Brachial Blood Pressure Parameters**

The systolic rate constant $k_s$ was moderately positively correlated with $k_d$ ($R=0.68$, $P<0.001$) and weakly correlated with cSBP ($R=0.15$, $P<0.01$), cDBP ($R=0.10$, $P=0.01$), and cPP ($R=0.13$, $P<0.01$). $k_s$ was not correlated with the central AIx or augmentation pressure. The diastolic rate constant $k_d$ was weakly positively correlated with both cSBP ($R=0.30$, $P<0.001$) and brachial SBP ($R=0.24$, $P<0.01$) but not with other indices. Reservoir pressure parameters were strongly correlated with central and brachial blood pressures (see online-only Data Supplement).
Predictors of Cardiovascular Events During Follow Up

The primary end point comprising fatal and nonfatal stroke and myocardial infarction was observed in 43 patients representing 5.1% of the total 838 patient cohort, whereas the combined cardiovascular end point was reached in 81 patients or 9.7% of the cohort. After adjustment for age and sex (Model 1), only the systolic rate constant \( k_s \) was independently predictive of the incidence of the primary end point (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.18–0.99; \( P=0.049 \); see Table S1). No other reservoir-wave or central pressure waveform parameter was found to significantly predict the incidence of the primary end point after accounting for age and sex. \( k_s \) also independently predicted the incidence of the combined cardiovascular end point (HR, 0.41; 95% CI, 0.22–0.77; \( P=0.006 \); see Table S2). Higher values of \( k_s \) were associated with a reduced incidence of both end points. Additionally, PPA ratio was predictive of the combined cardiovascular end point (HR, 1.95; 95% CI, 1.22–3.11; \( P=0.005 \)). Conversely, higher values of PPA were associated with a higher incidence of the combined cardiovascular end point. Treatment allocation was not associated with differences in the overall incidence of the primary or the combined cardiovascular end points.

Predictors of Outcome After Adjustment for Known Risk Markers

Reservoir wave and central aortic pressure waveform parameters found to significantly predict either end point in Model 1 were subsequently entered into Model 2, which adjusted for multiple a priori identified cardiovascular risk markers in addition to age and sex. The systolic rate constant \( k_s \) remained independently associated with the primary end point (HR, 0.33; 95% CI, 0.13–0.82; \( P=0.016 \); Table 2). Female sex was associated with a significantly reduced rate (HR, 0.38; 95% CI, 0.19–0.75; \( P=0.006 \)) whereas increasing age (HR, 1.10; 95% CI, 1.03–1.17; \( P=0.004 \)) and brachial blood pressure (HR, 1.02; 95% CI, 1.01–1.04; \( P=0.008 \)) were associated with an increased risk of the primary end point.

The systolic rate constant \( k_s \) also predicted the combined cardiovascular end point in Model 2 (HR, 0.38; 95% CI, 0.20–0.74; \( P=0.004 \); Table 2). Age, female sex, brachial SBP, and PPA also predicted the combined cardiovascular end point in this model. Both \( k_s \) and PPA remained significant predictors of outcome, despite simultaneous inclusion in Model 2. Increasing values of \( k_s \) were predictive of a reduced incidence of both the primary and combined cardiovascular outcomes, whereas the converse was observed with PPA values. A higher PPA (indicating higher brachial PP relative to central PP) was associated with a higher incidence of the combined cardiovascular end point. In this context, increased PPA was driven by higher brachial SBP in patients subsequently experiencing an event (mean brachial SBP 166 mm Hg versus 161 mm Hg in patients not experiencing an event, \( P=0.028 \)) rather than a decrease in central SBP. These findings are consistent with those observed previously in this cohort.\(^8\)

