Heart Rate Dependency of Large Artery Stiffness

Isabella Tan, Bart Spronck, Hosen Kiat, Edward Barin, Koen D. Reesink, Tammo Delhaas, Alberto P. Avolio, Mark Butlin

Abstract—Carotid-femoral pulse wave velocity (cfPWV) quantifies large artery stiffness, it is used in hemodynamic research and is considered a useful cardiovascular clinical marker. cfPWV is blood pressure (BP) dependent. Intrinsic heart rate (HR) dependency of cfPWV is unknown because increasing HR is commonly accompanied by increasing BP. This study aims to quantify cfPWV dependency on acute, sympathovagal-independent changes in HR, independent of BP. Individuals (n=52, age 40–93 years, 11 female) with in situ cardiac pacemakers or cardioverter defibrillators were paced at 60, 70, 80, 90, and 100 bpm. BP and cfPWV were measured at each HR. Both cfPWV (mean [95% CI], 0.31 [0.26–0.37] m/s per 10 bpm; P<0.001) and central aortic diastolic pressure (3.78 [3.40–4.17] mmHg/10 bpm; P<0.001) increased with HR. The HR effect on cfPWV was isolated by correcting the BP effects by 3 different methods: (1) statistically, by a linear mixed model; (2) mathematically, using an exponential relationship between BP and cross-sectional lumen area; and (3) using measured BP dependency of cfPWV derived from changes in BP induced by orthostatic changes (seated and supine) in a subset of subjects (n=17). The BP-independent effects of HR on cfPWV were quantified as 0.20 [0.11–0.28] m/s per 10 bpm (P<0.001, method 1), 0.16 [0.11–0.22] m/s per 10 bpm (P<0.001, method 2), and 0.16 [0.11–0.21] m/s per 10 bpm (P<0.001, method 3). With a mean HR dependency in the range of 0.16 to 0.20 m/s per 10 bpm, cfPWV may be considered to have minimal physiologically relevant changes for small changes in HR, but larger differences in HR must be considered as contributing to significant differences in cfPWV. (Hypertension. 2016;68:236-242. DOI: 10.1161/HYPERTENSIONAHA.116.07462.) • Online Data Supplement

Key Words: blood pressure ▪ heart rate ▪ pulse wave velocity ▪ pulse wave analysis

Carotid-femoral pulse wave velocity (cfPWV), a surrogate measure for aortic stiffness, is an independent marker for all-cause and cardiovascular mortality.1,2 It is widely used in hemodynamic research and is increasingly being recognized as an important parameter in the clinical assessment of patients at risk for cardiovascular disease.3 However, the uptake of cfPWV as part of the clinical routine has been slow, despite the large amount of evidence supporting its relevance as a cardiovascular clinical marker,4 as well as being recommended as a clinical tool in current guidelines.3 A potential reason for this is the lack of standardization of cfPWV methodology and reference values.4 Although this has recently been addressed by the investigators of the Arterial Stiffness’ Collaboration, whereby normative and reference values were determined for mean arterial pressure (MAP), and cardiovascular risk factors,5 other less well-established potential confounders of cfPWV were not considered. One such factor is heart rate (HR).

Despite studies that have investigated the effects of HR on arterial stiffness in the past, the relationship between the two has remained controversial. Although a few acute, pacing studies specifically investigating the association between HR and cfPWV found an independent HR effect on cfPWV,6,7 others found no significant change in cfPWV with HR4 or were unable to discriminate the measured increase in cfPWV from the concomitant pacing-induced increase in blood pressure (BP).9,10 In cross-sectional studies, only half of those that included HR as a parameter for predicting cfPWV in their model found a significant association.11 Because cfPWV is known to be pressure dependent,12–15 any change in cfPWV accompanied by a change in BP needs to be corrected for BP to isolate the true effect of the factor being investigated. This study aims to quantify the acute, BP-independent effect of HR on cfPWV.

Methods

Patients with implanted pacemakers or implantable cardioverter defibrillators with pacing function were recruited from the Cardiac Health Institute and Macquarie Heart clinics. Exclusion criteria included unstable angina, previous myocardial infarction within the last 12 months of the study, and uncontrolled congestive heart failure. A total of 52 subjects (age 40–93 years, 11 female) entered the study, and all were included in the analysis. The study protocol was approved by Macquarie University’s Human Ethics Committee and written consent to participate in the study was obtained from all subjects.
Hemodynamic Measurements
Brachial BP, central aortic BP, and cfPWV were determined by cuff-based pulse wave analysis (Sphygmocor XCEL, AtCor, Sydney, Australia). Brachial BP was obtained by oscillometric method with a brachial cuff positioned on the right arm, and central aortic waveform was derived from the brachial BP volume displacement waveform using a validated transfer function.14 For measurement of cfPWV, the carotid and femoral pulse waveforms were obtained by tonometry on the skin above the right carotid artery and by a cuff placed on the right upper thigh, respectively.17,18 Subtraction method for path length was used to calculate cfPWV, whereby the path length was calculated as the distance between the sternal notch and the carotid site subtracted from the distance between the sternal notch and top of the thigh cuff.17

