Central Pressure: Variability and Impact of Cardiovascular Risk Factors
The Anglo-Cardiff Collaborative Trial II

Carmel M. McEniery, Yasmin, Barry McDonnell, Margaret Munnery, Sharon M. Wallace, Chloe V. Rowe, John R. Cockcroft, Ian B. Wilkinson, on Behalf of the Anglo-Cardiff Collaborative Trial Investigators

Abstract—Pulse pressure varies throughout the arterial tree, resulting in a gradient between central and peripheral pressure. Factors such as age, heart rate, and height influence this gradient. However, the relative impact of cardiovascular risk factors and atheromatous disease on central pressure and the normal variation in central pressure in healthy individuals are unclear. Seated peripheral (brachial) and central (aortic) blood pressures were assessed, and the ratio between aortic and brachial pulse pressure (pulse pressure ratio, ie, 1/amplification) was calculated in healthy individuals, diabetic subjects, patients with cardiovascular disease, and in individuals with only 1 of the following: hypertension, hypercholesterolemia, or smoking. The age range was 18 to 101 years, and data from 10 613 individuals were analyzed. Compared with healthy individuals, pulse pressure ratio was significantly increased (ie, central systolic pressure was relatively higher) in individuals with risk factors or disease (P<0.01 for all of the comparisons). Although aging was associated with an increased pulse pressure ratio, there was still an average±SD difference between brachial and aortic systolic pressure of 11±4 and 8±3 mm Hg for men and women aged >80 years, respectively. Finally, stratifying individuals by brachial pressure revealed considerable overlap in aortic pressure, such that >70% of individuals with high-normal brachial pressure had similar aortic pressures as those with stage 1 hypertension. These data demonstrate that cardiovascular risk factors affect the pulse pressure ratio, and that central pressure cannot be reliably inferred from peripheral pressure. However, assessment of central pressure may improve the identification and management of patients with elevated cardiovascular risk. (Hypertension. 2008;51:1476-1482.)

Key Words: central pressure ■ brachial pressure ■ pulse pressure ratio ■ pulse pressure amplification ■ hypertension ■ cardiovascular risk factors

The value of brachial artery pressure as a predictor of future cardiovascular disease is firmly established.1 Recently, greater emphasis has been placed on pulse pressure (PP), a surrogate of large artery stiffness, especially in older individuals.2,3 However, there is a gradual widening of PP moving from the central to the peripheral arteries,4 mainly because of a rise in systolic pressure. Moreover, emerging data suggest that central PP may be more closely correlated with surrogate measures of cardiovascular risk, such as left ventricular mass5 and carotid intima-media thickness,6 than brachial PP. Furthermore, central PP appears to be an independent predictor of future cardiovascular risk in selected patient groups,7,8 although whether it outperforms brachial PP more generally remains to be confirmed. The Conduit Artery Function Evaluation Study9 further highlighted the potential importance of central pressure by confirming that antihypertensive drugs can have differential effects on central and peripheral PP, which translate into differences in outcome.

The disparity between central and peripheral pressure, which is often, but perhaps misleadingly, referred to as “pressure amplification,” is driven mainly by differences in vessel stiffness and wave reflection. Previous investigations suggest that factors such as age,10 heart rate,11,12 and height13 have differential effects on central and peripheral pressure. In addition, cardiovascular risk factors such as hypercholesterolemia,14 hypertension,15 smoking16 and the metabolic syndrome17 may have greater effects on central pressure. However, the relative importance of cardiovascular risk factors and atheromatous disease, per se, on central pressure is unclear. Moreover, the variation in the gradient between central and peripheral pressure in healthy individuals has not been examined in a large unselected cohort of individuals.

Noninvasive estimation of central pressure is now possible using a number of commercial devices,18 and we have reported previously the effect of aging on the gradient.

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between brachial and aortic PP in a cohort of 4001 healthy individuals from the Anglo-Cardiff Collaborative Trial.10 The aim of the present study was to determine the impact of cardiovascular risk factors and cardiovascular disease on the gradient between central and peripheral PP and to investigate the variation in central pressure in healthy individuals across a wide spectrum of age and brachial pressure in a large cohort of individuals in the Anglo-Cardiff Collaborative Trial. Such information is required before studies can be designed to compare treatment strategies based on central versus peripheral pressure reduction and to define reference values for central pressure.