### Table 1. Baseline Demographic Characteristics and Reservoir-Wave Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SEM)</th>
<th>No Event (n=757)</th>
<th>Event (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.6 (0.17)</td>
<td>73.47 (0.55)*</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.0 (0.32)</td>
<td>165.9 (1.10)†</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.9 (0.46)</td>
<td>73.8 (1.34)†</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.6 (0.14)</td>
<td>26.73 (0.35)</td>
<td></td>
</tr>
<tr>
<td>Central SBP, mm Hg</td>
<td>161.8 (1.10)</td>
<td>161.2 (3.00)</td>
<td></td>
</tr>
<tr>
<td>Central DBP, mm Hg</td>
<td>81.0 (0.39)</td>
<td>82.8 (1.29)</td>
<td></td>
</tr>
<tr>
<td>Central PP, mm Hg</td>
<td>80.8 (0.99)</td>
<td>78.4 (2.95)</td>
<td></td>
</tr>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>160.9 (0.75)</td>
<td>166.2 (2.25)†</td>
<td></td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>81.7 (0.39)</td>
<td>83.6 (1.25)</td>
<td></td>
</tr>
<tr>
<td>Brachial PP, mm Hg</td>
<td>79.2 (0.63)</td>
<td>82.6 (2.20)</td>
<td></td>
</tr>
<tr>
<td>Brachial MBP, mm Hg</td>
<td>113.1 (0.56)</td>
<td>114.1 (1.61)</td>
<td></td>
</tr>
<tr>
<td>Heart Rate, bpm</td>
<td>69.9 (0.37)</td>
<td>69.5 (1.41)</td>
<td></td>
</tr>
<tr>
<td>AIx, %</td>
<td>34.5 (0.45)</td>
<td>33.1 (1.31)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.6 (0.04)</td>
<td>5.6 (0.11)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4 (0.02)</td>
<td>1.3 (0.06)</td>
<td></td>
</tr>
<tr>
<td>Non-fasting glucose</td>
<td>5.4 (0.07)</td>
<td>5.3 (0.154)</td>
<td></td>
</tr>
<tr>
<td>Plasma creatinine, μmol/L</td>
<td>87.2 (0.71)</td>
<td>94.5 (2.35)†</td>
<td></td>
</tr>
<tr>
<td>Male sex, % (N)</td>
<td>42 (332)</td>
<td>64 (56)*</td>
<td></td>
</tr>
<tr>
<td>Randomized to ACEI, % (N)</td>
<td>50 (389)</td>
<td>55 (48)</td>
<td></td>
</tr>
<tr>
<td>Ex smoker/current smoker, % (N)</td>
<td>43.7 (342)</td>
<td>58.0 (51)†</td>
<td></td>
</tr>
<tr>
<td>Hypertension history, % (N)</td>
<td>73.6 (576)</td>
<td>73.9 (65)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction history, %</td>
<td>2.2 (17)</td>
<td>8.6 (7)*</td>
<td></td>
</tr>
<tr>
<td>Angina history, % (N)</td>
<td>3.3 (25)</td>
<td>11.0 (8)†</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, % (N)</td>
<td>6.0 (47)</td>
<td>6.8 (6)</td>
<td></td>
</tr>
</tbody>
</table>

#### Results

- Male sex: \( P=0.05 \)
- Randomized to ACEI: \( P<0.001 \)
- Ex smoker/current smoker: \( P=0.001 \)
- Hypertension history: \( P=0.001 \)
- Myocardial infarction history: \( P<0.001 \)
- Angina history: \( P=0.001 \)
- Diabetes mellitus: \( P=0.001 \)

#### Effect of Treatment Allocation, Age, and Patient Sex

We separated the 838 patients by randomized treatment into diuretic- and ACEI-treated subgroups. \( k_s \) was significantly associated with both end points among diuretic-treated patients (HR, 0.13; 95% CI, 0.04–0.50; \( P=0.003 \) for the primary end point and HR, 0.21; 95% CI, 0.08–0.54; \( P=0.001 \).
Discussions

This analysis represents the first application of the reservoir-wave model in a large hypertensive patient cohort in whom prerandomization, direct measurements of central (carotid) BP were available and in whom outcome was formally documented. The systolic rate constant $k_s$ was independently associated with incident cardiovascular events over a mean 4.4-year follow-up period and significantly improved the discriminative power of the FRS to predict incident cardiovascular events. These findings highlight the potential utility of reservoir-wave analysis applied to noninvasive tonometric recordings of central arterial pressure in risk prognostication.

The compliance (C) of the proximal ascending aorta is known to decrease with advancing age caused by elastin fatigue, increasing atherosclerosis, and other factors. Changes in $k_s$ in all probability represent manifestations of large artery stiffening, with the increased incidence of adverse cardiovascular outcomes

<table>
<thead>
<tr>
<th>Table 2. Multivariate Cox Proportional Hazards Analysis: Primary and Combined Cardiovascular Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Primary end point</td>
</tr>
<tr>
<td>Systolic rate constant $k_s$</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex (Female)</td>
</tr>
<tr>
<td>Brachial SBP</td>
</tr>
<tr>
<td>Combined cardiovascular end point</td>
</tr>
<tr>
<td>Systolic rate constant $k_s$</td>
</tr>
<tr>
<td>Pulse pressure amplification ratio</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex (Female)</td>
</tr>
<tr>
<td>Brachial SBP</td>
</tr>
</tbody>
</table>

Hazard ratios for the primary or secondary end points following adjustment for known risk factors (sex, age, total and HDL cholesterol, brachial SBP, smoking, diabetes mellitus, heart rate, ECG evidence of LVH and treatment allocation).