In a subset of the study’s cohort (n=45), beat-to-beat stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) were determined from the finger arterial pressure waveform using the Modelflow method (Finometer PRO, Finapres Medical Systems, Amsterdam, The Netherlands).19

Study Protocol
Subjects were advised to refrain from caffeine and fatty meals 4 hours before their study appointment, but to continue with their prescribed medications. There were no current tobacco users in the cohort. After 10 minutes of seated rest, seated brachial BP was measured in duplicate (Sphygmocor XCEL). After a further 10 minutes of supine rest, finger arterial pressure waveform was measured from the left middle finger (SphygmoCor XCEL). After a further 10 minutes of supine rest, finger arterial pressure waveform was measured from the left middle finger (SphygmoCor XCEL). Subjects were then paced in a randomized sequence at 60, 70, 80, 90, and 100 bpm using their prescribed pacemaker settings, with BP and cfPWV measurements repeated at each pacing step after 3 minutes of stabilization. ECG was also acquired continuously for the duration of the study for monitoring of HR (PowerLab acquisition system, LabChart software, ADInstruments, Dunedin, New Zealand), and SV, CO, and TPR from the Finometer PRO device were also recorded via PowerLab and LabChart. The average duration for study protocol completion was 60 minutes.

Data Analysis
For pulse wave analysis, brachial and central aortic BP waveforms were averaged >5 s, and cfPWV was averaged >10 s. Observations with measured HR differing from the paced rate by >5 bpm were excluded from the analysis, and the lowest pace rates of 60 and 70 bpm were not achievable in some subjects because of a higher unpaced resting HR. A linear mixed model with maximum likelihood was used to determine the effects of HR on each measured variable, with paced HR modeled as the fixed effect and the random effect modeled as the intercept for each individual (Equation 1).

\[ Y_{ij} = \beta_0 + \beta_1 \times HR + \epsilon_{ij} + u_i \]  (1)

where \( Y_{ij} \) denotes the outcome measure at a particular paced HR for each subject, \( \epsilon_{ij} \), the residual of variances, and \( u_i \), the random effect because of individual subject variances, that is, variance of the random intercepts. The correlation between repeated measures from the same subject is accounted for via the random effect. Linear mixed modeling was chosen because, as opposed to ANOVA, it accounts for unbalanced data,6 which in this study resulted from the lowest paced rates of 60 and 70 bpm being unachievable in some individuals. Descriptive statistics are presented as mean±SD unless otherwise stated. A P value of <0.05 was considered as statistically significant. Data analysis was performed using the software R.20 and mixed model was performed using R’s lme package.21

BP Correction
To isolate the HR effects on cfPWV from any influence of BP, 3 methods were used to correct for BP.

Method 1: BP Correction Through Statistical Methods
Central aortic diastolic BP (cDBP), as well as the interaction term between cDBP and HR, were added as fixed effects to the mixed model in Equation 1 (Equation 2).

\[ cfPWV_j = \beta_0 + \beta_1 \times HR + \beta_2 \times cDBP + \beta_3 \times HR \times cDBP + \epsilon_{ij} + u_i \]  (2)

In the case of a significant interaction term (\( \beta_3 \)) between HR and cDBP, the HR dependency of cfPWV would be dependent on cDBP, such that at any given fixed cDBP level:

\[ cfPWV = \beta_0 + (\beta_1 + \beta_3 \times cDBP) \times HR + \beta_2 \times cDBP \]  (3)

Thus, the HR dependency of cfPWV is denoted by \((\beta_1+\beta_3\times cDBP)\) at any given fixed cDBP level. For this study, the reported HR dependency of cfPWV was calculated for the sample average of cDBP.

Method 2: BP Correction Through Mathematical Modeling
On the basis of the principle that in the physiological range, pressure (P) and arterial lumen cross-sectional area (A) relate exponentially,23 the P–A relationship is formulated as

\[ P = P_{ref} e^{\left(\frac{\Delta cDBP}{\alpha}\right)} \]  (4)

PWV is also related to pressure and cross-sectional area changes, as defined by the Bramwell–Hill equation.24 By combining Equation 4 and the Bramwell–Hill equation (Equation S2 in the online-only Data Supplement), an expression for exponent \( \alpha \) can be derived as a function of systolic and diastolic BP and PWV (Equation S4), and denotes the BP dependency of PWV.

