Epidemiology/Population Science

An Analysis of Prospective Risk Factors for Aortic Stiffness in Men
20-Year Follow-Up From the Caerphilly Prospective Study

Carmel M. McEniery, Michael Spratt, Margaret Munnery, John Yarnell, Gordon D. Lowe, Ann Rumley, John Gallacher, Yoav Ben-Shlomo, John R. Cockcroft, Ian B. Wilkinson

Abstract—Arterial stiffness is an important determinant of cardiovascular risk. The precise risk factors for arterial stiffening remain unclear. We aimed to identify potential risk factors using prospective exposure data from the Caerphilly Prospective Study. Aortic pulse wave velocity and augmentation index were measured in 825 men and related to current (2004) and baseline (1979–1988) anthropometric, hemodynamic, and biochemical factors. The mean age of the men was 74 years, with an average follow-up of 20 years. The only independent baseline predictors of current velocity were pulse pressure (standardized β-coefficient: 0.58), C-reactive protein (0.35), glucose (0.25), and waist circumference (0.23). The sole baseline predictor of current augmentation index was fibrinogen (0.78). After additional adjustment for the corresponding current risk factor, pulse wave velocity was best related to cumulative exposure to C-reactive protein, whereas augmentation index was most strongly related to current levels. Velocity was also more strongly correlated with baseline levels of triglycerides and smoking but with current waist circumference. The pulse pressure heart rate product assessed over the whole of 20 years was independently correlated with aortic pulse wave velocity but not augmentation index. Other than blood pressure, established cardiovascular risk factors have only a modest effect on aortic stiffness and wave reflection. Inflammation and the level of repetitive cyclic stress are important predictors of aortic stiffness, whereas wave reflection is predicted by acute inflammation only. Adequate control of pulse pressure and heart rate, as well as reducing inflammation, may, in the long-term, retard aortic stiffening, although this remains to be tested directly. (Hypertension. 2010;56:36-43.)

Key Words: arterial stiffness ■ pulse wave velocity ■ aorta ■ blood pressure ■ heart rate

The large arteries play an important physiological role in buffering the cyclic changes in pressure resulting from intermittent ejection of blood. As these vessels stiffen, there is a reduction in buffering capacity and a concomitant rise in pulse pressure and fall in shear stress.1 These effects are thought to promote cardiovascular disease.2 Indeed, aortic pulse wave velocity (aPWV) is a predictor of future cardiovascular risk in a variety of populations,3,4 and this may be independent of blood pressure (BP).5 As such, it is frequently considered as the gold-standard measure of arterial stiffness.

The precise mechanisms responsible for arterial stiffening are incompletely understood but are thought primarily to involve structural changes within the medium, such as fatigue fracture of elastin6 and deposition of collagen and calcium.7 Functional changes in smooth muscle tone, mediated, in part, by endothelial-derived factors, such as NO, may also be important.8,9 Interestingly, there is considerable variability in arterial stiffness, suggesting that it is subject to environmental and genetic influences.9-10 Traditional cardiovascular risk factors, as well as renal dysfunction, excessive sodium intake, and the metabolic syndrome, have all been linked to arterial stiffness.11 However, the majority of these associations stem from small, cross-sectional studies, which have a number of limitations, such as inherent bias and reverse causality, limiting our ability to attribute causality. A recent systematic review suggested that the impact of established cardiovascular risk factors, other than BP, on aPWV was very modest.11 Longitudinal studies may provide better evidence of causality. However, although data concerning longitudinal changes in pulse pressure, an indirect surrogate of aortic stiffening, are available,12 only 2 studies on the basis of aPWV measurements in a single French cohort have been published.13,14

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We hypothesized that aPWV would relate to exposure to traditional cardiovascular risk factors over time but also to the pulse pressure heart rate product as a measure of the long-term cyclic stress that the elastic arteries experience. The aim of the present study was to test this hypothesis in a population-based longitudinal cohort of men enrolled in the Caerphilly Prospective Study,\textsuperscript{15} by relating current aPWV and augmentation index (AIx) to anthropometric, hemodynamic, and biochemical data assessed both cross-sectionally and prospectively over the last 25 years.

**Methods**

**Population**

The Caerphilly Prospective Study is a population-based cohort study of all men (\textsuperscript{\textgreater}99\% white, born in Wales) aged 45 to 59 years residing in the town of Caerphilly.\textsuperscript{16} It was set up to investigate risk factors for cardiovascular disease. The initial examination (phase I) was between 1979 and 1983 and involved 2512 men. An additional 447 patients were recruited at phase II (July 1984 to June 1988).\textsuperscript{18} Men were reseen approximately every 5 years. The last follow-up (phase V) occurred between 2002 and 2004 and specifically included aPWV and AIx. Subjects gave written informed consent, and the study had the approval of the local research ethics committee and adhered to the Declaration of Helsinki.