Methods

Subjects
Subjects were drawn from the Anglo-Cardiff Collaborative Trial population, which consists of ~12,000 individuals selected at random from local general practice lists and open-access cardiovascular-risk assessment clinics across East Anglia and Wales in the United Kingdom. The overall response rate was 85%. Subjects with secondary forms of hypertension were excluded, as were subjects in whom hemodynamic and biochemical data were incomplete at the time of analysis. This yielded a total of 11,340 individuals who were available for the current analyses. Healthy control subjects were defined as those individuals without cardiovascular disease or risk factors who were free from medication. Other subjects without overt cardiovascular disease were then grouped according to the presence of any of the following risk factors: hypertension (documented or brachial systolic blood pressure [BP] ≥140 mm Hg and/or brachial diastolic BP ≥90 mm Hg), hypercholesterolemia (documented or fasting total cholesterol >6.2 mmol/L) or smoking (>1 cigarette per day). Subjects were excluded from these groups if >1 risk factor was present to minimize the potentially confounding influence of individuals with multiple risk factors. Two further groups were formed: subjects with diabetes mellitus (World Health Organization criteria) but without cardiovascular disease, and those with overt cardiovascular disease (International Classification of Diseases, 10th Revision, criteria). However, because of the strong clustering of risk factors associated with each of these conditions, it was not feasible to exclude subjects with multiple risk factors. Overall, data from 10,613 individuals were included in the current analyses. Approval for all of the studies was obtained from the local research ethics committees, and written informed consent was obtained from each participant.

Hemodynamics
Seated BP was recorded in the dominant arm using a validated oscillometric technique (HEM-705CP, Omron Corporation). Radial artery waveforms were then recorded with a high-fidelity micromanometer (SPC-301, Millar Instruments) from the wrist of the dominant arm. Pulse wave analysis (SphygmoCor, AtCor Medical) was then used to generate a corresponding central (ascending aortic) waveform using a generalized transfer function,19 which has been prospectively validated for the assessment of ascending aortic BP.20 Using the integral software, augmentation pressure was calculated as the difference between the second and first systolic peaks, and augmentation index was calculated as augmentation pressure expressed as a percentage of the PP. Heart rate and mean arterial pressure were obtained from the pressure waveform. All of the measurements were made in duplicate by trained investigators, and the mean values were used in the subsequent analysis. The within- and between-observer measurement reproducibility values for the augmentation index were in agreement with our previously published data.21

Protocol
Height and weight were assessed. After 15 minutes of seated rest, BP and radial artery waveforms were recorded. Ten milliliters of blood were drawn from the antecubital fossa into plain tubes. The samples were centrifuged at 4°C (4000 rpm for 20 minutes), and the serum was separated and stored at −80°C for subsequent analysis. Cholesterol, triglycerides, glucose, and C-reactive protein were determined using standard methodology in an accredited laboratory.

Data Analysis
Traditionally, the term “amplification” has been used to describe the disparity between central and peripheral pressure and is calculated as peripheral PP:central PP. However, in the current study we have chosen to express aortic PP relative to brachial PP (ie, the reciprocal of PP amplification), which we refer to as the PP ratio. Thus, a higher ratio represents a relatively higher aortic pressure for a given brachial pressure. Data were analyzed using SPSS software (version 12.0). Comparisons between healthy subjects and individual risk factors were made using Student’s t tests with Bonferroni corrections. Analyses were performed separately for men and women. Stepwise multiple linear regression analyses were also performed to determine the factors influencing pressure amplification. Variables entered into the model were chosen if significantly associated in simple correlation analyses, and those variables known or previously associated with pressure amplification, from published observations. Values represent means±SDs unless otherwise stated, and a P value of <0.05 was considered significant.

Results
The characteristics of the healthy subjects versus those individuals with cardiovascular risk factors or disease are presented in Table 1. With the exception of smoking, subjects with cardiovascular risk factors or disease tended to be older and heavier, have elevated brachial and aortic BPs, and have adverse biochemical profiles. In contrast, smokers were younger and had lower aortic augmentation pressure and systolic pressure than healthy subjects, although diastolic BP and triglyceride levels were higher.

Effect of Cardiovascular Risk Factors on PP Ratio
To examine the influence of cardiovascular risk factors and disease on the ratio between central and peripheral PP, comparisons were made between healthy subjects and individuals with risk factors or disease at baseline (unadjusted values) and after adjustment for confounding variables (Table 2). With the exception of smoking, all of the cardiovascular risk factors and disease were associated with an increased PP ratio (ie, aortic pressure was relatively higher in these individuals) compared with healthy individuals at baseline. However, after adjustment for differences in age, height, and heart rate between the groups, all of the risk factors and cardiovascular disease, per se, were associated with an increased PP ratio in men and women (P<0.01 for all of the comparisons). Diabetes and cardiovascular disease in men and hypertension, diabetes, and cardiovascular disease in women were associated with the most marked elevation in the PP ratio. In addition, as a posthoc analysis, the influence of obesity on the PP ratio was examined by comparing healthy individuals with a BMI of <25 kg/m² with those with a BMI of >30 kg/m² and without additional risk factors. After adjustment for confounding variables, the PP ratio did not differ between nonobese and obese men (0.70±0.10 versus 0.70±0.08, nonobese versus obese; P=0.5) but was significantly increased in obese women (0.72±0.10 versus 0.74±0.09, nonobese versus obese; P=0.003).
Given the substantial variability in the PP ratio, we investigated the interindividual variability in aortic systolic pressure as a function of brachial systolic pressure. Categories were based on 10-mm Hg increments of brachial systolic BP within the 2007 European Society of Hypertension and of the European Society of Cardiology definitions of BP. Throughout the range of categories for brachial systolic pressure, there was substantial interindividual variation in
aortic systolic pressure in both men and women. Again, this variability led to extensive overlap in aortic systolic pressures between categories, without any overlap between brachial pressures, which was more pronounced in men than in women. For example, the overlap in aortic systolic BP between subjects with normal BP and those with high-normal BP was 78% in men and 63% in women. Similarly, the overlap in aortic systolic BP between high-normal BP and stage 1 hypertension was 78% in men and 73% in women. The overlap in aortic systolic BP between individuals with normal BP and stage 1 hypertension was 32% for men and 10% for women.

