Physiological relationships between central vascular haemodynamics and left ventricular structure

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ABSTRACT

Left ventricular hypertrophy is an independent cardiovascular risk factor. In hypertensives, the pattern of hypertrophy is influenced by central haemodynamic characteristics. Central haemodynamics may also determine physiological differences in left ventricular structure and predispose to particular responses of the left ventricle to pathological increases in load. M-mode echocardiography was used to measure left ventricular diastolic dimension and to estimate left ventricular mass index, relative wall thickness and stroke volume in 159 healthy volunteers aged between 19 and 74 years. Tonometric sphygmography was used to estimate augmentation index, central end-systolic and mean arterial blood pressure. Effective arterial elastance was calculated as the ratio of end-systolic pressure to stroke volume. Left ventricular mass index and relative wall thickness were adjusted for variation in age, sex and blood pressure before analyses. Left ventricular diastolic dimension exhibited significant inverse correlations with both effective arterial elastance ($r = -0.72$, $P < 0.0001$) and augmentation index ($r = -0.23$, $P = 0.004$). Adjusted left ventricular mass index was inversely correlated with effective arterial elastance ($r = -0.35$, $P < 0.0001$), but no correlation was observed between left ventricular mass index and augmentation index ($r = 0.04$). Adjusted relative wall thickness correlated with increasing effective arterial elastance ($r = 0.32$, $P < 0.0001$) and augmentation index ($r = 0.18$, $P = 0.02$). Relative wall thickness ($r = 0.34$, $P < 0.0001$), but not left ventricular mass index, correlated with age. Higher elastance and augmentation correlates with relatively smaller left ventricular cavity size but larger relative wall thickness. Age-related changes in left ventricular afterload may affect relative wall thickness more significantly than left ventricular mass index and may contribute to a particular change in left ventricular geometry with age.

INTRODUCTION

Increased left ventricular afterload is a stimulus for left ventricular hypertrophy, and this association may play a role in the increased cardiovascular risk associated with the presence of left ventricular hypertrophy [1–3]. Traditionally, brachial arterial pressure measurements are used as an indication of left ventricular afterload. However, the pressure profile at the brachial artery differs from that observed in the ascending aorta. Factors such as compliance and elastance of the aorta and amplitude and timing of reflected pressure waves are relevant to the central arterial haemodynamics to which the left ventricle is exposed. Arterial hypertension is associated with a spectrum of left ventricular geometric adaptations matched to
different central haemodynamic profiles [4,5]. Ganau et al. [4] identified four different types of left ventricular geometry within a hypertensive population: normal left ventricular geometry; concentric remodelling with normal left ventricular mass index, but increased relative wall thickness; concentric hypertrophy with increased left ventricular mass index and relative wall thickness; and eccentric hypertrophy with increased left ventricular mass index, but normal relative wall thickness. Ganau et al. [4] also showed that systemic haemodynamics paralleled left ventricular geometry, with the highest peripheral resistance in the groups with concentric remodelling and hypertrophy, whereas cardiac index was supernormal in those with eccentric hypertrophy and low normal in patients with concentric remodelling.

However, the influence on normal cardiac geometry of left ventricular afterload in terms of central arterial compliance, effective arterial elastance and/or reflected pressure waves has not been defined clearly. Such knowledge may help us to further understand important interactions between the ventricle and central vasculature that may be relevant to different geometric patterns of cardiac hypertrophy as a result of increased load.

Aortic impedance, i.e. the relationship between pulsatile pressure and flow in the aorta analysed in the frequency domain [6], is considered the most accurate index of left ventricular afterload, since it comprises the steady-state as well as the pulsatile component of vascular load [6,7]. However, its use in the clinical setting is made difficult by the need for invasive measurements of pressure and flow to integrate data with time-domain or pressure-volume measurements of ventricular function [8–10]. The ratio of stroke volume to pulse pressure is considered a simple, but informative, estimate of total arterial compliance [11–15]. However, the ratio of stroke volume to pulse pressure does not take into account the pulsatile characteristics of blood flow in arteries [7,16], and other investigators [17–20] have suggested the use of effective arterial elastance, estimated as the steady-state ratio of end-systolic pressure divided by stroke volume [8,17].

The pressure wave generated by cardiac contraction is reflected by the peripheral arteries [21]. The augmentation index is a measure of the amplitude of the reflected systolic waveform with respect to the overall pulse pressure, and can be estimated reliably using tonometric sphygmography of peripheral arteries. Alterations in vascular properties (in particular reduced vessel wall compliance) due to aging, hypertension, atherosclerosis and high salt intake increase pulse wave velocity and result in earlier return of reflected waves and increased left ventricular afterload [21–27].