By using cfPWV and BP values at the lowest paced HR for each subject, \( \alpha \) can be calculated. Subsequently, these \( \alpha \) values can be used to calculate the predicted PWV values in each subject given the change in systolic and diastolic BP, compared with the reference level, at each higher paced rate (Equation S3). Thus, for each subject at each HR, the difference (\( \Delta cfPWV \)) between measured cfPWV (cfPWVmeas) and predicted cfPWV (cfPWVpred) was calculated as:

\[ \Delta cfPWV = cfPWV_{meas} - cfPWV_{pred} \]  (5)

The following mixed statistical model was then fitted to the data:

\[ \Delta cfPWV_j = \beta_1 \times HR + \epsilon_{ij} + u_i \]  (6)

where \( \beta_1 \) is the estimate of the BP-independent HR effect on cfPWV.

Method 3: Empirical BP Correction From Experimental Data
As PWV varies with BP, individual variations in PWV with BP changes can be determined experimentally by varying a subject’s BP through different body positions and measuring PWV at each position.25 A subset of this study’s cohort (n=17) had their BP and cfPWV measured in both the seated and the supine positions. In the seated position, a hydrostatic pressure gradient is present along the aorta and carotid artery because of gravity (Figure 1A). In the supine position, this gradient is absent (Figure 1B). In the seated position, hydrostatic pressure varies with height relative to the position of the aortic arch (Equation S6), thus cfPWV also varies. On the contrary, cfPWV remains constant along the aortic trunk in the supine position. Assuming a linear relationship between PWV and BP, the measured differences in cfPWV between the seated and the supine positions were used to calculate the BP dependency of cfPWV for each individual (Data Supplement). The averaged BP dependency across the 17 subjects was then used to calculate the BP-corrected cfPWV (cfPWV, Equation S20), and the effect of HR on cfPWV was determined (Equation S21).

Results
Clinical characteristics of the study cohort are outlined in Table 1. Baseline hemodynamic measurements, which did not differ with pacing modality (data not shown), are shown in Table 2. cfPWV increased significantly with HR, but brachial and central aortic BP parameters, except for central aortic systolic BP, also increased significantly (Table 3). SV and TPR decreased significantly, and CO increased with increasing HR (Table 3).
Results From BP Correction for cfPWV

After correction for BP, the effect of HR on cfPWV remained significant regardless of the correction method used. The average BP-independent HR dependency of cfPWV across the 3 methods was 0.17 m/s per 10 bpm.

BP Correction Using Statistical Methods

The parameters of the statistical model are shown in Table 4. Adding cDBP ($\chi^2(2)=108.66, P=0.008$) and the interaction between HR and cDBP ($\chi^2(2)=10.71, P=0.001$) significantly improved the model when compared with a model with HR as the sole predictor. Because of the significant negative interaction between HR and cDBP, the HR dependency of cfPWV decreased with increasing BP (Figure 2A). At the mean cDBP of this cohort (80±12 mm Hg), the HR dependency of cfPWV was calculated as 0.20 (0.11–0.28) m/s per 10 bpm ($P<0.001$).

BP Correction Using Mathematical Modeling

Figure 2B shows the predicted and actual measured cfPWV values using mathematical modeling for each paced HR. The resulting BP-independent HR dependency of cfPWV was 0.16 (0.11–0.22) m/s per 10 bpm ($P<0.001$).

Empirical BP Correction Using Experimental Data

From the seated-supine experimental data (Figure 2C), the average BP dependency of cfPWV was 0.04 (0.02–0.06) m/s per mm Hg ($P<0.001$, 1-sample 2-sided t test). The resulting BP-independent HR dependency of cfPWV was 0.16 (0.11–0.21) m/s per 10 bpm ($P<0.001$).

Discussion

To the best of our knowledge, this is the first study to quantify the intrinsic effect of HR on cfPWV independent of observed BP changes with acute changes in HR.

Evidence from previous studies investigating the effects of HR on arterial stiffness in the past has been inconclusive. In acute studies, where HR was manipulated pharmacologically or through pacing, most observed an increase in measured cfPWV with increasing HR. However, although some studies did show an increase in arterial stiffness in the absence of significant BP changes, other studies observed a concurrent increase in BP with increasing HR, making it difficult to determine whether HR contributed to the increase in cfPWV in addition to the BP contribution.

In this study, cardiac pacing was used to induce HR changes because pacing allowed HR to be controlled directly and independently without introducing systemic changes to modify HR. However, the increase in HR led to a decrease in SV, resulting from reduced diastolic filling time and ejection duration. Despite the decrease in SV and TPR, CO increased because of the large increases in HR, which likely drove the increase in MAP in addition to the increase in both peripheral and central diastolic BP. Because cfPWV is highly influenced by BP, much of the increase in cfPWV observed in this study can be attributed to the increase in pressure. To determine whether HR further influenced cfPWV changes, we used 3 different methods to correct for BP; similar correction procedures were not conducted in previous studies.