### Discussion

The aim of the current study was to assess the extent to which the disparity between central and peripheral pressure is affected by cardiovascular risk factors and cardiovascular disease, per se, and to examine the degree of variation in central pressure in healthy individuals. Our major, novel findings were that individual cardiovascular risk factors and atherosclerosis were all associated with an increased PP ratio in both men and women, and all of these factors remained independently associated with PP ratio in multiple regression analyses. In addition, although PP ratio increased with increasing age, differences between central and peripheral PP were apparent, even in the oldest individuals, and there was also considerable interindividual variability between individuals. Finally, stratifying individuals by brachial BP highlighted the considerable overlap in aortic systolic pressure between discrete brachial BP categories, such that >70% of individuals with high-normal brachial systolic BP had similar aortic systolic pressures to those individuals with stage 1 hypertension. Overall, these data show that the PP ratio depends on a number of factors, and that there is significant variation in central pressure between individuals despite similar brachial pressures. This suggests that central pressure cannot be reliably inferred from measurements of brachial pressure, and that measuring central pressure may improve the identification and management of patients with elevated cardiovascular risk.

The disparity between central and peripheral PP is mainly determined by differences in vessel stiffness and wave reflection. Therefore, any factor increasing wave reflections is likely to increase central pressure independently of brachial pressure. Indeed, several studies have suggested that cardiovascular risk factors such as hypercholesterolemia, hypertension, smoking, and the metabolic syndrome may have a greater effect on central pressure. However, these previous studies did not control for the inclusion of patients with multiple cardiovascular risk factors, or they examined the impact of various physiological factors, such as heart rate, on the PP gradient within risk-factor groups. Therefore, the relative impact of different cardiovascular risk factors or disease on central pressure is unclear. In the current study, all of the cardiovascular risk factors and the presence of cardiovascular disease were associated with a significantly increased PP ratio in both men and women compared with healthy individuals, even after adjusting for the potentially confounding effects of differences in age, height, and heart rate between the groups. Diabetes and cardiovascular disease in men and hypertension, diabetes, and cardiovascular disease in women were associated with more profound increases in

### Table 2. Influence of Cardiovascular Risk Factors and Disease on PP Ratio

<table>
<thead>
<tr>
<th>Model</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Data, Mean±SD</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>Data, Mean±SD</td>
<td>P</td>
</tr>
<tr>
<td>Healthy</td>
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<tr>
<td>Unadjusted</td>
<td>0.70±0.12</td>
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</tr>
<tr>
<td>Fully adjusted</td>
<td>0.72±0.10</td>
<td></td>
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<tr>
<td>Hypertensive</td>
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<tr>
<td>Unadjusted</td>
<td>0.76±0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.74±0.09</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypercholesterolemia</td>
<td></td>
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<tr>
<td>Unadjusted</td>
<td>0.76±0.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.74±0.06</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
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<tr>
<td>Unadjusted</td>
<td>0.64±0.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.74±0.10</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
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</tr>
<tr>
<td>Unadjusted</td>
<td>0.76±0.10</td>
<td>&lt;0.001</td>
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<tr>
<td>Fully adjusted</td>
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<td>&lt;0.001</td>
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<tr>
<td>Cardiovascular disease</td>
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<tr>
<td>Unadjusted</td>
<td>0.78±0.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.76±0.06</td>
<td>&lt;0.001</td>
</tr>
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</table>

Fully adjusted refers to data adjusted for age, height, and heart rate. P values refer to comparisons with healthy subjects.
the PP ratio than the other risk factors. In addition, the PP ratio was increased in obese subjects without any additional risk factors. Overall, these data suggest that, for a given level of brachial BP, central (aortic) BP is higher in those individuals with risk factors or disease compared with healthy subjects.

