The effects of blood pressure reduction on abnormal left ventricular diastolic function in hypertensive patients

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To investigate whether reduction in blood pressure has a beneficial effect on left ventricular diastolic function, we investigated 20 hypertensive patients with evidence of diastolic dysfunction at baseline and at 3 and 6 months after initiation of captopril therapy. Two-dimensional echocardiography was used to determine left ventricular mass index and Doppler ultrasound to assess diastolic function.

Fifteen of the 20 patients had a significant reduction in blood pressure at 3 and 6 months and left ventricular mass index remained unchanged during the study period. Despite reduction in blood pressure, no difference in isovolumic relaxation time, early and atrial filling velocities or their ratio was observed. Our results suggest that a direct relationship between blood pressure and left ventricular diastolic function does not exist and that other factors such as alterations in muscle or collagen composition of the left ventricle may be more important in determining abnormal diastolic function in hypertension.

Introduction

It has become apparent that abnormalities of left ventricular diastolic function are common in patients with essential hypertension[1,3]. Such abnormalities frequently occur in patients with mild or borderline hypertension[4] and often prior to the onset of left ventricular hypertrophy[5]. Moreover, these abnormalities may represent early markers of left ventricular systolic failure, a common complication in hypertensive patients, which carries high morbidity and mortality[6]. Whilst it is not yet known whether diastolic dysfunction is an independent risk factor in hypertension, it has been proposed that reversal of these abnormalities may prevent progression to hypertensive heart failure.

The cause of abnormal diastolic function in hypertension is not fully understood. Several investigators have shown that both blood pressure and/or left ventricular hypertrophy are important determinants[7-11], but others have failed to show any significant relationship with these parameters[5,12]. Such conflicting reports may, in part, be due to the difference in techniques used to assess diastolic function and the heterogeneous groups of hypertensive patients studied. There has also been a broader appreciation that age in itself has an important influence on diastolic function[13].

In animal experiments, it has been shown that when blood pressure is acutely increased, the time constant of the left ventricular pressure decline (tau) also increases, which in turn decreases the early left ventricular diastolic filling rate. To compensate for this action, the atrial contribution to left ventricular filling is increased[14,15]. These findings are analogous to those observed in chronic hypertensive patients and therefore reduction in blood pressure may potentially reverse these abnormalities.

There has been much recent interest in the use of Doppler ultrasound to examine transmitral flow velocities to provide a useful non-invasive method for assessing left ventricular diastolic function in man[16,17]. This technique has been validated with haemodynamic indices of diastolic function[18] and compares favourably with cine-angiographic[19] and radionuclide techniques[20]. It has therefore become possible safely to investigate patients with asymptomatic diastolic dysfunction over long periods. Furthermore, transmitral flow velocities have been shown to have a low day-to-day variability and to be highly reproducible[21,22].

The aim of the present study was to investigate whether reduction in blood pressure in hypertensive patients with abnormal left ventricular diastolic function, has a beneficial effect on left ventricular diastolic function.

Methods

PATIENT POPULATION

Patients attending the hypertension clinic who satisfied the following inclusion criteria were recruited into the study: (a) patients with essential hypertension who had either never been previously treated or whose blood pressure was uncontrolled on existing anti-hypertensive therapy (BP > 160/90) (b) normal haematological and biochemical indices (c) normal systolic function (fractional shortening) determined by two-dimensional echocardiography (d) no evidence of valvular stenosis or regurgitation determined by Doppler ultrasound (e) abnormal Doppler indices of left ventricular diastolic function (below the normal age related reference values[23,24]) and (f) high quality echocardiograms and Doppler recordings.
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Figure 1  Two-dimensional technique for the determination of left ventricular mass. Upper left: apical four chamber view; upper right: length of left ventricle from mitral annulus to epicardial and endocardial borders; lower left: parasternal short axis view; lower right: planimetered epicardial and endocardial areas. See text for method of calculation.