ACEI indicates angiotensin-converting enzyme inhibitor; AIx, augmentation index; CI, confidence interval; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; and SBP, systolic blood pressure.

for the combined cardiovascular end point), whereas no significant association was observed among the ACEI-treated patients (see Table S3). Similarly, after separation into male and female subgroups, $k_s$ was found to be significantly associated with both end points among male patients (HR, 0.26; 95% CI, 0.08–0.83; $P=0.024$ for the primary end point and HR, 0.30; 95% CI, 0.13–0.70; $P=0.005$ for the combined cardiovascular end point), whereas this was not observed among female. No significant interaction between $k_s$ and age was evident for either end point.

Incremental Predictive Utility of $k_s$

The c-statistic for $k_s$ was lower than that for the FRS in prediction of the primary end point (0.58 versus 0.66, $P=0.03$). However, there was no significant difference noted between the c-statistics for $k_s$ and the FRS in predicting the combined cardiovascular end point (0.60 versus 0.62; $P=0.99$).

Addition of $k_s$ to the FRS resulted in a nonsignificant increase in the c-statistic from 0.66 to 0.68 ($P=0.280$) with regard to the primary end point with a nonsignificant increase from 0.62 to 0.66 ($P=0.084$) noted with the combined cardiovascular end point (see Figures S1 and S2). As comparison of c-statistics is known to underestimate improvements in discrimination with the addition of novel biomarkers, we tested the incremental utility of $k_s$ added to the FRS with the IDI and NRI statistics.

The systolic rate constant $k_s$ significantly improved discrimination of the FRS for the primary end point as assessed by IDI (IDI=0.0072; $P=0.003$). Similarly, with regard to the combined cardiovascular end point, addition of $k_s$ to the FRS resulted in a significant improvement in discrimination (IDI=0.015; $P=0.001$). A significant improvement in NRI was observed with the addition of $k_s$ to the FRS in predicting the combined cardiovascular end point, but not with regard to the primary end point (NRI=0.27; $P=0.02$ for the combined cardiovascular end point versus NRI=0.14; $P=0.37$ for the primary end point).

| Figure. Pressure waveform separation into reservoir and excess pressures. A, Calculation of the reservoir pressure waveform permits separation of the pressure waveform into excess (wave-related) and reservoir (conduit-related) pressures with diastolic pressure taken as a baseline. The excess pressure integral (XSPI) and reservoir pressure integral (RPI) are defined by the areas enclosed as shown. B, Effect of changes in $k_s$ and $k_d$ on the final reservoir pressure waveform. The reservoir pressure waveform is represented by the solid blue line. An increase in $k_s$ results in an upward shift of the waveform (represented by the upper blue dashed line), whereas a decrease in $k_d$ results in a downward shift of the waveform (represented by the lower blue dashed line). |
in patients with a low \( k_s \) explainable as a consequence of major organ system exposure to ill-matched rates of pressure transmission. As derived, the systolic rate constant \( k_s \) is inversely proportional to the product of \( Z_0 \) and \( C \) (see online-only Data Supplement).\(^{15,21}\) This cohort of elderly hypertensive patients is likely to represent a group with uniformly low aortic compliance. Although it is difficult to separate individual contributions of each constituent parameter, from the water hammer equation \( Z_0 \) is proportional to pulse wave velocity; therefore, lower values of pulse wave velocity (representing lower \( Z_0 \)) may account for higher \( k_s \) values, potentially explaining the protective effect of this parameter on outcomes in our analysis. Against this background, a high \( k_s \) may identify a cohort of patients with lower aortic characteristic impedance and arterial stiffening who subsequently have a lower incidence of cardiovascular events. The lack of an independent association between the diastolic rate constant \( k_d \) and primary hard outcomes highlights the potential predominance of systolic aspects of ventriculo–vascular interaction, aortic systolic pressure generation, and transmission with regard to end-organ damage and cardiovascular events in elderly hypertensives.