The first correction method we used was a straightforward statistical method, with the effect of BP accounted for by including cDBP and the interaction between cDBP and HR in the mixed model. Diastolic BP was chosen as cfPWV was measured at the diastolic point of the cardiac cycle. As expected, the additional predictors significantly improved the model, indicating a significant effect of BP on cfPWV. The effect of HR remained significant, but the significant negative interaction between HR and cDBP indicated that the influence of HR on cfPWV decreased as BP increased. This is contrary to our previous study in the rat aorta, whereby, when compared with the same MAP, aortic PWV increased more with HR at higher mean pressures. The difference in observations may be because of the difference in arterial wall structure in humans and rats, with the rat aorta being more muscular than the human aorta, hence in rats, even at higher
pressures where collagen fibres take the load bearing, the smooth muscle may have contributed further to the increase in stiffness with HR. At the averaged cDBP level of this study’s cohort, HR effect on cfPWV remained significant.

The second-correction method used mathematical modelling to predict the changes in PWV given a known change in pressure. The dependence of PWV on pressure was derived by assuming an exponential relationship between artery cross-sectional area and BP. Using this relationship, we predicted the BP-induced change in cfPWV with respect to the measured cfPWV at the lowest paced HR. As with the statistical correction method, we found that there remained the HR effect on cfPWV even after correction for BP.

The third-correction method, similar to the correction of BP by mathematical modeling, individualized each subject’s BP dependency of cfPWV by measuring cfPWV at different orthostatic positions. However, as only a subset of the cohort underwent the additional experimental protocol, the averaged BP dependency from the individuals was applied to the whole cohort to obtain a BP-independent HR effect on cfPWV. The resulting HR dependency of cfPWV obtained via this method was of the same order as both the statistical and the mathematical modeling methods.

From the study establishing normal and reference values for PWV in a large European cohort of >11000 subjects, a regression model found that for individuals aged ≥70 years, there was a mean BP dependency of PWV of 0.0676 m/s per mm Hg, which was similar to the BP dependency we obtained when fitting a mixed model predicting cfPWV using MAP only (0.0613 m/s per mm Hg, P<0.001). The BP change observed in this study was 3.71 mm Hg/10 bpm, which, if using the reference BP dependency, would equate to an approximate increase in cfPWV of 0.25 m/s per 10 bpm. However, from the 3 different BP correction methods, the average BP-independent HR dependency of cfPWV obtained was much higher at 0.17 m/s per 10 bpm. This difference may be because of the fact that reference values were established from a cross-sectional study, as opposed to this study where the acute effects of HR on cfPWV were investigated. Interestingly,

### Table 1. Clinical Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant indications</td>
<td></td>
</tr>
<tr>
<td>SSS</td>
<td>10</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>17</td>
</tr>
<tr>
<td>Irregular heart rate</td>
<td>4</td>
</tr>
<tr>
<td>Heart block</td>
<td>11</td>
</tr>
<tr>
<td>Syncope</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
<tr>
<td>Pacemaker mode</td>
<td></td>
</tr>
<tr>
<td>AAI/DDD</td>
<td>6</td>
</tr>
<tr>
<td>DDD</td>
<td>34</td>
</tr>
<tr>
<td>WI</td>
<td>11</td>
</tr>
<tr>
<td>VDD</td>
<td>1</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>α-Blocker</td>
<td>3</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>24</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>11</td>
</tr>
<tr>
<td>Nitrates</td>
<td>5</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>14</td>
</tr>
<tr>
<td>Ang II-blockers</td>
<td>16</td>
</tr>
<tr>
<td>Diuretics</td>
<td>13</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>16</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>24</td>
</tr>
<tr>
<td>Antiplatlets</td>
<td>10</td>
</tr>
<tr>
<td>Statins</td>
<td>31</td>
</tr>
<tr>
<td>Aspirin</td>
<td>10</td>
</tr>
</tbody>
</table>

AAI indicates atrial pacing and sensing; ACE, angiotensin-converting enzyme; Ang II, angiotensin II; DDD, dual chamber (atrium and ventricle) pacing and sensing; SSS, sick sinus syndrome; VDD, ventricular pacing and atrial tracking; and WI, ventricular sensing and pacing.

### Table 2. Baseline Haemodynamic Measurements of the Study Cohort

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>64±7</td>
</tr>
<tr>
<td>cfPWV, m/s</td>
<td>9.5±1.6</td>
</tr>
<tr>
<td>Brachial SBP, mmHg</td>
<td>126±15</td>
</tr>
<tr>
<td>Brachial DBP, mmHg</td>
<td>72±9</td>
</tr>
<tr>
<td>Central aortic SBP, mmHg</td>
<td>115±13</td>
</tr>
<tr>
<td>Central aortic DBP, mmHg</td>
<td>72±8</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>88±9</td>
</tr>
</tbody>
</table>

cfPWV indicates carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; and SBP, systolic BP.