ECHOCARDIOGRAMS

Each subject underwent two-dimensional and Doppler echocardiography at baseline, 3 and 6 months using a phased array sector scanner (General Electric Pass II, 3·5 MHz transducer) with the patient examined in the left lateral supine position using a standardized examination protocol. Left ventricular septal, posterior wall thickness and cavity dimensions were measured from parasternal left ventricular short axis projections at the chordae and papillary muscle junction using two-dimensionally guided M-mode echocardiography. Left ventricular mass was determined using an area x length method which has been previously validated in man\textsuperscript{[25, 26]} with all measurements taken at end diastole and at end expiration. Two echocardiographic views are required to make this calculation: a parasternal short axis view of the left ventricle at the papillary muscle tip level to determine the area of the myocardium and an apical four-chamber view that maximizes the distance from the mitral valve annulus to the left ventricular apex to determine the length of the ventricle (Fig. 1). The following algorithm is then used to calculate left ventricular mass:

\[ \text{LV mass} = 1·04 \left( \frac{5}{6} A_1 \times l_1 - \frac{5}{6} A_2 \times l_2 \right) \]

where \(A_1\) and \(A_2\) represent the epicardial and endocardial areas planimetered respectively and \(l_1\) and \(l_2\) the length of the left ventricle from mitral annulus to epicardial and endocardial borders respectively. Left ventricular mass index is then determined by dividing left ventricular mass by the patient's body surface area.

DOPPLER STUDIES

Pulsed Doppler examination of transmitral flow was recorded from the apical four chamber view with reference to the two dimensional echocardiographic image. The sample volume was positioned between the mitral annulus and the tips of the mitral leaflets with the position adjusted to maintain the sample volume at an angle as near parallel to transmitral flow as possible by using the audible signal and spectral velocity display. When the maximum transmural velocity for the early filling wave was detected, the velocity profile was recorded at 50 mm/s, with the patient in passive end expiration. The peak flow velocity of the early and atrial waves were measured from the three consecutive cardiac cycles displaying the highest measurable velocity profiles. In addition, early filling time, atrial filling time, acceleration time, deceleration time and flow velocity integral for both early and atrial filling waves were measured (Fig. 2).

The isovolumic relaxation time was measured from the apical five chamber view by placing the continuous wave Doppler beam between the mitral and aortic valve junction. The time interval between the end of the aortic velocity envelope and the onset of the early filling wave was taken to represent the isovolumic relaxation time.

DRUG THERAPY

After baseline echocardiographic and Doppler studies were performed, each patient was commenced on captopril 12.5 mg twice daily. The dose was increased at four weekly intervals to a maximum of 50 mg twice daily.
with the addition of a diuretic (bendrofluazide 5 mg) until adequate blood pressure control was obtained. Blood pressure was measured at each visit using an automated sphygnomomanometer after the patient had been seated for at least 10 min. Readings were performed by a clinic nurse experienced in the management of these patients. The average dose of captopril was 85 mg, day⁻¹ with 12 patients requiring the addition of a diuretic.

The study protocol was approved by the hospital ethics committee and informed consent was obtained from all patients.

**ANALYSIS OF DATA**

Data are expressed as means± standard deviation. Statistical analysis was performed by Student’s two-tailed t-test for paired data. A P value of less than 0.05 was considered to be significant.

**Results**

Twenty patients (mean age 48 years, range 32–68 years) fulfilled the inclusion criteria for the study. There were 13 males and seven females; the mean duration of hypertension was 5 years (range 4 months–11 years). Ten patients had never been treated before and 10 were uncontrolled on existing anti-hypertensive therapy. Twelve of the patients were caucasian and eight were black.

**BLOOD PRESSURE**

Five of the 20 patients (three black and two caucasian) had blood pressures that failed to respond to the regimen of anti-hypertensive therapy and were removed from the analysis. Of the remaining 15 patients, systolic, diastolic and mean blood pressures at baseline were 173±25, 97±17 and 106±15 mmHg respectively and fell significantly at 3 months 156±15, 95±8, 115±9 (P<0.001) and 6 months 142±13, 88±9, 106±9, (P<0.001) after initiation of captopril therapy. There was no significant change in heart rate with captopril therapy (baseline 70±12, at 3 months 68±8 and 6 months 73±11 beats min⁻¹).

**LEFT VENTRICULAR HYPERTROPHY**

The mean left ventricular mass index at baseline of the 15 patients who responded to anti-hypertensive therapy was 127±8±27 g. m⁻² (range 74–180) and did not change significantly at 3 months (130±8±31.7) or at 6 months (125±2±27.4). There was no significant change in left ventricular septal wall thickness, posterior wall thickness or left ventricular cavity diameter from baseline (1·26±0·26, 0·98±0·22, 4·66±0·59 respectively) at 3 months (1·26±0·21, 0·88±0·21, 4·65±0·48) or at 6 months (1·20±0·23, 1·03±0·24, 4·5±0·42).