Interactions between \( k_s \) randomized treatment, and sex were observed in subgroup analyses. Although these results should be considered hypothesis generating only, possible pathophysiological explanations may relate to differing mechanisms of antihypertensive action and to sex-related differences in ventriculo–vascular coupling. Diuretic therapy, particularly with longer acting agents, has been shown to reduce rates of cerebrovascular and coronary events.\(^{22}\) The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial demonstrated the superiority of diuretic therapy over either lisinopril or amlodipine in hypertensive patients aged >55 years.\(^{23}\) A higher \( k_s \) value may identify patients with lower baseline characteristic impedance, relatively less fixed large vessel stiffness, and a greater potential to respond to diuretic-induced volume depletion. With respect to sex differences, the lower incidence of both end points in females may have resulted in reduced power to detect a significant association between \( k_s \) and outcomes. Alternatively, this disparity may relate to the recognized differences in markers of arterial stiffness between age-matched males and females.\(^{24}\) Our findings merit further investigation in an adequately powered study.

Higher PPA was associated with a higher subsequent incidence of the combined cardiovascular end point. Although this may seem to run counter to currently accepted dogma,\(^{25}\) it is important to recognize that increased PPA in our population was driven by higher brachial SBP with relatively uniform central SBP in the population experiencing events. Previous analyses linking lower PPA with cardiovascular outcomes typically report higher central SBP values for a given brachial SBP value.\(^{26}\) This distinction is pertinent as greater transmission of pulsatile pressure may be operative in the former setting (resulting in greater end-organ exposure to pulsatile stress), whereas relatively increased wave reflection may be responsible for the latter (resulting in greater LV afterload). As a simple ratio of peripheral PP to central PP, PPA is unable to distinguish between these distinct scenarios.

The novel aspect of the aortic reservoir-wave model is its inclusion of aortic Windkessel function in accounting for the relationship between aortic blood pressure and blood flow. In particular, the model accounts for the relative absence of diastolic blood flow that has traditionally been explained by the influence of reverse travelling pressure and flow waves.\(^{13,27}\) Our results are consistent with the hypothesis that the central aortic pressure waveform is principally influenced by local ventriculo–vascular interactions involving stroke volume, aortic diameter, and stiffness of the vascular compartment into which the stroke volume is ejected (ie, a more or less compliant proximal aorta) than by reflection of discrete waves. These observations could account for the noted lack of predictive association between pulse wave analysis parameters and cardiovascular outcomes in ANBP2 and the weak associations seen in CAFE and Strong Heart\(^{22,4}\) and suggests that the relevance of wave reflection may be no greater in elderly hypertensives (with presumably stiffer aortas) than in the younger groups included in the other 2 studies.\(^{11}\)

Hametner and colleagues recently reported that peak reservoir pressure was independently and positively correlated with clinical outcome.\(^{25}\) Davies et al, however, found the excess pressure integral, but not peak reservoir pressure, when measured directly from radial tonometric pressure waveforms was predictive of events in a subanalysis of the CAFE cohort.\(^{16}\) These divergent results may be a consequence of multiple methodological differences between studies. We used tonometric carotid pressure waveforms as a surrogate for the central aortic pressure waveform, and the study performed by Hametner and colleagues used radial tonometry with the Sphygmocor generalized transfer function to estimate the central aortic waveform after application of a transfer function, whereas Davies et al used untransformed radial tonometric traces.\(^{15,16}\) Additionally, the patient groups differed significantly with an inclusive definition of cardiovascular events applied in the ANBP2 cohort.\(^{7}\) Our findings may be of particular applicability to older patients (>65 years of age) where vascular stiffening and generalized reductions in compliance may be well established.

Limitations and Strengths

As this is a post hoc analysis performed in a subgroup of the larger ANBP2, the results as described are hypothesis generating and require prospective confirmation in a larger cohort of patients. Conclusions relating to subgroups, including those defined by sex or treatment allocation, should be interpreted within this context. Additionally, echocardiographic data relating to left ventricular function as assessed by ejection fraction was not available for this cohort. As ventricular function is an important determinant of prognosis, we cannot exclude the possibility that inclusion of left ventricular ejection fraction in the survival analysis could have altered our results. Conversely, important strengths of this analysis include its large size and the prospective collection of end point events and subsequent independent adjudication by an end point committee blinded to treatment allocation.

Perspectives

Although these findings can be considered as hypothesis generating, the clear differences in clinical outcome seen between patients with varying \( k_s \) and the incremental prognostic benefit seen with this parameter strongly suggests that the reservoir-wave hypothesis applied to noninvasively
obtained carotid pressure waveforms is of potential clinical utility. From a practical standpoint, acquisition of the carotid pressure waveform from the common carotid pulsation with a hand-held tonometer is safe and easily performed, with acquisition typically complete within 5 to 10 minutes. The tonometer is widely commercially available and the analysis required to estimate $k_i$ is easily performed with computational software. These findings support the concept that the time course of aortic pressure rise and fall in the proximal conduit vessels may be of greater importance than traditional pulse wave morphology parameters, including pulse pressure and AIx that assess pressure amplitude only.

