Augmentation Index, Left Ventricular Contractility, and Wave Reflection

James E. Sharman, Justin E. Davies, Carly Jenkins, Thomas H. Marwick

Abstract—Augmentation index (Alx), a correlate of mortality, is thought to be influenced by left ventricular contractility and wave reflections. However, the relationship of Alx with left ventricular contractility changes has never been assessed, and the wave reflection theory has recently been questioned. This study sought to examine arterial waveform changes in response to reduced “wave reflection” and increased left ventricular contractility induced by dobutamine. Simultaneous radial tonometry (for Alx) and tissue Doppler echocardiography (for peak longitudinal systolic strain rate [SR] as an analogue of left ventricular contractility) were recorded at rest and peak dobutamine-induced stress in 50 patients (41 men; aged 62±10 years). From baseline to peak stress there was an increase in heart rate (70±11 to 127±17 bpm; \(P<0.001\)) and SR (−0.88±0.23 to −1.81±0.43 1/s; \(P<0.001\)), whereas Alx decreased (27±9% to −7±15%; \(P<0.001\)). There was also a greater increase in the systolic (compared with diastolic) pressure-time integral relative to cardiac cycle length (3.2±1.9 versus 1.8±1.1 mm Hg; \(P<0.001\)), indicating that wave reflection was not shifted into diastole as per the current belief. Alx was significantly associated with ejection duration \((r=0.88)\), heart rate \((r=−0.81)\), and SR \((r=0.72; P<0.001\) for all). However, when SR was heart rate corrected, there was no significant association with Alx \((r=0.18; P=0.11)\). The strongest independent correlate of Alx was ejection duration, accounting for 78% variance \((\beta=0.88; \text{model } R^2=0.77; P<0.001)\). Neither SR \((\beta=0.12; P=0.18)\) nor heart rate–corrected SR \((\beta=0.02; P=0.72)\) was associated with Alx. We conclude that Alx is determined by chronotropic rather than inotropic effects, as well as factors other than wave reflection. (Hypertension. 2009;54:1099-1105.)

Key Words: left ventricle ■ heart contractility ■ cardiac inotropism ■ blood pressure ■ hemodynamic ■ cardiovascular physiology ■ augmentation index

Augmentation index (Alx) is a surrogate indicator of left ventricular (LV) systolic loading that may be recorded noninvasively from superficial arteries (eg, radial or carotid artery) or estimated at the ascending aorta from the radial artery using a generalized transfer function. Several studies suggest that Alx may be a useful therapeutic target in selected patient populations. For example, the change in Alx in response to antihypertensive therapy was shown recently to be a robust predictor of the change in LV mass in hypertensive patients treated over 1 year. The Alx has also been shown to independently correlate with the extent of coronary artery disease, LV hypertrophy, urinary albumin excretion, diabetic retinopathy, maximal aortic intima-media thickness, cardiovascular events, and all-cause mortality.

There is a widely held belief that Alx is principally determined by the magnitude of arterial wave reflection where, in instances of increased heart rate (eg, that induced by drugs, pacing, or exercise), ejection duration is shortened and the reflected pressure wave is shifted from systole to diastole, thereby decreasing both Alx and LV systolic stress. However, recent findings with new methodology have suggested that wave reflection only plays a minor role in arterial pressure waveform morphology. Discrepancy between the 2 explanations may be resolved by analyzing the relative changes in discrete components of arterial pressure waveforms (ie, systolic and diastolic pressure-time integrals, as well as arterial reservoir pressure and wave pressure) in response to changes in heart rate. The first aim of this study was to assess these waveform parameters in response to increased heart rate induced by dobutamine. We hypothesized that an increase in heart rate would be accompanied by an increase in the magnitude of systolic, rather than diastolic, components of the waveform.

Furthermore, Alx is known to be influenced by numerous factors, including alterations in either cardiac or vascular function, because the shape of the arterial pressure waveform is a result of the interaction between the heart and the arterial system. As such, the pattern of LV contractility is commonly cited as playing an influential role on the magnitude of Alx. These conclusions are based on pacing studies in humans that show a strong negative correlation...
between heart rate and AIx.\textsuperscript{13,25,26} However, a degree of positive inotropy will occur in concert with increased heart rate through the Bowditch effect,\textsuperscript{27} in which case, LV contractility may either be associated with AIx or may confound the association between heart rate and AIx. The relationship between LV contractility and AIx has never been examined in response to alterations in LV contractility, and this study also aimed to assess this by simultaneous echocardiography and radial tonometry after dobutamine infusion.