We investigated in healthy subjects the relationship between left ventricular geometry and two non-invasive measurements of left ventricular afterload, effective arterial elastance and augmentation index, to help better understand the ventricular–vascular interaction of potential relevance to the pathogenesis of cardiac hypertrophy.

**METHODS**

**Subjects**

Subjects were drawn from the Victorian Family Heart Study [28], which is a population-based study of the familial patterns of cardiovascular risk factors. The total sample comprised 2959 volunteers from 783 families. Families were recruited without respect to the presence or absence of cardiovascular disease. The aim was to obtain a representative sample of the general population. Each family is composed of a minimum of a mother and father and one natural child. At the time of original recruitment, two age bands were sampled: parents were aged between 40 and 70 years and offspring were aged between 18 and 30 years of age. We invited a random selection of subjects from the Victorian Family Heart Study to participate in this study. A total of 194 volunteers were enrolled. All subjects were seen by a cardiologist and assessed for the presence of cardiac disease (angina, cardiac failure, coronary angioplasty, coronary bypass surgery or valvular disease). Excluded from the analyses were 23 such subjects and two women who were pregnant. In addition, 11 subjects were excluded because of technical difficulties with M-mode echocardiography measurements, and three subjects were excluded because of technically unsatisfactory radial artery waveform recordings. Some subjects had more than one exclusion criteria. The data in this paper are derived from the remaining 159 individuals. These experiments were approved by the Ethics Committee of the Royal Melbourne Hospital, and all participants provided written consent.

**Echocardiography**

The M-mode echocardiographic study of the left ventricle was performed under cross-sectional control with a Hewlett-Packard 2500 or 1000 Echocardiography machine. The mean value of at least three measurements of each dimension of the left ventricle was determined: interventricular septal thickness (IVS), left ventricular diastolic dimension (LVID) and posterior wall thickness (PWT). Penn measurements of the left ventricle (excluding endocardial echoes from wall measurements and including endocardial echoes in left ventricular internal diameter measurements) were taken from M-mode strip chart recordings and applied to the Penn formula [29,30]:

\[
1.04[(\text{IVS} + \text{LVID} + \text{PWT})^3 - \text{LVID}^3] - 13.6
\]

Left ventricular mass was indexed to body surface area to calculate left ventricular mass index. In addition, the
PWT alone and the relative wall thickness (2 × PWT/LVID) were recorded and included in analyses.

Left ventricular volume was estimated by M-mode echocardiography using Teicholz’s correction of the cube method [4,31,32]. This method uses the American Society of Echocardiography (ASE) measurements of left ventricular internal dimensions (leading edge to leading edge):

\[
\text{Volume} = \frac{7}{(2.4 + \text{LVID})} \times \text{LVID}^3
\]

Stroke volume was calculated as the difference between end-diastolic volume and end-systolic volume.

M-mode recordings and linear dimension measurements were made by two of us (J.A.D. and C.M.W.). Measurements of the intra- and inter-observer errors for Penn measurements (average difference divided by the average of the measurements) were 0.5% and 2.5% respectively. A total of 11 subjects were excluded because of technical difficulties with M-mode echocardiographic measurements.

**Pulse wave analysis**

We used the SphygmorCor \(^\text{TM}\) (PWV Medical Pty Ltd, Sydney, Australia) for pulse wave analysis. This system uses radial artery tonometry, calibrated using brachial sphygmomanometry, and a validated generalized transfer function to derive central aortic pressure waveforms [21,24,27]. From pressure waveforms a range of central arterial indices can be calculated, including end-systolic pressure, mean arterial pressure, pulse pressure and augmentation index. One operator performed all measurements. Three subjects were excluded because of technically unsatisfactory radial artery waveform recordings.

The mean arterial pressures calculated by this system are derived from the area under the curve in waveform analysis. Pulse pressure was calculated as systolic pressure minus diastolic pressure, and end-systolic pressure was measured at the time of aortic valve closure (the incisura on the arterial pulse).

Two central arterial haemodynamic characteristics relevant to left ventricular afterload were measured: effective arterial elastance as the ratio of end-systolic pressure to stroke volume \([8,19]\), and augmentation index as the ratio of augmentation pressure to pulse pressure.

In addition, left ventricular elastance was estimated as the ratio of end-systolic pressure to LV end-systolic volume \([8,19]\). The coupling of the left ventricle and central vasculature \([17–20]\) was calculated as the ratio of effective arterial elastance to left ventricular elastance, which simplifies to the ratio of left ventricular end-systolic volume and the stroke volume.