Acknowledgments

We acknowledge the support of the clinical trial doctors, nurses, and support staff involved in the ANBP2 Aortic Mechanics sub-study. We also acknowledge the patients who participated in the study.

Sources of Funding

Dr Narayan is supported by a National Health and Medical Research Council Postgraduate Scholarship (Australia). Dr A.D. Hughes received support from the Biomedical Research Centre Award to Imperial College Academic Health Sciences Centre and the BHF Council Postgraduate Scholarship (Australia). Dr A.D. Hughes is supported by a National Health and Medical Research Council Postgraduate Scholarship (Australia). Dr Narayan is supported by a National Health and Medical Research Council Postgraduate Scholarship (Australia). Drs A.D. Hughes and John J. Reid are supported by National Health and Medical Research Council Postgraduate Scholarships (Australia). Drs A.D. Hughes and John J. Reid are supported by Imperial College Academic Health Sciences Centre and the BHF-funded Academic Unit.

Disclosures

None.

References


**Novelty and Significance**

**What Is New?**
- This study demonstrates the prognostic utility of a systolic rate constant ($k_s$), derived from reservoir wave analysis, in a large, prospectively evaluated cohort of patients with rigorously adjudicated follow-up of clinical events.
- Addition of $k_s$ to the Framingham risk score incrementally improves predictive accuracy for cardiovascular events.
- Measurement of $k_s$ from noninvasively acquired carotid pressure waveforms is straightforward, without the need for pressure calibration or vascular transfer functions.
- First demonstration of conduit artery systolic function predicting cardiovascular outcomes.

**What Is Relevant?**
- Calculation of $k_s$ from the central aortic pressure waveform enhances prediction of cardiovascular risk and provides important insights into ventricular–vascular interaction.
- Aortic systolic behavior is an important determinant of outcomes in hypertension.

**Summary**
The systolic rate constant $k_s$ measured from the central aortic blood pressure waveform indicates disturbed cardiovascular function and independently predicts cardiovascular outcomes.
Central Aortic Reservoir-Wave Analysis Improves Prediction of Cardiovascular Events in Elderly Hypertensives
Om Narayan, Justin E. Davies, Alun D. Hughes, Anthony M. Dart, Kim H. Parker, Christopher Reid and James D. Cameron

Hypertension. published online December 22, 2014;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2014/12/22/HYPERTENSIONAHA.114.04824

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2014/12/22/HYPERTENSIONAHA.114.04824.DC1
http://hyper.ahajournals.org/content/suppl/2016/04/11/HYPERTENSIONAHA.114.04824.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension 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 Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
Online Supplement

Central Aortic Reservoir-Wave Analysis Improves Prediction of Cardiovascular Events in Elderly Hypertensives

Running title: Reservoir--Wave analysis and CV risk prediction

Om Narayan¹,⁷, Justin E Davies², Alun D Hughes³, Anthony M Dart⁴, Kim H Parker⁵, Christopher Reid⁶, James D Cameron¹,⁷

¹Monash Cardiovascular Research Centre, School of Clinical Sciences at Monash, Monash University, Melbourne Australia, ²International Centre for Circulatory Health, Imperial College London United Kingdom, ³UCL Institute of Cardiovascular Science, University College London, United Kingdom, ⁴Baker IDI Heart and Diabetes Institute, Melbourne, Australia, ⁵Department of Bioengineering, Imperial College, London, United Kingdom, ⁶Epidemiology & Preventative Medicine, Monash University, Melbourne, Australia, ⁷MonashHeart, Monash Health, Victoria, Australia.

Address for correspondence:
Professor James D Cameron
Monash Cardiovascular Research Centre
Monash Medical Centre
Clayton Road, Clayton
Victoria 3150
Australia
Telephone: +61395942243
Fax: +61395946939
Email: james.cameron@monash.edu
Supplementary Methods

ANBP2 Inclusion and exclusion criteria

The primary objective of ANBP2 was to determine if there was any difference in total cardiovascular events between an ACE inhibitor based and diuretic based regimen in hypertensive patients aged 65 – 84. The arterial mechanics sub-study was designed to explore the interactions between arterial properties, cardiac function and cardiovascular outcomes.