**Clinical Measures**

A detailed medical questionnaire was administered. Height, weight, and waist circumference were recorded at each visit. Seated brachial artery BP was measured in duplicate using a Hawksley random 0 sphygmomanometer at phases I through IV and the validated Omron-705CP at phase V.\textsuperscript{17}

**Arterial Hemodynamics**

Additional measurements of aPWV and AIx were undertaken at phase V. AIx, a measure of wave reflection, was determined from the waveform analysis of the radial pulse. The radial waveform was obtained by the non-invasive Arteriograph, which measures the pulse wave velocity for a 1-SD change in the exposure (we have defined this as the “standardized coefficient”).

Data Analysis

Because of the inclusion of additional subjects at phase II, we used an average of phase I and II values as baseline measures. To identify factors underlying current arterial stiffness and wave reflection, we compared the strength of association between aPWV and AIx with baseline variables and variables measured at phase V (current). There was only limited collinearity between our 2 exposure measures over time, and even waist circumference, which showed stronger correlation, was not so strong as to distort the SEs.\textsuperscript{23}

For the quoted regression coefficients, the outcome variable is in its natural units, whereas the exposure variable has been rescaled to a z score (the mean value of that variable has been subtracted from the raw value, and the variable's SDs have then been divided by an SD, thereby converting the mean value to 0 and the SD to 1). The coefficients from our regression therefore indicate the change in pulse wave velocity for a 1-SD change in the exposure (we have defined this as the “standardized coefficient”).

aPWV was automatically adjusted for age, MAP, heart rate, and vasoactive drug use. With AIx, we automatically adjusted for age, heart rate, height, and vasoactive drug use. Logarithmic transformations were used for skewed variables. Multivariable linear regression was used to assess the strength of associations, derive 95\% CIs, and determine significance. The variables entered into the model were chosen if significantly associated in simple correlation analyses, as well as those variables known or previously associated with the dependent variable from published observations.

The heart rate pulse pressure product was calculated for the whole follow-up period by multiplying heart rate and brachial pulse pressure recorded at each screening visit (phases I to V) and integrating across the time interval between visits by using the area under the curve. The area under the curve is approximated by the area under the graph of the predictor when linearly interpolated between the measurement time points, thereby calculating the areas of a series of trapezoids. This was then repeated while also including the systolic BP value at each phase.

**Results**

A total of 1225 men were identified for the main phase V study, but arterial stiffness measurements were completed in 825 men (67\%) because of a delay in starting the measurements (Figure 1). The average duration of follow-up was 20±2 years. Table 1 provides the baseline (phase I/II) and current (phase V) demographic, hemodynamic, and biochemical data for the whole cohort, as well as those men with stiffness measurements. The latter were, at baseline, on average younger, less likely to smoke, and had a lower waist circumference, BP, heart rate, triglyceride level, CRP, and fibrinogen levels but higher creatinine than those who died or were lost to follow-up. Compared with 20 years ago, body mass index and waist circumference, pulse and mean pressures, and heart rate had increased, whereas smoking frequency and diastolic pressure had declined in those men with stiffness measurements. Total and low-density lipoprotein cholesterol declined, and high-density lipoprotein cholesterol and CRP levels increased over the 20-year follow-up.
Table 1. Subject Characteristics at Baseline and Phase V, for Those With and Without Arterial Stiffness Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without Measures, Phase I/II</th>
<th>With Stiffness Measures</th>
<th>Significance Phase I/II With and Without PWV</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>2134</td>
<td>825</td>
<td>825</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±4</td>
<td>56±5</td>
<td>74±4†</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.2±3.8</td>
<td>26.2±3.7</td>
<td>27.7±3.6†</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>94.4±10.9</td>
<td>93.2±10.3</td>
<td>100.5±9.6†</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>61</td>
<td>41</td>
<td>16†</td>
</tr>
<tr>
<td>Peripheral systolic BP, mm Hg</td>
<td>146±20</td>
<td>142±20</td>
<td>141±20‡</td>
</tr>
<tr>
<td>Mean pressure, mm Hg</td>
<td>108±13</td>
<td>106±13</td>
<td>97±13†</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>57±15</td>
<td>55±15</td>
<td>67±16†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±11</td>
<td>66±10</td>
<td>64±11†</td>
</tr>
<tr>
<td>aPWV, m/s</td>
<td>10.3</td>
<td>11.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Aortic AIx, %</td>
<td>29.8</td>
<td></td>
<td>7.8</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.8±1.1</td>
<td>5.8±1.0</td>
<td>4.8±1.0†</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mmol/L</td>
<td>3.8±1.1</td>
<td>3.8±1.0</td>
<td>2.8±0.9†‡</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.7 (1.1 to 2.3)</td>
<td>1.6 (1.1 to 2.1)</td>
<td>1.5 (1.0 to 1.9)†</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.0±0.5</td>
<td>5.0±0.5</td>
<td></td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>97 (89 to 106)</td>
<td>98 (91 to 106)</td>
<td>97 (84 to 108)</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>2.3 (1.0 to 4.0)</td>
<td>1.6 (0.8 to 2.3)</td>
<td>2.6 (1.5 to 5.6)†</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.1 (2.6 to 3.7)</td>
<td>2.8 (2.4 to 3.2)</td>
<td></td>
</tr>
</tbody>
</table>