**DOPPLER RESULTS**

Baseline Doppler indices of left ventricular filling (mean E/A ratio 1·01, range 0·57–1·68) in our patients were all below the normal age-related reference values established by previous investigators[P, 124]. The E/A ratio of patients between the ages of 20 and 30 years was less than 1·7, between 31 and 50 years was less than 1·5, between 51 and 60 years was less than 1·3 and between 61 and 70 years was less than 1·0. No significant change was observed at baseline, 3 months or 6 months in (a) isovolumic relaxation time (117·9±33, 116·7±32 and 110·7±28 ms) (b) early peak flow velocity (55±12, 55±14 and 56±13 cm s⁻¹) (c) atrial peak flow velocity (59±13, 58±11 and 60±12 cm s⁻¹) or (d) the E/A ratio (1·00±0·35, 0·98±0·31 and 0·95±0·26) although there was considerable individual variation (Fig. 3).

Of the other indices of transmural flow velocities a significant increase in the acceleration time of the early filling wave was observed at 3 months (75·1±14·6 at baseline, 82·9±14·4 at 3 months P<0·05) but not at 6 months (70·7±8·2). There was no difference from baseline in the early deceleration time, flow velocity integral, early filling time, atrial acceleration/deceleration time, atrial flow velocity integral or atrial filling time at 3 and 6 months (Table 1).

Patients were also stratified according to race and prior anti-hypertensive therapy but no significant difference was noted in the left ventricular filling response comparing these subgroups.

**Discussion**

The principal finding of this study is that in hypertensive patients with abnormal left ventricular diastolic function and normal systolic function, reduction in blood pressure does not improve Doppler indices of diastolic function over a 6-month period.

**BLOOD PRESSURE**

Captopril therapy significantly reduced systolic and diastolic blood pressure at the 3- and 6-month
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Figure 3  Changes in individual patients of isovolumic relaxation time (top left), early filling velocity (top right), atrial filling velocity (bottom left) and E/A ratio (bottom right) from baseline and at 3 and 6 months following captopril therapy.

Table 1  Doppler parameters (mean, SD) at baseline and at 3 and 6 months

<table>
<thead>
<tr>
<th></th>
<th>0 months</th>
<th>3 months</th>
<th>6 months</th>
</tr>
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<tbody>
<tr>
<td>Early filling wave</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceleration time</td>
<td>75 (15)</td>
<td>83 (14)*</td>
<td>71 (8)</td>
</tr>
<tr>
<td>Deceleration time</td>
<td>162 (48)</td>
<td>148 (34)</td>
<td>162 (32)</td>
</tr>
<tr>
<td>Flow velocity integral</td>
<td>6.8 (2.5)</td>
<td>7.5 (2.3)</td>
<td>7.1 (2.1)</td>
</tr>
<tr>
<td>Filling time</td>
<td>227 (40)</td>
<td>236 (42)</td>
<td>233 (37)</td>
</tr>
<tr>
<td>Atrial filling wave</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceleration time</td>
<td>65 (14)</td>
<td>65 (8)</td>
<td>68 (17)</td>
</tr>
<tr>
<td>Deceleration time</td>
<td>74 (20)</td>
<td>78 (18)</td>
<td>78 (15)</td>
</tr>
<tr>
<td>Flow velocity integral</td>
<td>5.1 (2.1)</td>
<td>5.3 (1.7)</td>
<td>5.4 (2.1)</td>
</tr>
<tr>
<td>Filling time</td>
<td>143 (23)</td>
<td>148 (15)</td>
<td>147 (20)</td>
</tr>
</tbody>
</table>

*P<0.05.

Doppler study periods in 15 of the 20 patients studied. This is similar but slightly less than previous studies which have shown an efficacy of 80–90% with a combination of captopril and diuretic therapy[27,28]. The slight difference may be due to the number of black hypertensives recruited into our study who are known to respond less effectively to ACE inhibition therapy than white hypertensives[29].