### Methods

#### Study Design

Simultaneous radial tonometry (for AIx and arterial waveform components) and echocardiography (for LV contractility) were recorded in 76 consecutive patients undergoing standard, clinically indicated dobutamine stress echocardiography (as per usual practice, \(\beta\)-blockers were withdrawn on the day of testing). Measurements were recorded at rest and at peak stress (30 to 40 \(\mu\)g/kg per minute of dobutamine\(\pm\)atropine). Four patients were excluded because of arrhythmia, and a further 12 patients were excluded because of a heart rate difference of >5 bpm between echocardiography and tonometry measurements. Data from another 10 patients were excluded because of suboptimal quality of pressure waveforms (eg, low quality control index) or echocardiography (eg, aliasing). Characteristics of the study population (\(n=50\)) are shown in Table 1. Procedures were carried out in accordance with the Declaration of Helsinki (2000). The research received approval from the institution’s ethics committee, and participants provided informed consent.

#### Radial Tonometry

Duplicate recordings of the radial artery pulse were acquired by radial applanation tonometry using customized equipment (SphygmoCor 7.01; AtCor Medical). This technology synthesizes a central (ascending aortic) pressure waveform from the radial pressure waveform using a validated generalized transfer function\textsuperscript{1,28} that has good reproducibility under major hemodynamic changes.\textsuperscript{29} Systolic-to-diastolic pressure shifts were assessed by the systolic and diastolic pressure-time integral. The Buckberg index was the percentage ratio of the diastolic systolic pressure-time integral, which correlates with LV subendocardial/subepicardial flow ratio (an apparent marker of subendocardial ischemia).\textsuperscript{30}

Brachial systolic and diastolic blood pressures were used to calibrate the radial pressure waveform. Blood pressure was obtained in duplicate at rest and peak stress by an automated device (Dinamap Plus; Critikon). Mean arterial pressure was derived by integration of the radial pressure waveform. Figure 1 depicts an example central pressure waveform with relevant indices noted. The AIx (percentage) was defined as follows: (central \(P_2\)–\(P_1\) \(\times\) central pulse pressure)\(\times\)100.\textsuperscript{23} Timing of the returning reflected wave was calculated as the time (in milliseconds) from the beginning of the systolic upstroke to the first inflection point and is a surrogate marker of aortic pulse wave velocity (stiffness).\textsuperscript{4} Pressure pulse amplification was the ratio of brachial:central pulse pressure. The SphygmoCor software incorporates an algorithm (based on previous literature\textsuperscript{13}) that normalizes AIx to a heart rate of 75 bpm.

#### Calculation of Arterial Reservoir Pressure and Wave Pressure

The ensemble-averaged radial pressure waveforms (acquired by the SphygmoCor equipment) were separated into 2 components using Matlab (Mathworks, Inc). The arterial reservoir pressure waveform component was calculated by iteration of the equation (below) and by fitting a monoexponential function to the falling pressure during diastole.\textsuperscript{18} The wave pressure was derived by the subtraction of arterial reservoir pressure from total pressure (see examples in Figure 2).\textsuperscript{16} These waveform components provide information that is incremental to the radial artery systolic and diastolic pressure-time integrals. All of the reservoir and wave pressures are quoted with diastolic pressure subtracted.

\[
P_{\text{reservoir}} - P_a = e^{-\alpha t} \int_0^t \left\{ aP(t') + bP_a \right\} e^{\alpha t'} dt + (P_d - P_a) e^{-\alpha t}
\]

\(P_{\text{reservoir}}\) is reservoir pressure, \(P_a\) is the asymptotic pressure, \(P_d\) is the measured diastolic pressure at \(t=0\), \(b=1/RC\), where \(R=\)resistance and \(C=\)compliance of the system; \(a\) is a rate constant that can be determined by fitting during the diastolic period.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Example central pressure waveform. \(T_R\) indicates timing of the reflected pressure wave; \(P_1\) and \(P_2\) represent the first and second systolic peaks, respectively.

### Table 1. Characteristics of Study Participants (n=50)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62(\pm)10</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170(\pm)9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83(\pm)18</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>28.4(\pm)5.2</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>28(\pm)10</td>
</tr>
<tr>
<td>Women, %</td>
<td>18</td>
</tr>
<tr>
<td>Smokers, former/current/never; %</td>
<td>26/16/58</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, %</td>
<td>36</td>
</tr>
<tr>
<td>Statin therapy, %</td>
<td>89</td>
</tr>
<tr>
<td>Anthypertensive therapy, %</td>
<td>82</td>
</tr>
<tr>
<td>Inducible wall motion abnormalities, %</td>
<td>50</td>
</tr>
</tbody>
</table>