Values represent mean±SD, or geometric mean and (interquartile range). Differences between phase I values for those with and without stiffness measures are indicated in the final column. Significant differences between phase I and V for those with stiffness measures are indicated by *P<0.05 and †P<0.001.

Association Between Baseline (Phases I/II) Variables With PWV and AIx

After adjustment for age, MAP, heart rate, and vasoactive drug use at phase V, aPWV was positively associated with baseline systolic BP, MAP, pulse pressure, heart rate, fibrinogen, CRP, triglycerides, waist circumference, and heavy cigarette smoking (Table 2) and inversely associated with creatinine. In contrast, AIx only showed associations with baseline fibrinogen, CRP, and heavy smoking status.

Association Between Current (Phase V) Variables With PWV and AIx

aPWV was significantly associated with age, MAP, and heart rate measured at phase V. After adjustment for these variables and drug usage, aPWV remained significantly associated with current CRP, creatinine, and waist circumference (Table 2). Likewise, AIx was associated with age, heart rate, and height at phase V. After adjustment for these parameters and drug usage, only current CRP, total cholesterol, and waist circumference remained predictive (Table 2).

Multivariable Analyses of Baseline Variables

Baseline pulse pressure, CRP, glucose, and waist circumference were all independently associated with current aPWV (Table 3 and Figure 2). We chose only to include pulse pressure rather than both pulse pressure and SBP in the model because of their collinearity. Similarly, for AIx, only fibrinogen remained a predictor.

Comparison of Baseline and Current Variables

To investigate whether lifetime cumulative exposure or whether past/current exposure was relatively more important, we compared the strength of association with baseline and current values after mutual adjustment (Table 4). These variables were only moderately correlated across time (0.20 to 0.41), except for waist circumference, which showed a higher correlation (0.78). This model is algebraically equivalent to modeling the difference in levels between the 2 time points and conditioning on the later measure.24

For aPWV, both baseline and current CRPs showed strong positive associations, suggesting that life course accumulative exposure was the best predictor. For triglycerides, only baseline exposure remained a predictor, so that, conditional on the midlife value, later changes in triglycerides add little to current aPWV. A similar pattern was seen with heavy...
smoking, although the baseline value was consistent with chance. In contrast, current waist circumference was a stronger predictor than baseline waist circumference, although again this was attenuated and was consistent with chance variation. Neither of the paired values for triglycerides, waist circumference, or smoking was significantly associated with AIx after mutual adjustment, but current CRP showed a stronger association than baseline CRP with marginal significance.

Heart Rate Pulse Pressure Product

aPWV was correlated with heart rate brachial pulse pressure product over the 20-year follow-up ($R=0.57; P<0.001$). This remained significant after adjusting for current age, heart rate, MAP, and vasoactive drug use. The relationship between tertiles of average pulse pressure and tertiles of heart rate on mean aPWV is illustrated in Figure 3. There were significant linear effects for each variable within each strata ($P<0.001$). The highest aPWV was observed in individuals in the highest tertile of pulse pressure and heart rate. There was no evidence of any interaction between these 2 covariates ($P=0.84$). There was no relationship between pulse pressure heart rate product and AIx. We then divided the pulse pressure and heart rate product into quintiles and used this as a predictor of aPWV. This showed a significant linear effect (0.60 m/s [95% CI: 0.38 to 0.82 m/s]; $P<0.001$) per unit quintile increase. This persisted after adjustment for fibrinogen, CRP, triglycerides, waist circumference, and smoking status at baseline (0.53 m/s [95% CI: 0.29 to 0.76 m/s]; $P<0.001$). We repeated these results using the heart rate SBP product. This gave very similar results, so that in the simple model, aPWV increased by 0.54 m/s ([95% CI: 0.35 to 0.73 m/s]; $P<0.001$) per quintile unit increase, and after adjustment this was 0.52 m/s ([95% CI: 0.32 to 0.73 m/s]; $P<0.001$).