### Table 3. Estimated Effect of HR on All Measured Variables

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Estimated Value for the Effect of HR per 10 bpm Increase (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cfPWV, m/s</td>
<td>0.31 (0.26 to 0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>bSBP, mmHg</td>
<td>1.03 (0.56 to 1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>bDBP, mmHg</td>
<td>3.55 (3.18 to 3.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cSBP, mmHg</td>
<td>0.33 (−0.09 to 0.75)</td>
<td>0.120</td>
</tr>
<tr>
<td>cDBP, mmHg</td>
<td>3.78 (3.40 to 4.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>3.71 (3.33 to 4.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SV, mL</td>
<td>−6.10 (−6.85 to −5.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>0.21 (0.16 to 0.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPR, dyn-s-cm⁻³</td>
<td>−30.33 (−31.00 to −29.65)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

bDBP indicates brachial diastolic blood pressure; bSBP, brachial systolic BP; cPWV, carotid-femoral pulse wave velocity; cSBP, carotid SBP; cSBP, carotid DBP; CI, confidence interval; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; and TPR, total peripheral resistance.
although the reference values study did not include HR in the final regression model, it was stated that PWV was in fact significantly dependent on HR, albeit with much smaller influence compared with MAP and age.5

It has previously been shown that an increase in HR of 10 bpm is equivalent to an increase in systolic BP of 10 mm Hg in terms of associated cardiovascular risk.32 In this study, cfPWV increased on average 0.17 m/s per 10 bpm increase in HR, independent of BP changes. This was equivalent to a 1.8% increase in cfPWV, slightly lower than but of the same order as the 2.5% increase in cfPWV observed by Lantelme et al6 for the same increase in HR, where the investigators reported no change in BP with HR. Another study found an increase in cfPWV of almost 6% with 10 bpm increase in HR in the absence of significant BP changes.7 The moderate increase in cfPWV observed in this study is equivalent to a 6% increase in the risk of all-cause mortality in end-stage renal disease patients per 10 bpm increase in HR, as it has been shown that 1 m/s increase in PWV translates to a 39% increase in risk in this population.33 Thus, although the influence of HR on large artery stiffness may be small, it cannot be ignored when a large change in HR is present.

The mechanism behind the influence of HR on arterial stiffness is still largely unknown. Investigators have often attributed the change in arterial stiffness with HR to the viscoelasticity of the arterial wall.6,34 Previous studies in both animals and humans have shown a frequency dependency of elastic modulus.35–37 Other investigators explained the effect by the reduced time for the artery to recoil at increased HRs, thus resulting in a stiffer artery.38,39 This is consistent with the presence of viscoelasticity. However, no studies to date have been able to conclusively determine whether viscoelasticity per se is indeed the mechanism involved.

Another potential mechanism for the change in arterial stiffness may be a change in smooth muscle tone in the large arteries, induced by a change in sympathetic activity. Although cardiac pacing, as performed in this study, does not directly influence the sympathetic nervous system, indirect effects because of the changed hemodynamics, such as baroreceptor activation because of the increased BP, cannot be excluded. However, baroreceptor activation in response to increased BP would cause a decrease in sympathetic activity, potentially decreasing smooth muscle recruitment and reducing arterial wall stiffness. Finally, the HR dependency of cfPWV could be a measurement artifact, caused by a change in pulse waveform because of the increased HR at either the carotid or the femoral site, influencing the detected location of the diastolic foot. However, a previous study by Millasseau et al10 demonstrated a significant HR effect on cfPWV regardless of whether the pulse propagation time was referenced to the diastolic foot or to the

Table 4. Model Parameters for Model Used for BP Correction in Method 1

<table>
<thead>
<tr>
<th>Model Parameters</th>
<th>β (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept (β0)</td>
<td>0.73 (−2.79 to 4.25) m/s</td>
<td>0.685</td>
</tr>
<tr>
<td>HR (β1)</td>
<td>0.09 (0.05 to 0.13) m/s per bpm</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cDBP (β2)</td>
<td>0.10 (0.05 to 0.15) m/s per mm Hg</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR-cDBP (β3)</td>
<td>−0.0009 (−0.0013 to −0.0004) m/s per (mm Hg∙bpm)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mixed model was defined as \( cfPWV_{ij} = \beta_0 + \beta_1\times HR + \beta_2\times cDBP + \beta_3\times HR\times cDBP + \varepsilon_{ij} \), BP, blood pressure; cDBP, carotid diastolic BP; cfPWV, carotid-femoral pulse wave velocity; CI, confidence interval; and HR, heart rate.