Patients were considered eligible for randomization if they were aged between 65-84 years of age with an average untreated sitting systolic blood pressure of at least 160 mmHg or an average diastolic blood pressure of at least 90mmHg (and a systolic blood pressure of at least 140 mmHg). Eligibility was determined by the average of 2 brachial blood pressure measurements taken with a standard mercury sphygmomanometer on 2 occasions at least 1 week apart and after withdrawal of antihypertensive therapy.

Patients with a recent history of cardiovascular events in the preceding 6 months, any life-threatening illness, contraindication to ACEi or diuretic, a plasma creatinine of greater than 221 μmol/L, malignant hypertension or dementia were excluded\(^1\). Only patients capable of and willing to provide informed consent were included. Once identified as being suitable for inclusion, patients were randomized either to initial ACE inhibitor or diuretic based treatment.

For calibration of the carotid pressure waveform, brachial blood pressures were measured with a Dinamap 1846 SXP (Critikon) by a trained study investigator in triplicate with the means of these values used in subsequent calculations. Ensemble averaged pressure waveforms were analyzed to determine the reservoir pressure and the excess pressure (Matlab, The MathWorks Inc., Massachusetts, USA) using previously described methods\(^2\).
Calculation of excess and reservoir pressure from tonometry recordings

Reservoir pressure $\bar{P}$ is defined to satisfy the overall mass conservation equation for the arterial system

$$\frac{d\bar{P}}{dt} + \frac{\bar{P} - P_\infty}{RC} = \frac{Q_{in}}{C}$$

(1)

where $Q_{in}$ is the flow into the arteries from the ventricle. This equation assumes that the compliance of the arterial system $C = \frac{dV}{dP}$ is constant and that the flow out of the arteries into the microcirculation due to $\bar{P}$ is resistive $Q_{out} = \frac{P - P_\infty}{R}$, where $R$ is the net resistance of the arterial system and $P_\infty$ is the pressure at which flow through the microcirculation is zero (the 'zero-flow' pressure).

During diastole, $T_d < t < T$ where $T_d$ is the time of the start of diastole and $T$ is the cardiac period, $Q = 0$ and the mass conservation equation becomes

$$\frac{d\bar{P}}{dt} + k_d(\bar{P} - P_\infty) = 0$$

(2)

This has the solution

$$\bar{P} - P_\infty = (\bar{P}_d - P_\infty)e^{-k_d t}$$

(3)

where $k_d = (RC)^{-1}$ is the rate constant of the pressure decay during diastole (the reciprocal of the diastolic time constant $\tau$) and $P_d = P(T_d)$.

If we further assume that the excess pressure $P - \bar{P} = Q_{in}Z_0$, where $P$ is the measured pressure and $Z_0$ is the characteristic impedance of the root of the aorta, we obtain the first order ODE

$$\frac{d(\bar{P} - P_\infty)}{dt} + (k_s + k_d)(\bar{P} - P_\infty) = k_s(P - P_\infty)$$

(4)

where we have defined a second rate constant $k_s = (Z_0C)^{-1}$ which is related to the inverse of the time it takes for a wave to traverse the arterial system. This equation can be solved by quadrature using the integrating factor $e^{(k_s + k_d)t}$

$$\bar{P} - P_\infty = k_se^{-(k_s + k_d)t} \int_0^t (P(t') - P_\infty)e^{(k_s + k_d)t'} dt' + (\bar{P}_0 - P_\infty)e^{-(k_s + k_d)t}$$

(5)

where $P_0 = P(0)$. This equation is valid over the whole of the cardiac period, reducing to eq.(3) when $\bar{P} = P$.

The Matlab algorithm to calculate the reservoir pressure $\bar{P}$ from the measured pressure $P$ calculates the three model parameters in two stages. The time of the start of diastole $T_d$ is taken as the minimum of the first derivative of the measured pressure calculated using a 7-point Savitsky-Golay first derivative filter function. The first stage of the algorithm determines the rate constant $k_d$ and the zero-flow pressure $P_\infty$ by a nonlinear fit of eq.(3) to the measured pressure during diastole $T_d < t < T$ using moments and the function fminsearch. The second stage determines the other rate constant $k_s$ by iteratively minimising the integral of the square error between $\bar{P}$ calculated from eq.(5) and $P$ during diastole. The three fitted constants are then used in eq.(5) to calculate $\bar{P}$ during the entire cardiac period.
Supplementary Results