**Statistical analyses**

Summary data are expressed as the median and inter-quartile range, unless specified otherwise. Because not all variables fitted a normal distribution, non-parametric testing of the difference between groups was used (Mann–Whitney U Test). To examine the association between variables, both univariate and stepwise multiple regression techniques were used. Where particular variables such as age, gender and blood pressure exerted significant effect the analyses were adjusted for the influence of these variables in the multiple regression analysis. When left ventricular mass index was the dependent variable in multiple regression analysis only sex and systolic blood pressure emerged as independent variables. Because of the selection from two generations, the age distribution was not continuous, and all analyses were performed separately within generations as well as throughout the population using non-parametric statistics. All statistical analyses were performed using SPSS 8.0 for Windows. Statistical significance was reached when \(P < 0.05\).

**RESULTS**

The basic characteristics of the participants grouped according to sex are shown in Table 1. As expected, females had lower blood pressures, left ventricular mass indexes and stroke volumes than males. However, there was no sex difference in relative wall thickness, and females had higher augmentation indexes, effective arterial elastance and left ventricular elastance than males (Table 1). The ratio of effective arterial elastance and left ventricular elastance was not different between males and females.

Ages ranged from 19 to 74 years of age. Non-parametric correlation analyses revealed that increasing age was associated with higher diastolic \((P = 0.01)\) and systolic \((P = 0.001)\) blood pressures, lower stroke volume \((r = -0.19, P = 0.03)\), higher effective arterial elastance \((r = 0.38, P < 0.0001)\) and left ventricular elastance \((P < 0.0001)\), but no difference in the ratio of effective arterial elastance and left ventricular elastance \((r = 0.05, P = 0.53)\). There was also a strong association between augmentation index and age \((r = 0.63, P < 0.0001)\). While there was no significant correlation between left ventricular mass index and age, both relative wall thickness \((r = 0.34, P < 0.0001)\) and PWT \((r = 0.29, P < 0.0001)\) correlated with age.

Because of significant influences of age, sex and systolic blood pressure, the variables left ventricular mass index, relative wall thickness and augmentation index were adjusted using multiple regression analysis to control for these effects.

**Left ventricular wall thickness and cavity dimensions**

PWT showed a slight, but significant correlation with augmentation index \((r = 0.16, P = 0.04)\) and stroke volume \((r = 0.18, P = 0.02)\), but no significant correlation
Table 1  Cardiovascular phenotypes according to sex
Values shown are medians (interquartile range)

<table>
<thead>
<tr>
<th></th>
<th>Female (n = 90)</th>
<th>Male (n = 69)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>125 (120–130)</td>
<td>130 (120–150)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80 (70–85)</td>
<td>70 (70–80)</td>
<td>0.05</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>22 (14–28)</td>
<td>12 (2–25)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular mass index</td>
<td>59.7 (49.1–73.6)</td>
<td>81.3 (66.8–94.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.24 (0.20–0.29)</td>
<td>0.25 (0.23–0.29)</td>
<td>0.07</td>
</tr>
<tr>
<td>PWT (cm)</td>
<td>0.6 (0.5–0.7)</td>
<td>0.7 (0.6–0.8)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>64.7 (56.4–72.4)</td>
<td>76.8 (64.3–88.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Effective arterial elastance</td>
<td>1.6 (1.1–1.9)</td>
<td>1.3 (1.2–1.7)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Left ventricular elastance</td>
<td>2.8 (2.3–3.5)</td>
<td>2.2 (1.8–2.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ratio of effective arterial elastance to left ventricular elastance</td>
<td>0.6 (0.5–0.7)</td>
<td>0.6 (0.5–0.7)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Figure 1  Scatter diagram of left ventricular mass index adjusted for sex and systolic blood pressure against augmentation index

with effective arterial elastance or left ventricular elastance. Both augmentation index ($r = -0.23, P = 0.004$) and effective arterial elastance ($r = -0.72, P < 0.0001$) correlated inversely with LVID.

**Left ventricular mass index and relative wall thickness**

We found no significant correlation between augmentation index and adjusted left ventricular mass index ($r = 0.04, P = 0.63$; Figure 1.) When augmentation index was adjusted for age, we still found no significant correlation with adjusted left ventricular mass index ($r = -0.24, P = 0.78$). However, both effective arterial elastance ($r = 0.44, P < 0.0001$) and left ventricular elastance ($r = 0.37, P < 0.0001$) correlated significantly with augmentation index. We observed a significant inverse correlation between effective arterial elastance and adjusted left ventricular mass index ($r = -0.35, P < 0.0001$; Figure 2). No significant correlation was found between left ventricular elastance and adjusted left ventricular mass index. We observed a significant

correlation between adjusted left ventricular mass index, stroke volume ($r = 0.46, P < 0.0001$) and left ventricular diastolic dimension ($r = 0.40, P < 0.0001$).
In contrast to left ventricular mass index, relative wall thickness showed a slight, but significant, positive correlation with augmentation index ($r = 0.18, P = 0.02$; Figure 3). We also found a significant positive correlation between relative wall thickness and both effective arterial elastance ($r = 0.32, P < 0.0001$) and left ventricular elastance ($r = 0.36, P < 0.0001$; Figure 4). After adjustment of relative wall thickness for sex and systolic blood pressure, we found an inverse relationship between adjusted relative wall thickness, stroke volume ($r = -0.21, P = 0.007$) and left ventricular diastolic dimension ($r = 0.32, P < 0.0001$).