Discussion

This study investigated the impact of novel and established cardiovascular risk factors, assessed over 20 years, on current aortic stiffness and wave reflections, in a cohort of 825 men. The main novel finding is that, other than BP, traditional cardiovascular risk factors have only a modest influence on aPWV and AIx but that CRP is relatively strongly related to baseline disease prevention, whereas inflammation shows a persistent effect, although this may reflect reverse causation rather than primary etiologic significance. Interestingly, as hypothesized,
A number of potential risk factors for arterial stiffening have been identified, from cross-sectional studies, including aging, hypercholesterolemia, diabetes, cigarette smoking, and the metabolic syndrome. However, follow-up was only 6 years, the sample size was modest, and data concerning wave reflection, an important predictor of outcome, were not available. While awaiting further longitudinal data, an alternative approach is to make use of existing prospective studies, which have only assessed aPWV and AIx recently, and examine predictors of stiffness and wave reflection using historical and concomitant cross-sectional data. Although this approach does not take into account initial differences in stiffness (because the data were not collected), it has the advantage that long-term follow-up is often available and is likely to provide earlier insights into the pathophysiology of stiffening.

We conducted an initial cross-sectional analysis between stiffness measures and factors assessed concomitantly. We confirmed previous observations that aPWV was significantly and positively correlated with MAP, heart rate, CRP, creatinine, and waist circumference. aPWV was not associated with any lipid parameters or smoking. Although some studies have reported an inverse relationship between high-density lipoprotein cholesterol and a positive relationship with total/low-density lipoprotein cholesterol, others have not. The present study is among the largest reported and supports the findings of a recent systematic review that the impact of traditional risk factors, other than BP, on aPWV is very modest. Surprisingly creatinine at baseline was inversely associated with aPWV, in contrast with previous findings, although at follow-up it showed the expected positive association, which may be a type I error. Wave reflection was significantly associated with current heart rate, MAP, height, CRP, and total cholesterol, as expected.

We then examined the relationship between aortic stiffness and variables assessed 20 years previously. After adjustment for concomitant confounders, including age, MAP, heart rate, and drug use, only pulse pressure, CRP, glucose, and waist circumference were independent predictors of aPWV. Examining the strength of association between pairs of variables measured at baseline and follow-up indicated that, for CRP, both were strongly related to current aPWV, suggesting that the long-term inflammation may play a role in aortic stiffening. Indeed, data indicate that CRP predicts the development of hypertension, which may, in part, be a consequence of arterial stiffening. However, we and others have shown that functional polymorphisms in the CRP gene do not predict.
that inflammation and smoking have a relatively short-term strongly correlated with AIx than baseline data, suggesting the current values for each of these factors were more predictor, with a very modest effect size. In paired comparisons, multivariable models only fibrinogen remained a weak pre-

animal data suggest that this is not the case, data in humans likely to be overestimated in obese individuals. Although confounding, because carotid-femoral path length is more 

Only baseline values of fibrinogen, CRP, and smoking were independently associated with current AIx, and in multivariable models only fibrinogen remained a weak predictor, with a very modest effect size. In paired comparisons, the current values for each of these factors were more strongly correlated with AIx than baseline data, suggesting that inflammation and smoking have a relatively short-term influence on wave reflection. This fits with the notion that AIx is a more dynamic factor than aPWV, depending on vascular tone in the small arteries, rather than on long-term structural alterations. Moreover, the disparity between factors linked to aPWV and AIx reinforces the concept that they are not interchangeable and provide different but complementary information.

Fatigue fracture of the elastic elements is often considered to be responsible for the age-related increase in aPWV. The rate of elastin fracture depends on the number of stress cycles and level of stress, that is, the number of heartbeats and pulse pressure. Our data demonstrate a significant, independent relationship between the heart rate pulse pressure product, assessed over 20 years, and aPWV. These effects appear to be additive and are only minimally attenuated by potential confounders. This supports O’Rourke’s original hypothesis and may provide an explanation for the cross-sectional association between high heart rate and aPWV, as well as epidemiological observations that high heart rate is associated with increased cardiovascular risk. However, because pulse pressure is, in part, determined by wall stiffness, it will be important to replicate these observations in cohorts with baseline aPWV. Nevertheless, our data suggest that arterial stiffening may be reduced by lowering heart rate and/or pulse pressure, although this remains to be tested.