The integrals of both the reservoir (RPI) and excess pressure (XSPI) curves were strongly correlated with cSBP (R = 0.82, P < 0.001 and R = 0.72, P < 0.001), cPP (R = 0.86, P < 0.001 and R = 0.80, P < 0.001) and moderately correlated with brachial SBP (R = 0.47, P < 0.001 and R = 0.47, P < 0.001) in keeping with previously reported findings3, 4. The peak reservoir and excess pressures were also strongly correlated with cSBP (R = 0.89, P < 0.001 and R = 0.71, P < 0.001), cPP (R = 0.94, P < 0.001 and R = 0.79, P < 0.001) and brachial SBP (R = 0.52, P < 0.001 and R = 0.41 and P < 0.001).
References


Table S1

<table>
<thead>
<tr>
<th>Central Pressure Parameter</th>
<th>Hazard ratio</th>
<th>95.0% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_s$</td>
<td>0.42</td>
<td>0.18</td>
<td>0.99</td>
</tr>
<tr>
<td>$k_d$</td>
<td>0.78</td>
<td>0.49</td>
<td>1.26</td>
</tr>
<tr>
<td>Reservoir Pressure Integral (mmHg.sec)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Excess Pressure Integral (mmHg.sec)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.01</td>
</tr>
<tr>
<td>Peak Reservoir Pressure (mmHg)</td>
<td>0.99</td>
<td>0.98</td>
<td>1.01</td>
</tr>
<tr>
<td>Central SBP (mmHg)</td>
<td>1.00</td>
<td>0.99</td>
<td>1.01</td>
</tr>
<tr>
<td>Augmentation Pressure (mmHg)</td>
<td>1.00</td>
<td>0.98</td>
<td>1.01</td>
</tr>
<tr>
<td>AIx (%)</td>
<td>1.02</td>
<td>1.00</td>
<td>1.05</td>
</tr>
<tr>
<td>Pulse Pressure Amplification</td>
<td>1.28</td>
<td>0.64</td>
<td>2.60</td>
</tr>
</tbody>
</table>

Table S2

<table>
<thead>
<tr>
<th>Central Pressure Parameter</th>
<th>Hazard ratio</th>
<th>95.0% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_s$</td>
<td>0.41</td>
<td>0.22</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Pulse Pressure Amplification</strong></td>
<td>1.95</td>
<td>1.22</td>
<td>3.11</td>
</tr>
<tr>
<td>$k_d$</td>
<td>0.75</td>
<td>0.52</td>
<td>1.06</td>
</tr>
<tr>
<td>Reservoir Pressure Integral (mmHg.sec)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Excess Pressure Integral (mmHg.sec)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Peak Reservoir Pressure (mmHg)</td>
<td>0.99</td>
<td>0.98</td>
<td>1.01</td>
</tr>
<tr>
<td>Central SBP (mmHg)</td>
<td>1.00</td>
<td>0.99</td>
<td>1.01</td>
</tr>
<tr>
<td>Augmentation Pressure (mmHg)</td>
<td>1.00</td>
<td>0.99</td>
<td>1.01</td>
</tr>
<tr>
<td>AIx (%)</td>
<td>1.01</td>
<td>0.99</td>
<td>1.03</td>
</tr>
</tbody>
</table>

**Table S1**: Association of Reservoir-Wave and central blood pressure parameters with the primary outcome adjusted for age and sex. **Table S2**: Association of reservoir-wave parameters measured at baseline and the combined CVD outcome. All data are adjusted for age and sex. $k_s$ = Rate constant of systolic aortic filling, $k_d$ = rate constant of diastolic aortic emptying, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, AIx = Augmentation index.
Table S3

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio primary endpoint</th>
<th>95.0% CI</th>
<th>P-value</th>
<th>Hazard ratio combined CVD endpoint</th>
<th>95.0% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.26</td>
<td>0.08</td>
<td>0.83</td>
<td>0.024</td>
<td>0.30</td>
<td>0.13</td>
</tr>
<tr>
<td>Females</td>
<td>0.50</td>
<td>0.12</td>
<td>2.07</td>
<td>0.340</td>
<td>0.50</td>
<td>0.18</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.13</td>
<td>0.04</td>
<td>0.50</td>
<td>0.003</td>
<td>0.21</td>
<td>0.08</td>
</tr>
<tr>
<td>ACEi therapy</td>
<td>0.67</td>
<td>0.22</td>
<td>2.06</td>
<td>0.488</td>
<td>0.60</td>
<td>0.25</td>
</tr>
<tr>
<td>$k_s \ast$ age (centred)</td>
<td>1.14</td>
<td>0.96</td>
<td>1.34</td>
<td>0.127</td>
<td>1.05</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Table S2: Subgroup analyses: age, sex and randomized antihypertensive treatment. Hazard ratios for $k_s$ following adjustment for known cardiovascular risk factors (Model 2) stratified accord to gender, randomized therapy and age are shown. The associations between $k_s$ and both the primary and combined CVD endpoints were stronger amongst men and those patients randomized to diuretic therapy. = Rate constant of systolic aortic filling, ACEi = Angiotensin Converting Enzyme Inhibitor.
Figure S1: A non-significant increase in the c-statistic from 0.66 to 0.68 was noted with addition of $k_s$ to the FRS for prediction of the primary endpoint.
Figure S2: Addition of $k_s$ to the FRS resulted in an increase in the c-statistic from 0.62 to 0.66 for prediction of the combined CVD endpoint.
体位性心动过速综合征（摘要）