**DISCUSSION**

Increased left ventricular afterload is a stimulus for left ventricular hypertrophy, and this association may play a role in the increased cardiovascular risk associated with the presence of left ventricular hypertrophy [1,2]. Understanding the contribution of afterload to left ventricular adaptation (including the different geometric variants of hypertrophy) may be of clinical relevance. If afterload phenotypes were found to predict the structural characteristics of the left ventricle, then reliable non-invasive techniques to estimate afterload may be useful in population screening of cardiovascular risk for both clinical and research purposes.

We observed the expected correlations between arterial pressure and left ventricular size and geometry that in large part reflect the afterload associated with systemic vascular resistance. However, other afterload characteristics, such as the reflected pressure waves (as assessed by augmentation index) and the physical nature of the large vessels (as assessed by effective arterial elastance), may also be important. Our observations reveal an increase in effective arterial elastance and augmentation index with age, as reported by others [21,23,33], which is likely to indicate reduced compliance of the large vessels and increases in the pulse wave velocity and degree of pressure wave reflection. However, after adjustment for age, sex and blood pressure, we found no positive correlation between left ventricular mass index and either effective arterial elastance or augmentation index. In fact, greater effective arterial elastance was associated with a lower left ventricular mass index, and greater effective arterial elastance and augmentation index were associated with smaller left ventricular cavity diastolic dimensions. However, when we investigated left ventricular wall thickness relative to cavity size we found that greater afterload in the form of either effective arterial elastance or augmentation index was associated with significant increases in the thickness of the left ventricular wall relative to cavity size, independent of age, sex and blood pressure.

These observations are consistent with the idea that the response of normal ventricles to increases in effective arterial elastance and augmentation index is predominantly via remodelling to provide a thicker wall at the expense of the left ventricular cavity, but with no increase in left ventricular mass. This is analogous to the adaptation seen in response to isometric resistance exercise [34]. The unexpected observation was that increased afterload in the form of effective arterial elastance correlated with lower left ventricular mass index. However, from a different perspective, in normal subjects more compliant large vessels are associated with greater left ventricular mass index. Moreover, there was a strong correlation between greater compliance (reduced elastance) and the diastolic dimensions of the left ventricular cavity. It is possible that, within the bounds of normal physiological variation, the most effective coupling between left ventricle and arteries is one of larger cavity dimensions (with a slight increase in left ventricular mass index) with compliant arteries, where the left ventricle can deliver larger stroke volume without significant pressure loads. This is analogous to the adaptation seen in response to dynamic aerobic exercise [34–36].

There are interesting parallels between our findings in normal subjects and those reported in patients with hypertension. Ganau et al. [4] found that hypertensive patients with concentric remodelling of the left ventricle (increased relative wall thickness and normal left ventricular mass index) had a relatively higher peripheral resistance and lower cardiac index. Our findings in a normal population show that higher relative wall thickness is found in participants with higher elastance and lower stroke volume. In addition, Ganau et al. [4] found that hypertensive patients with eccentric hypertrophy of the left ventricle (increased left ventricular mass index and normal relative wall thickness) had supernormal cardiac indexes and relatively lower peripheral resistance. Our findings in a normal population show that higher
left ventricular mass index is found in participants with lower elastance and higher stroke volume.

Another relevant finding was the strong effect of age on both measures of left ventricular afterload and relative wall thickness, as opposed to the lack of significant correlation of age with left ventricular mass index. This suggests that age-related changes in left ventricular afterload (increased elastance and increased augmentation of the systolic waveform) may cause a specific pattern of changes in left ventricular geometry, affecting relative wall thickness rather than left ventricular mass index.

In summary, our findings suggest that in a healthy cross section of the population physiological variation in effective arterial elastance and augmentation may determine particular patterns in left ventricular geometry. They may also explain the lack of correlation between left ventricular mass index and augmentation index, and why left ventricular mass index does not increase with age, despite increased reflection of pressure waves and augmentation of the systolic waveform.

ACKNOWLEDGMENTS

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