LEFT VENTRICULAR HYPERTROPHY

Left ventricular mass did not change in the group during the 6-month study period and therefore it was possible to assess solely the effect of reduction in blood pressure on left ventricular diastolic function. The lack of regression of left ventricular hypertrophy at 6 months is in accord with some previous investigators who were also unable to show regression within this time period with captopril therapy[30,31] but not with others who have shown regression as early as 4 months[32]. Possible explanations for the variance of these reports may have been due to different severities of left ventricular hypertrophy being present in the various study populations; patients who have a higher left ventricular mass are more likely to show regression than those with a left ventricular mass in the normal range. However, another explanation may have been the different methods used to measured left ventricular mass. Most investigators have reported an M mode echocardiographic technique (with two-dimensional guidance) which requires measurement of septal and
posterior wall thickness and internal diameter of the left ventricle; this has to be determined and then cubed in a formula to calculate left ventricular mass. However, in our study, we used a two-dimensional technique which requires the length and cross-sectional area of the left ventricle to be determined and subsequently multiplied in a formula to calculate left ventricular mass. The latter method overcomes the problem of small measurement inaccuracies contributing disproportionate weight to the calculation and has also been shown to have a lower intra and inter observer error and day to day variability when compared to the M mode technique\[33\].

**DOPPLER INDICES**

Changes in transmitral filling velocities have been previously observed both in human and animal studies during alterations in loading conditions\[34,35\]. The antihypertensive effect of captopril is predominantly due to a reduction in peripheral vascular resistance which affects afterload and to a lesser extent preload\[36\]. In our study, we were unable to demonstrate any significant change in the isovolumic relaxation time, early and atrial peak flow velocities or their ratio at 3 or 6 months despite significant reduction in blood pressure. This is in keeping with the study of Inouye et al.\[37\] who were also unable to demonstrate any changes in left ventricular filling in hypertensive patients treated with diuretics, \( \beta \)-blockers or calcium channel blockers. However, other studies have shown some improvement in early filling velocities with combined \( \alpha \) and \( \beta \) adrenergic blockade\[38\], long acting ACE-inhibitors\[39\] and with intravenous verapamil\[40\]. The majority of these studies, however, have employed smaller study populations and have not provided details of whether changes in heart rate, which are known to profoundly affect Doppler indices of transmitral flow\[41\], occurred in their patients after administration of antihypertensive medication.

Of the other Doppler indices or left ventricular diastolic function, the deceleration time of the early filling wave has been shown to be a sensitive indicator of abnormal left ventricular compliance\[42\]. In our hypertensive patients, decreasing blood pressure did not alter the deceleration time of the early filling wave at the 3 and 6 month study period suggesting that reducing afterload in hypertensive patients has little effect on left ventricular compliance. This finding is further supported by the studies of Colan et al.\[43\] and Smith et al.\[44\] who were unable to show changes in left ventricular diastolic function in normal subjects when blood pressure was acutely increased. The significant increase in acceleration time of the early filling velocity observed at 3 months but not at 6 months is most likely due to chance when multiple t tests are performed rather than being directly attributable to any change in diastolic filling.

The results of this study suggest that a direct relationship between blood pressure and left ventricular diastolic function does not exist in hypertensive patients. One explanation may be that during the early stages of hypertension, alterations in the matrix composition of the pressure-overloaded left ventricle occur (i.e. changes in muscle and collagen) which result in a decrease in left ventricular compliance and abnormal diastolic function. Reduction in blood pressure without concomitant change in cardiac structure may therefore have no significant effect on diastolic function.

**LIMITATIONS OF THE STUDY**

One of the limitations of our study was the inclusion of both untreated hypertensive patients and those with inadequately controlled blood pressure being grouped together as a homogeneous group. The patients who had been on previous anti-hypertensive therapy may well have already altered their diastolic function and therefore further changes may not have occurred. However, subgroup analysis comparing the untreated and previously treated patients did not show any difference in left ventricular diastolic function. Another limitation was that left ventricular preload may have been altered by ACE-inhibitor therapy and masked changes in left ventricular filling caused by blood pressure reduction. Although, this cannot be ruled out in our study there is evidence from Cody and colleagues\[45\] that both pulmonary artery and pulmonary wedge pressures are unaltered after administration of ACE-inhibitor therapy in patients with hypertension. Lastly, coronary artery disease, which also gives rise to abnormal diastolic function, was excluded on clinical history, by resting electrocardiogram and with two-dimensional echocardiography rather than by exercise testing or invasive techniques. Therefore the possibility of occult coronary artery disease could not be excluded in our patients.

In summary, we have shown that in hypertensive patients with abnormal left ventricular diastolic function, reduction in blood pressure has no effect on Doppler indices of diastolic function. Other factors such as left ventricular mass, collagen content, small vessel coronary artery disease or as yet unknown factors may be more important in determining abnormal diastolic function in hypertensive patients.

**References**