**Limitations**
Because we did not have baseline measures of arterial stiffness, we could not relate risk factors to changes in arterial stiffness, that is, stiffening. We did not assess the effect of metabolic syndrome, per se, on stiffness, rather investigating the independent predictive value of the individual components of the syndrome using multivariable models, because recent data suggest that the metabolic syndrome is not itself independently predictive of events. We could only assess men who were available for rescreening. The missing men had a worse cardiovascular risk profile, suggesting that there was an element of a “healthy survivor effect.” As such, it is likely that we may have underestimated the strength of the

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**Table 4. Association Between Pairs of Variables Measured at Phases I/II and V and Current aPWV and AIx**

<table>
<thead>
<tr>
<th>Variable</th>
<th>aPWVβ</th>
<th>95% CI</th>
<th>Significance</th>
<th>AIx†</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, baseline</td>
<td>0.43</td>
<td>0.20 to 0.66</td>
<td>&lt;0.001</td>
<td>0.30</td>
<td>–0.34 to 0.95</td>
<td>0.4</td>
</tr>
<tr>
<td>CRP, follow-up</td>
<td>0.32</td>
<td>0.12 to 0.51</td>
<td>0.001</td>
<td>0.53</td>
<td>0.0 to 1.06</td>
<td>0.05</td>
</tr>
<tr>
<td>Cholesterol, baseline</td>
<td>0.01</td>
<td>–0.18 to 2.12</td>
<td>0.9</td>
<td>0.14</td>
<td>–0.40 to 0.69</td>
<td>0.6</td>
</tr>
<tr>
<td>Cholesterol, follow-up</td>
<td>–0.01</td>
<td>–0.19 to 0.18</td>
<td>0.9</td>
<td>0.46</td>
<td>–0.03 to 0.95</td>
<td>0.07</td>
</tr>
<tr>
<td>Triglycerides, baseline</td>
<td>0.25</td>
<td>0.04 to 0.46</td>
<td>0.01</td>
<td>0.15</td>
<td>–0.43 to 0.72</td>
<td>0.6</td>
</tr>
<tr>
<td>Triglycerides, follow-up</td>
<td>0.07</td>
<td>–0.12 to 0.26</td>
<td>0.4</td>
<td>0.09</td>
<td>–0.44 to 0.62</td>
<td>0.7</td>
</tr>
<tr>
<td>Waist circumference, baseline</td>
<td>–0.04</td>
<td>–0.35 to 0.28</td>
<td>0.8</td>
<td>0.26</td>
<td>–0.60 to 1.13</td>
<td>0.5</td>
</tr>
<tr>
<td>Waist circumference, follow-up</td>
<td>0.29</td>
<td>–0.01 to 0.59</td>
<td>0.06</td>
<td>–0.61</td>
<td>–1.43 to 0.22</td>
<td>0.1</td>
</tr>
<tr>
<td>Heavy smoker, baseline</td>
<td>0.35</td>
<td>–0.03 to 0.73</td>
<td>0.07</td>
<td>0.89</td>
<td>–0.23 to 2.02</td>
<td>0.12</td>
</tr>
<tr>
<td>Heavy smoker, follow-up</td>
<td>–0.09</td>
<td>–0.60 to 0.42</td>
<td>0.7</td>
<td>0.58</td>
<td>–0.91 to 2.06</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Paired variables are mutually adjusted for each other. β-Coefficients represent the change in dependent variable (meters per second for aPWV or percentage for AIx) for a 1-SD change in the exposure variable.

*Data were adjusted for age, MAP, heart rate, and drug use.
†Data were adjusted for age, heart rate, height, and drug use.

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**Figure 3.** Integrated heart rate and pulse pressure tertiles across 20 years and their association with aPWV in later life. Subjects are grouped into tertiles of pulse pressure and heart rate on the basis of integrated values over the average 20-year follow-up period. The highest values of velocity are observed in those in the highest tertiles of pulse pressure and heart rate. P values for linear effects were <0.001 for each of the 6 strata.
risk factors for aPWV and Ax. Finally, we cannot comment on the relevance of our observations to women.

**Perspectives**

Our data indicate that inflammation and the level of repetitive cyclic stress are important predictors of aortic stiffening. Conversely, wave reflection appears to be a much more dynamic variable and influenced in the short term by inflammation and cigarette smoking. Traditional cardiovascular risk factors have more modest, or no, effect on aortic stiffness and wave reflection. Adequate control of pulse pressure and heart rate may, in the long term, retard aortic stiffening.

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**Disclosures**

None.

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