波动性脑血流与体位性心动过速综合征分级倾斜试验中受损的神经认知及功能性充血有关

Oscillatory Cerebral Blood Flow Is Associated With Impaired Neurocognition and Functional Hyperemia in Postural Tachycardia Syndrome During Graded Tilt

Julian M. Stewart, Andrew T. Del Pozzi, Akash Pandey, Zachary R. Messer, Courtney Terilli, Marvin S. Medow

浦晓东 译

我们假设体位性心动过速综合征（postural tachycardia syndrome，POTS）患者直线位认知损害是由于脑血流（cerebral blood flow, CBF）减少所导致。在少数间歇性过度呼吸/低血糖症的患者中，倾斜70°时经颅多普勒超声测量的CBF速度（CBFV）明显减慢。斜率增加平均CBFV没有明显变化。但是N-back记忆训练显示进行性训练损害，功能性充血减轻和减少神经血管连接。静态平衡位引起CBFv缓慢波动与POTS患者的动脉压波动有关。我们还假波性CBFv降低神经血管相互作用。我们对11例POTS患者和9例对照组进行了2个位时后至倾斜至15°、30°、45°和60°的2-back测试。仰卧位时波动性动脉压、波动性CBFv和神经血管连接均相似。POTS患者倾斜试验时波动性动脉压分别增加31%、45%、6%和93%，对照组保持不变；波动性CBFv分别增加61%、82%、116%和264%，对照组保持不变。功能性充血从4.1%增加到3.0%、1.1%、0.2%和0.04%，而对照组保持在4%。POTS患者N-back正确响应率从78%减至33%，而对照组保持在89%。POTS患者波动性CBFv与功能性充血呈线性相关（γ² = 0.76）。增加的波动性CBFv与POTS患者神经血管连接及认知表现减弱有关。

（Hypertension. 2013;65:636-643.）

心血管风险预测（摘要）

中心动脉储备波形分析有助于老年高血压患者的心血管风险预测

Central Aortic Reservoir-Wave Analysis Improves Prediction of Cardiovascular Events in Elderly Hypertensives

Omi Narayan, Justin E. Davies, Alun D. Hughes, Anthony M. Dart, Kim H. Parker, Christopher Reid, James D. Cameron

郭丰芹 译 李燕 审校

中心动脉压力波的一些形态学参数被认为是心血管风险的标志物。然而，目前没有研究证实任何一种波形参数，在已知危险因素外对老年高血压患者提供额外预测价值。储备波的概念结合了波传导和Windkessel模型元素，定义一个基本储备血管及在其基础上叠加的额外血管。目前尚不清楚从储备波分析中获得的压力波形参数是否可以用作预测心血管事件发生风险。澳大利亚全国第二次血压研究的一个子项目中的838例研究对象在随机分组治疗前进行了中心脉波压力波形测量。储备波分析获得收缩期、舒张期压力波形参数等反映动脉功能的指标。我们利用生存分析来研究储备波参数与心血管事件之间的关系，并评估了除了弗雷明汉风险评分之外储备波参数的预测价值。结果显示：基线的收缩期速率常数能独立预测临床终点事件（对致死及非致死性脑卒中和心肌梗死的风险比为0.33，95%可信区间：0.13-0.82，P=0.016；对包括所有心血管事件在内的复合终点的风险比为0.38，95%可信区间：0.20-0.74，P=0.004）。通过净重新分类改善指数（net reclassification improvement indices，NRI）和综合判决改善指数（integrated discrimination improvement，IDI）分析显示，在弗雷明汉风险评分基础上增加这个储备波参数能够提高心血管风险预测的准确性。此研究说明基线的收缩期速率常数能够预测老年高血压患者的临床结局，进一步改善心血管预后的风险评估。

（Hypertension. 2013;65:629-635.）