Data is mean\(\pm\)SD or percentage.
Echocardiography

Peak longitudinal systolic strain rate (SR; ie, the maximal negative SR within 350 ms after the QRS complex), an analogue of LV contractility, was recorded by color tissue Doppler imaging in the apical 4 chamber view. This is a relatively load-independent measure, which quantifies the velocity of myocardial deformation and is associated with LV dP/dt maximum. Analyses of SR curves were performed offline in the basal septal segment using dedicated software (EchoPACPC; GE Vingmed). Briefly, the region of interest (12×6 mm) was tracked manually in the 2D image on a frame-to-frame basis and maintained in a fixed midmyocardial position to make sure that SR traces represented the same myocardial segment over the whole cardiac cycle.

Measurements of stroke volume, ejection fraction, and end diastolic and systolic volumes were obtained using the software installed on the ultrasound machine and in accordance with the American Society of Echocardiography guidelines. Measures of end diastolic volume were recorded at the time of mitral valve closure and end systolic volume on the image with the smallest LV cavity. Volumes using Simpson biplane were obtained from the apical 4- and 2-chamber views, with the papillary muscles being included in the LV cavity. Cardiac output was calculated as stroke volume×heart rate. Peripheral vascular resistance was defined as mean arterial pressure/cardiac output and expressed as peripheral resistance units.

Statistics

Data were presented as mean±SD, and P<0.05 was considered significant. Differences between resting and stress-induced variables were analyzed by paired t tests. Pearson product moment coefficient of correlation (r) was used to assess relationships between variables, and multiple linear regression was performed by the backward method. Data were analyzed using SPSS software version 11.0 (SPSS Inc).

Results

Stress Response

The hemodynamic changes in response to dobutamine are shown in Table 2. From baseline to peak dobutamine stress there was a significant increase in heart rate, cardiac output, pulse pressure amplification, and SR, whereas AIx, augmented pressure, ejection duration, central systolic blood pressure, central pulse pressure, central end systolic pressure, timing of the reflected wave, and peripheral vascular resistance were all significantly decreased. There was no significant change in mean arterial pressure, brachial pulse pressure, systolic blood pressure, or diastolic blood pressure. From baseline to peak stress there was a significant increase in SR after correcting for heart rate (from −0.0125±0.0035 to −0.0144±0.0033 l/s per beat per minute; P=0.02).

Shifts in Components of the Arterial Pressure Waveform

The systolic pressure-time integral increased at higher heart rates, but the diastolic pressure-time integral and the Buckberg index reduced significantly (Table 2). To assess changes in the systolic and diastolic pressure-time integrals relative to the change in heart period (in milliseconds), we corrected each of these variables for the cardiac cycle length (which was significantly decreased by dobutamine; Table 2). From rest to peak stress, there was a significant increase in both the systolic (2.8±1.1 to 6.0±1.9 mm Hg) and diastolic (3.5±0.7 to 5.3±1.2 mm Hg) pressure-time integrals relative to cardiac cycle length (P<0.001 for both). However, there was a significantly greater change in the systolic pressure-time integral/cardiac cycle length compared with the diastolic pressure-time integral/cardiac cycle length (3.2±1.9 versus 1.8±1.1 mm Hg; P<0.001).

Complete data analyses for peak stress arterial reservoir pressure and wave pressure variables were only able to be performed in 16 patients because of a negative inflection of