Figure 2. A, Carotid-femoral pulse wave velocity (cfPWV) increased with heart rate (HR), but there was a significant negative interaction between HR and blood pressure (BP), as shown by the decreasing slope of PWV with HR at different central diastolic BP (cDBP) levels. B, Measured cfPWV at each paced HR level and predicted cfPWV using BP correction method with mathematical modeling. C, BP dependency of cfPWV calculated from experimental data in a subset of this study’s cohort (n=17). Horizontal line indicates mean.
point of maximum systolic upstroke. In this study, a post hoc analysis of a subset of 10 subjects comparing cIPWV calculated with 2 different algorithms for determining pulse transit time, one referencing the foot of the wave and the other referencing the point of maximum slope of the systolic upstroke, also showed that the effect of HR on cIPWV was independent of the timing algorithm used (Data Supplement). It is beyond the current study’s scope to provide additional explanatory evidence of how HR affects arterial stiffness, but our results further support previous observations, whereby HR was shown to have a significant effect on measured large artery stiffness.

This study has potential limitations. The study cohort consisted of subjects with in situ cardiac pacemakers who were heterogeneous in their cardiac function and indication for pacemaker implantation. Over half of the cohort were on antihypertensives, but treatment was not homogenous across the cohort. As cardiac dysfunction and hypertensive treatment have been shown to influence PWV, and as the cohort consisted of mainly elderly male subjects, results from the current study cannot be extrapolated to the general population nor beyond the HR range studied. In addition, responses to acute changes in HR by means of cardiac pacing may not be reflective of long-term HR changes caused by pathological tachycardia, which involve numerous factors, including neural and hormonal influences. In addition, the BP correction methods involved several assumptions. For the statistical BP correction, it was assumed that for the BP changes observed in this study, cIPWV changed linearly with BP, HR, and their interaction. This assumption also holds for the empirical correction method. It has been shown in studies where MAP was changed pharmacologically, that cIPWV and BP exhibited a curvilinear relationship. However, as other empirical data have shown the 2 to be linearly associated, it is not unreasonable to assume a linear relationship between cIPWV and BP in this study. Our BP correction method using mathematical modeling incorporates the nonlinear relationship between BP and cIPWV, and it is based on an assumed exponential relationship. However, the exact exponential nature of this relationship can be debated, as other descriptives as well as empirical data have shown the effect of HR on pulse wave velocity to be independent of the actual wall constituents have also been proposed. Nevertheless, the exponential relationship provides an acceptable compromise between accuracy and practical use.

In conclusion, although the effect of acute changes in HR on large arterial stiffness may not be of the same order as that of BP, it cannot be dismissed. In particular, in addition to correction for BP, cIPWV should be corrected for large changes in HR.

Perspectives
Our study quantified the intrinsic effect of HR on large artery stiffness independent of BP effects, whereby there was a concurrent change in BP with HR. The HR effect, though moderate at 0.17 m/s per 10 bpm increase in HR, can still translate to a moderate increase in risk of stroke and all-cause mortality. Our results show that HR is a relevant parameter that needs to be accounted for when large changes in HR are present in the measurement of cIPWV, both in research and in a clinical setting.

Acknowledgments
We would like to express our gratitude to all the pacemaker technicians from Medtronic, Biotronik, Boston Scientific, and St. Jude Medical who provided technical assistance in this study.

Sources of Funding
This study was supported by the Australian Postgraduate Award (to I. Tan), Australian Research Council (ARC) Discovery grant DP11010134 (to A.P. Avolio and M. Butlin), and ARC Linkage grant LP12004063 (to A.P. Avolio and M. Butlin).

Disclosures
None.

References
What Is New?

- The largest human study to date investigating the effects of heart rate (HR) on large artery stiffness by the way of cardiac pacing and carotid-femoral pulse wave velocity (cPWV) measurement.
- First study to quantify the intrinsic effect of HR on cPWV (0.17 m/s per 10 bpm) in the presence of concurrent blood pressure changes with HR.

What Is Relevant?

cPWV, a surrogate for large artery stiffness, is an independent risk factor for cardiovascular and all-cause mortality, and it is recognized as a factor affecting prognosis of hypertension.

Because cPWV becomes more widely available in routine assessment of hypertension, and with its wide usage in research on hypertension, it is important to recognize all factors that may confound the measurement.

Novelty and Significance

Summary

In a cohort of 52 mostly elderly males, HR increases by way of cardiac pacing resulted in a moderate but significant blood pressure-independent change in cPWV of 0.17 m/s per 10 bpm increase in HR. Although the effect of acute changes in HR may not be of the same order as that of blood pressure, it cannot be dismissed especially when large changes in HR are present.
Heart Rate Dependency of Large Artery Stiffness
Isabella Tan, Bart Spronck, Hosen Kiat, Edward Barin, Koen D. Reesink, Tammo Delhaas, Alberto P. Avolio and Mark Butlin

Hypertension. 2016;68:236-242; originally published online May 31, 2016;
doi: 10.1161/HYPERTENSIONAHA.116.07462

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 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/68/1/236

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2016/05/31/HYPERTENSIONAHA.116.07462.DC1

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 Data Supplement

HEART RATE DEPENDENCY OF LARGE ARTERY STIFFNESS

I Tan\textsuperscript{1}, B Spronck\textsuperscript{1,2}, H Kiat\textsuperscript{1,3}, E Barin\textsuperscript{1,4}, KD Reesink\textsuperscript{2}, T Delhaas\textsuperscript{2}, AP Avolio\textsuperscript{1}, M Butlin\textsuperscript{1}.