Other factors that affect the disparity between central and peripheral PP have been identified, particularly age, heart rate, and height.\textsuperscript{10–13,23} Consistent with these previous data, we observed that the major, independent influences on PP ratio in the current study were age, heart rate, height, and gender. In addition, all of the cardiovascular risk factors and the presence of cardiovascular disease remained independently associated with the PP ratio after adjusting for confounding variables. Our data are in close agreement with those of a previous study in which stepwise multiple regression analyses were used to determine the most important influences on PP amplification (brachial:aortic PP).\textsuperscript{23} However, in the current study and in that of Camacho et al,\textsuperscript{23} only \(\approx 70\%\) of the variability in the PP ratio was explained by the regression models. Given that a 2- to 3-mm Hg difference in brachial BP results in a 20\% to 30\% difference in cardiovascular risk,\textsuperscript{24} these data suggest that central BP cannot be predicted with sufficient accuracy from brachial pressure by a statistical model, but rather, needs to be assessed directly, using appropriate methodologies.

Aging exerts a powerful influence on PP gradient,\textsuperscript{10,25} and we have confirmed this finding in the current study. We have also demonstrated that aging exerts a marked influence on the absolute difference between brachial and aortic systolic pressure in healthy subjects. However, despite this age-related effect, differences between brachial and aortic press-
future cardiovascular events. There are also important European Society of Cardiology guidelines.22 The range of values. The dashed lines indicate BP classifications according to the 2007 European Society of Hypertension and of the distribution), and the whiskers represent the range of values. The dashed lines indicate BP classifications according to the 2007 European Society of Hypertension and of the European Society of Cardiology guidelines.22

Perspectives

Current guidelines for the diagnosis and treatment of hypertension are based solely on brachial BP. However, brachial and central BPs are not the same, even in older individuals, as demonstrated by the current data where differences of 8 to 10 mm Hg between brachial and aortic systolic BP are standard. Increased central BP is associated with a number of pathophysiological mechanisms, such as left ventricular hypertrophy,4 altered myocardial perfusion,10 and carotid artery remodeling,6 all of which increase the risk of cardiovascular events. Moreover, central pressure may be a better predictor of future cardiovascular risk in selected patient groups than brachial pressure.7,8 Therefore, it seems likely that the assessment of central pressure will improve the identification and management of patients with elevated cardiovascular risk. However, if central pressure is ever to replace brachial pressure in clinical decision-making, new guidelines that focus on central pressure will be required. In addition, the acceptance and, ultimately, success of such guidelines will greatly depend on the widespread use of devices to assess

Figure 2. Box plot of aortic systolic pressure per 10-mm Hg increments in brachial systolic pressure in men (left, n = 3603) and women (right, n = 3176). Analyses were performed in all of the healthy subjects and treatment-naive hypertensive subjects. The vertical line within the box represents the median, the box represents the interquartile range (50% of the distribution), and the whiskers represent the range of values. The dashed lines indicate BP classifications according to the 2007 European Society of Hypertension and of the European Society of Cardiology guidelines.22

For example, according to current definitions for the classification of hypertension based on brachial BP,23 >78% of men with normal brachial BP had aortic systolic BP in common with men classified as having high-normal brachial BP (63% of women), and, again, 78% of men with high-normal brachial BP had aortic systolic BP in common with men with Stage 1 hypertension (73% of women). Moreover, 32% of men and 10% of women with normal brachial BP had aortic systolic BP in common with individuals with stage 1 hypertension. These observations suggest that a large proportion of individuals who are classified as being normotensive based on current guidelines might actually be at increased risk according to their central BP. Conversely, some individuals labeled as being hypertensive or at increased risk of developing hypertension might actually have lower cardiovascular risk, because they have a lower central BP.

A limitation of the current study is its cross-sectional design, and further longitudinal follow-up studies are required to confirm the age-related changes in the PP ratio described here. In addition, many of the patients with hypertension, diabetes, or overt cardiovascular disease were taking vasoactive medication, which may have influenced the degree of disparity between central and peripheral pressure observed in these subjects. However, none of the healthy subjects, hypercholesterolemic subjects, or smokers were taking vasoactive medication. Central (aortic) BP was derived noninvasively, using a generalized transfer function, which has been criticized in the past.27,28 However, the transfer function has been prospectively validated and is accurate to within 1.0 mm Hg,20,29 and our previous data demonstrate a tight correlation between derived aortic and measured carotid indices.10 Moreover, our key findings focus on the ratio between central and peripheral PP. As a fiducial parameter, this is independent of any systematic calibration errors inherent in the brachial cuff pressure measurement, relying instead on the information contained within the arterial pressure waveform.
central pressure in primary care settings, a situation that may be considered somewhat unlikely, at least in the short-term. Therefore, further studies are urgently required to confirm the current data and to provide evidence that treatment decisions based on measurements of central BP result in better outcomes.

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Disclosures

None.

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