Table 2. Hemodynamic Variables at Rest and at Peak Dobutamine Stress (n=50)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>Peak Stress</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial systolic blood pressure, mm Hg</td>
<td>131±23</td>
<td>136±30</td>
<td>0.23</td>
</tr>
<tr>
<td>Brachial diastolic blood pressure, mm Hg</td>
<td>67±11</td>
<td>66±14</td>
<td>0.70</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>89±15</td>
<td>88±17</td>
<td>0.76</td>
</tr>
<tr>
<td>Central systolic blood pressure, mm Hg</td>
<td>119±21</td>
<td>109±22</td>
<td>0.006</td>
</tr>
<tr>
<td>Brachial pulse pressure, mm Hg</td>
<td>64±18</td>
<td>70±24</td>
<td>0.09</td>
</tr>
<tr>
<td>Central pulse pressure, mm Hg</td>
<td>51±16</td>
<td>39±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure amplification, ratio</td>
<td>1.27±0.16</td>
<td>1.81±0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central end systolic pressure, mm Hg</td>
<td>104±18</td>
<td>94±18</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±11</td>
<td>127±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection duration, ms</td>
<td>319±22</td>
<td>225±27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac cycle length, ms</td>
<td>872±125</td>
<td>480±71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Timing of the reflected pressure wave, ms</td>
<td>140±12</td>
<td>132±19</td>
<td>0.01</td>
</tr>
<tr>
<td>Augmented pressure, mm Hg</td>
<td>15±8</td>
<td>−3±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIx, %</td>
<td>27±9</td>
<td>−7±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak longitudinal strain rate, 1/s</td>
<td>−0.88±0.23</td>
<td>−1.81±0.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic pressure-time integral, mm Hg/s per min</td>
<td>2341±585</td>
<td>2806±685</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic pressure-time integral, mm Hg/s per min</td>
<td>2999±489</td>
<td>2489±504</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Buckberg index, %</td>
<td>134±31</td>
<td>92±20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>3.51±1.30</td>
<td>5.01±1.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular resistance, PRU</td>
<td>28.4±10.5</td>
<td>19.4±6.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data is mean±SD. PRU indicates peripheral resistance units.
The AIx was strongly associated with heart rate ($r = 0.81$), ejection duration ($r = 0.88$), and peak longitudinal systolic SR ($r = 0.72; P < 0.001$ for all). However, SR was also significantly correlated with heart rate ($r = 0.78; P < 0.001$). When SR was corrected for heart rate (ie, SR/heart rate), there was no significant association with AIx ($r = 0.18; P = 0.11$). A similar pattern of significant correlations was observed for the relationship between augmented pressure and heart rate ($r = 0.35; P < 0.01$) but not brachial pulse pressure ($r = -0.10; P = 0.37$).

A multiple-regression model for predictors of the change in AIx from baseline to peak dobutamine was also constructed, with the following variables entered: baseline AIx, change in SR, change in ejection duration, change in heart rate, change in mean arterial pressure, and the unstandardized residual of the heart rate and ejection duration regression. Significant independent variables were the change in ejection duration ($\beta = 0.59; P < 0.001$), the unstandardized residual of the heart rate and ejection duration regression ($\beta = 0.43; P = 0.001$), and ejection duration ($\beta = 0.82$).
Noninvasive estimation of central AIx from the radial or carotid artery is a marker of LV systolic loading that has clinical significance. The novel findings of this study were, first, that systolic, rather than diastolic, components of the arterial pressure waveform showed a relatively greater increase in response to elevations of heart rate. This is contrary to wave reflection theory in which there would be an expectation for the diastolic components of the arterial pressure waveform to increase relatively more than the systolic measures. Second, we found that AIx was not influenced by large increases in LV contractility induced by dobutamine. Finally, ejection duration was a more powerful determinant of AIx than heart rate. It should be noted that this study does not dispute the value of AIx as a useful tool for risk assessment or outcome prediction.

Wave Reflection and AIx

Profound vasodilatation stimulated by dobutamine is reflected by the absence of a brachial blood pressure increase, despite significantly elevated cardiac output. Our findings of a significant negative correlation between heart rate and AIx in response to β-adrenergic stimulation are consistent with previous studies that have induced tachycardia by vasoactive drugs (nitroglycerine), ventricular pacing, and atrial or atrio-ventricular pacing. Interestingly, the shapes of the radial and derived central waveforms after dobutamine infusion in this current study (Figure 3) are comparable with those found during high heart rates provoked by disparate mechanisms, including pacing, junctional tachycardia, and peak exercise. As heart rate increases, there is a concomitant reduction in the ejection duration, as well as the diastolic portion of the cardiac cycle, with a proportionally greater reduction in the diastolic phase. Because the augmented pressure (see Figure 1) is widely believed to represent the sum of outgoing and returning reflected pressure waves, a reduced ejection phase (with higher heart rates) leaves less time for reflected waves to return during systole, resulting in a lower AIx. Therefore, wave reflection is effectively shifted into diastole. This theory is based on frequency-domain analysis and is consistent with our findings of ejection duration being a stronger correlate of AIx than heart rate, as well as the significant reduction in peripheral vascular resistance, which will also result in lower AIx.

On the other hand, if reflected waves were shifted into diastole with higher heart rates (and reduced peripheral vascular resistance), we should have seen a relative increase in the area under the diastolic pressure-time integral after dobutamine infusion. However, there was a significantly greater increase in the systolic pressure-time integral relative to cardiac cycle length, suggesting that shifts in the timing of wave reflection may not be the principal factor driving changes in augmented pressure and AIx. What, then, may be the factors influencing AIx if not wave reflection? Recent work using wave intensity analysis and reservoir pressure analysis offers an alternative explanation for changes in arterial pressure waveform morphology and AIx. This technique derives a pressure signal resulting from the radial expansion of the aorta with the accumulation of blood during systole and the elastic recoil during diastole (arterial reservoir pressure).