\textsuperscript{1} Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia.
\textsuperscript{2} Department of Biomedical Engineering, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands.
\textsuperscript{3} Cardiac Health Institute, Sydney, Australia.
\textsuperscript{4} Macquarie Heart, Sydney, Australia.

1. Additional Details on Methods

Method 2. Blood pressure correction through mathematical modelling

The pressure ($P$) and arterial lumen area ($A$) relationship as formulated in Eq. 4 of the main manuscript can be expressed as

$$A = A_{\text{ref}} \left( \ln \frac{P}{P_{\text{ref}}} + \frac{1}{\alpha} \right)$$  \hspace{1cm} (S1)

where $P_{\text{ref}}$ denotes a reference pressure with corresponding cross-sectional area $A_{\text{ref}}$. PWV is also related to pressure and cross-sectional area changes, as defined by the Bramwell-Hill equation: \cite{1}

$$\text{PWV} = \sqrt{\frac{1}{\rho} \left( \frac{P_s - P_d}{A_s - A_d} \right)}$$  \hspace{1cm} (S2)

with $\rho$ being the mass density of blood, taken to be 1050 kg/m$^3$, and subscripts $s$ and $d$ denoting systolic and diastolic, respectively. Eq. S1 can be used to obtain an expression for $A_d$ as a function of $P_d$, and equivalently to obtain an expression for $A_s$ as a function of $P_s$. These expressions can be entered into Eq. S2, which yields

$$\text{PWV} = \sqrt{\frac{P_s - P_d}{\rho} \left( \frac{\ln \frac{P_d}{P_{\text{ref}}} + \alpha}{\ln \frac{P_s}{P_d}} \right)}$$  \hspace{1cm} (S3)

Note that no cross-sectional area terms are present in this equation as these terms cancel out.
Rearranging Eq. S3 yields an expression for exponent $\alpha$ as a function of systolic and diastolic BP and PWV:

$$\alpha = \ln \frac{P_s}{P_d} - \frac{\rho}{P_s - P_d} \text{PWV}^2 - \ln \left( \frac{P_d}{P_{\text{ref}}} \right)$$  \hspace{1cm} (S4)

**Method 3. Empirical blood pressure correction through experimental data**

PWV in each small arterial segment was assumed to scale linearly with local diastolic BP ($P_d$), i.e.

$$\text{PWV} = a \cdot P_d + b$$  \hspace{1cm} (S5)

In the seated position, hydrostatic pressure $P_{\text{hyd}}$ varies along the arteries with height $h$ in metres relative to the position of the aortic arch given the blood mass density ($\rho$) and gravitational constant ($g = 9.81 \text{ m/s}^2$):

$$P_{\text{hyd}} = \rho gh$$  \hspace{1cm} (S6)

Note that $P_{\text{hyd}}$ is positive relative to the pressure at the aortic arch at levels below the arch, and negative at levels above it (Figure 1A). $P_d$ along height $h$ is therefore

$$P_d = \rho gh + P_{d,\text{seated}}$$  \hspace{1cm} (S7)

where $P_{d,\text{seated}}$ is the central aortic diastolic BP (cDBP) measured in the seated position. By combining equations Eq. S5 and Eq. S7, PWV along the aortic trunk can be expressed as

$$\text{PWV} = a(\rho gh + P_{d,\text{seated}}) + b = a\rho gh + aP_{d,\text{seated}} + b$$  \hspace{1cm} (S8)

As velocity is the derivative of distance with respect to time, PWV can be denoted as

$$\text{PWV} = \frac{dh}{dt}$$  \hspace{1cm} (S9)

and, thus, transit time can be denoted as

$$dt = \frac{dh}{\text{PWV}}$$  \hspace{1cm} (S10)

The total transit time from the aortic arch to the carotid artery ($t_C$, along distance $C$ in Figure 1A) can be found by integrating $dt$ along that distance:

$$t_C = \int_{-C}^{0} \frac{1}{\text{PWV}} dh = \int_{-C}^{0} \frac{1}{a\rho gh + (aP_{d,\text{seated}} + b)} dh$$  \hspace{1cm} (S11)

which can be evaluated to

$$t_C = \frac{\ln|a\rho gh + aP_{d,\text{seated}} + b|_0}{a\rho g} \bigg|_{-C}^0$$  \hspace{1cm} (S12)
Similarly, the total transit time from the aortic arch to the femoral artery \( t_F \) can be evaluated to

\[
t_F = \frac{1}{\rho g} \ln \left( \frac{a P_{d,seated} + b}{a (P_{d,seated} - \rho g C) + b} \right)
\]  
(S13)