Human and animal studies indicate that arterial reservoir pressure and forward-traveling waves make a large contribution to the overall shape of the central pressure waveform (including the augmented pressure component), whereas reflected pressure waves play a very minor role. This theory would seem to be more in keeping with our findings of increased systolic pressure-time integral and wave pressure (probably from cardiac ejection and the forward-traveling wave), as well as reduced diastolic pressure-time integral and arterial reservoir pressure (from aortic recoil and an increase in outflow because of peripheral vasodilation) after dobutamine infusion. There are significant conceptual differences between this new arterial reservoir approach compared with traditional wave theory. This current study was not designed to answer these differences, but our findings underscore the need for further studies to clarify the physiological mechanisms that determine the shape of the arterial pressure waveform.

LV Contractility and AIx

Several cross-sectional studies have reported associations between AIx and crude measures of LV contractility (eg, ejection fraction and systolic tissue velocity). One other human study recorded more sensitive measures of LV systolic function simultaneously with carotid AIx but found no relation. A study in a simulated mathematical model of the human arterial system found a small positive association between LV systolic function (slope of the preload recruitable stroke-work relationship) and the amplitude of the aortic second systolic peak. The vastly different methodologies between this modeling study and that of our own disallow a direct comparison of findings. Importantly, none of the aforementioned investigations examined the effect of changes in LV contractility.

It is well accepted that there is an inverse relationship between AIx and heart rate. However, increased heart rate leads to an elevation of LV contractile force, which may confound this relationship. Although the analogue of LV contractility (peak systolic SR) was associated with AIx across a broad range of heart rates in our current study, when we corrected SR for heart rate, the relationship was no longer significant. Furthermore, neither SR nor heart rate–corrected SR was an independent correlate of AIx on multivariate analysis. Thus, cardiac contractile force does not appear to significantly affect the magnitude of central systolic augmented pressure. Our work may help explain the waveform changes believed to occur with advanced heart failure. In these patients, the central waveform presents as a "pseudo-normal" pattern with a reduction in augmented pressure that is attributed to myocardial weakening. Our results (albeit in a different patient population) suggest that this is likely because of low cardiac output and failure to mount sufficient pressure but not exclusively because of LV contractility, per se.
Limitations

The study population was composed of patients with a range of cardiovascular risk factors, as well as those with LV dysfunction. Although the results were similar between patients with contractile defects compared with those with none (Figure 4), we cannot say whether all of the findings would be reproducible in healthy subjects. Furthermore, central pressure indices have been derived indirectly using a generalized transfer function. The validity of this method has been shown to be robust in response to vasoactive medication that induces peripheral vasodilation and tachycardia. Nonetheless, invasive recordings would have been more accurate, and there is likely to be some error in the estimation of central pressure variables both at rest and after dobutamine infusion. Similarly, the brachial blood pressure measures are likely to have some degree of error, particularly at higher heart rates. Importantly, this will not change the principal findings, because AIx is a relative measure that does not change if the waveform is calibrated with different pressures. It is also possible that, whereas reservoir pressure is principally determined by the large, highly compliant elastic arteries (eg, the ascending aorta), smaller, less elastic and more muscular arteries may additionally contribute to reservoir pressure. However, because the capacitance of these smaller arteries is tiny when compared with the larger elastic arteries, it is likely that their contribution to overall reservoir pressure is small.

Perspectives

Recent reports indicate that central pressure indices, including AIx, have important clinical consequences.2,3,8,9 There is a widely held belief that AIx is influenced by the “pattern of LV contractility,” yet this is the first human study to assess the relationship between LV contractility and AIx in response to hemodynamic perturbations; we found no significant association after correcting for heart rate. Moreover, our findings expose a disparity between the traditional explanation for the shape of the augmented pressure wave (ie, accounted for by reflected pressure waves) and an emerging paradigm (ie, accounted for by the arterial reservoir and forward-traveling waves). More studies are needed to resolve this disparity.

Acknowledgments

We thank Jessica Jackson for her valuable assistance with this project.

Sources of Funding

This study was supported in part by a Centre for Clinical Research Excellence Award (National Health and Medical Research Council, Canberra, Australia). J.E.S. was supported by a National Health and Medical Research Council Australian Clinical Research Fellowship (reference 409940) and a National Health and Medical Research Council Career Development Award (reference 569519). J.E.D. is a British Heart Foundation fellow (FS/05/006) and is supported by the National Institute for Health Research Biomedical Research Centre funding scheme.

Disclosures

J.E.S. has research collaborations with AtCor Medical.

References