The total transit time from the carotid to femoral artery \( t_{seated} \) using the subtraction method for path length is

\[
t_{seated} = t_F - t_C
\]  
(S16)

In the supine case, no pressure gradient is present and PWV is assumed to be constant along the aorta for supine diastolic BP \( P_{d,\text{supine}} \):

\[
PWV = a \cdot P_{d,\text{supine}} + b
\]  
(S18)

Given that PWV is distance divided by transit time \( t_{\text{supine}} \),

\[
t_{\text{supine}} = \frac{F - C}{PWV} = \frac{F - C}{a \cdot P_{d,\text{supine}} + b}
\]  
(S19)

Using the two equations for \( t_{seated} \) and \( t_{\text{supine}} \) (Eqs. S17 and S19), the two unknown coefficients \( a \) and \( b \) can be evaluated for each subject, and \( a \) represents the BP dependency of cfPWV for each subject. The averaged \( a \) (\( \bar{a} \)) across the 17 subjects was used to calculate the BP corrected cfPWV (cfPWV\(_c\)):

\[
\text{cfPWV}_c = \text{cfPWV} - \bar{a} \cdot (\text{cDBP} - \text{cDBP}_{\text{ref}})
\]  
(S20)

where \( \text{cDBP}_{\text{ref}} \) denotes cDBP at the lowest paced HR for the individual. The following mixed model was then fitted to the BP-corrected PWV values:

\[
\text{cfPWV}_c = \beta_0 + \beta_1 \cdot \text{HR} + \epsilon_{ij} + u_j
\]  
(S21)

where \( \beta_1 \) denotes the BP-independent effect of HR on cfPWV.
2. Comparison of effect of HR on carotid-femoral pulse wave velocity using different algorithms for determination of pulse transit time

In order to determine whether the heart rate (HR) effect on carotid-femoral pulse wave velocity (cfPWV) observed in the current study was a measurement artefact due to possible changes in the foot of the pressure wave with HR, a post-hoc analysis was run on a subset of 10 subjects to compare cfPWV determined from two different pulse transit time algorithms. One method used the intersecting tangent method to identify the foot of the pressure wave² (default algorithm of SphygmoCor). The other method used the point of maximum slope of the systolic upstroke on the pressure wave as the timing point of reference³ (as used in the Complior device).

Methods

Carotid and femoral blood pressure waveforms measured from the SphygmoCor XCEL (AtCor Medical, Sydney, Australia) device were re-analysed with the SphygmoCor SCOR software (AtCor Medical) using the two different algorithms, both provided as options in the software. A linear mixed model, with HR and timing algorithm modelled as fixed effects and with random effect modelled as the intercept for each individual, was fitted to the cfPWV data as follows:

\[ cfPWV_{ij} = \beta_0 + \beta_1 \cdot \text{Method} + \beta_2 \cdot HR + \beta_3 \cdot \text{Method} \cdot HR + \varepsilon_{ij} + u_j \quad (2) \]

where “Method” was a dummy coded variable indicating the timing algorithm used for calculation of cfPWV, coded 0 for the intersecting tangent method and 1 for the maximum systolic upstroke method. \( \beta_2 \) represented the effect of HR on cfPWV for the intersecting tangent method; \( \beta_3 \) represented the difference in the effect of HR on cfPWV between the two methods, thus \( \beta_2 + \beta_3 \) represented the effect of HR on cfPWV for the maximum systolic upstroke method.

Results

The results from the mixed model indicated that the effect of HR was significant regardless of the transit time algorithm used (for the intersecting tangent method, \( \beta_2 = 0.05 [0.03, 0.06] \text{ m/s/bpm, } t=4.94, P<0.0001 \); for the maximum systolic upstroke method, \( \beta_2 + \beta_3 = 0.03 [0.01, 0.05] \text{ m/s/bpm, } t=3.09, P=0.03 \)). The values obtained were identical to those obtained by Millasseau et al. in their study of 11 subjects,⁴ where there was a 0.05 m/s/bpm change in cfPWV with HR (2.1 m/s change in cfPWV from 80 bpm to 120 bpm) using the intersecting tangent method, and a 0.03 m/s/bpm change in cfPWV with HR (1.1 m/s change in cfPWV from 80 bpm to 120 bpm) using the maximum slope of systolic upstroke algorithm. The absence of a significant interaction term between HR and the timing algorithm (\( \beta_3 = 0.02 [-0.04, 0.01], t=1.33, P=0.19 \)) indicated that the effect of HR on cfPWV was not dependent of the algorithm employed for determination of pulse transit time.
References


