Effects of blood pressure lowering and metabolic control on systolic left ventricular function in Type II diabetes mellitus

Niels H. ANDERSEN*, Steen H. POULSEN†, Per L. POULSEN*, Søren T. KNUDSEN*, Kjeld HELLEBERG‡, Klavs W. HANSEN§, Dines S. DINESEN*, Hans EISKJÆR†, Allan FLYVBJERG* and Carl E. MOGENSEN*

*Medical Department M (Diabetes and Endocrinology) and The Medical Research Laboratories, Aarhus University Hospital, DK-8000 Aarhus C, Denmark, †Department of Cardiology, Aarhus University Hospital, DK-8000 Aarhus C, Denmark, ‡Department of Internal Medicine, Viborg County Hospital, DK-8800 Viborg, Denmark, and §Department of Internal Medicine, Silkeborg Hospital, DK-8600 Silkeborg, Denmark

ABSTRACT

Decreased left ventricular long-axis function may be the earliest stage in subclinical heart failure in Type II diabetes. To assess whether a decrease in SBP (systolic blood pressure) or a change in metabolic control would improve the long-axis function, 48 Type II diabetic patients participating in the CALM II (Candesartan and Lisinopril Microalbuminuria II) study were included in the present study. Patients were examined with tissue Doppler echocardiography at baseline and after 3 and 12 months of follow-up. Corresponding blood pressure, fructosamine and HbA1c (glycated haemoglobin) values were obtained. During the follow-up period, a decrease in SBP of 8 mmHg was seen (from 141±11 mmHg at baseline to 133±12 mmHg; P<0.001) and the peak systolic strain rate was significantly improved (from −1.10±0.25 at baseline to −1.25±0.22; P<0.01). There was a highly significant relationship between the changes in systolic strain rate, HbA1c (P<0.001) and fructosamine (P<0.05), and similarly to changes in left ventricular mass (P<0.05), whereas the correlation to the SBP reduction was not significant. Patients with improved glycaemic control, defined as a reduced HbA1c value after 12 months of follow-up, had a significantly improved strain rate (from −1.07±0.3 s−1 at baseline to −1.32±0.25 s−1; P<0.01) compared with patients with increases in HbA1c (from −1.14±0.25 s−1 at baseline to −1.16±0.27 s−1; P=not significant). The two groups had comparable baseline values of SBP, left ventricular mass, age and disease duration. In conclusion, changes in left ventricular systolic long-axis function are significantly correlated with changes in left ventricular mass, as well as metabolic control, in hypertensive patients with Type II diabetes mellitus.

INTRODUCTION

There is a close association between the incidence of congestive heart failure and Type II diabetes [1]. The Type II diabetic patient is far more susceptible to the development of heart failure, i.e. due to the close relationship to hypertension, left ventricular hypertrophy and coronary artery disease. Type II diabetic patients with congestive heart failure have far worse prognoses [2]. Subclinical changes in left ventricular function already appear in the earliest stages of Type II diabetes mellitus [3]. Until recently, the main focus has been on the diastolic

Key words: cardiomyopathy, congestive heart failure, hyperglycaemia, hypertension, systole, Type II diabetes, ventricular function.

Abbreviations: AGE, advanced glycation end-product; A-wave, peak atrial filling velocity; BP, blood pressure; CALM II, Candesartan and Lisinopril Microalbuminuria II; CV, coefficient of variance; DT, deceleration time; E-wave, peak early mitral inflow velocity; E/A ratio, E-wave/A-wave; HbA1c, glycated haemoglobin; LV, left ventricular; LVEF, LV ejection fraction; NS, not significant; SBP, systolic BP; UACR, urinary albumin creatinine ratio; Vp, velocity flow propagation.

Correspondence: Dr Niels Andersen (email holmark@ki.au.dk).
properties of the left ventricle [4,5], but new data using tissue Doppler imaging have documented impaired systolic long-axis function in patients without cardiac symptoms as well as in patients with normal LVEF [LV (left ventricular) ejection fraction] [3,6,7].

The pathophysiological mechanism responsible for long-axis myocardial dysfunction is unresolved, but it seems likely that the presence of hypertension and LV hypertrophy may have a significant impact on LV long-axis function [8]. In addition, chronic hyperglycaemia may also contribute to diabetic vascular complications [8,9]. These could be caused by the formation of AGEs (advanced glycation end-products), i.e. irreversibly formed biochemical end-products of non-enzymatic glycation. AGEs appear to be closely related to a decrease in systolic function [10].

Since only cross-sectional data are available, it is still not clear whether decreased systolic long-axis function is a chronic and unchangeable phenomenon, or possibly changeable by BP (blood pressure) lowering or improved glycaemic control. Therefore the aim of the present study was to investigate the influence of BP lowering, LV mass reduction and changes in the blood glucose homoeostasis on systolic long-axis function of the left ventricle.

**METHODS**

**Patients**

The CALM II (Candesartan and Lisinopril Microalbuminuria II) study investigated over a follow-up period of 12 months the effects of dual blockade with lisinopril (20 mg/day) and candesartan (16 mg/day) compared with lisinopril alone (40 mg/day) on SBP (systolic BP) in hypertensive patients with diabetes mellitus [11]. Seventy-five patients were enrolled in the CALM II study (dual blockade with candesartan cilexetil and lisinopril in patients with diabetes mellitus) and, out of these, we included 48 Type II diabetic patients who had all completed 12 months of follow-up. Ineligible patients for this sub-study were Type I diabetic patients (n = 13), patients with LVEF < 55 % or fractional shortening < 25 % as evaluated by echocardiography (n = 3), patients with angina pectoris, dyspnoea or prior myocardial infarction (n = 2), and patients with chronic obstructive lung disorder, atrial fibrillation or poor image quality (n = 4). Five eligible patients were excluded per protocol (three with SBP > 160 mmHg despite active treatment, and two due to hyperkalaemia). The effect on SBP was similar in the two treatment regimes [11].

The study was conducted in accordance with the Helsinki II Declaration and was approved by the Local Ethics Committee. All participants gave written informed consent. The study followed good clinical practice rules and regulations.

**Echocardiography**

All patients underwent an echocardiographic examination by the same observer at baseline and at 3 and 12 months of follow up. The echocardiographic examination was performed before any clinical data were obtained (BP measurements and blood sampling) thereby blinding the observer. Also all post-hoc off-line analyses were done in a blinded manner and in a random order.

The echocardiography examinations were performed on a GE Vivid Five ultrasound machine (GE Medical System) with a 2.5 MHz transducer.

LV mass was estimated according to the recommendations of the American Society of Echocardiography, based on the average of five measurements of LV diameters and wall thickness. When optimal orientation of LV M-mode recordings could not be obtained, correctly oriented linear dimension measurements were made using two-dimensional imaging [12]. LV hypertrophy was defined as > 51 g/m² in men and > 47 g/m² in women [13].

LV geometry was assessed by measuring relative wall thickness, which is the ratio between wall thickness and LV cavity dimension (2 x posterior wall thickness/LV diastolic diameter). LV volumes and ejection fraction were estimated using Simpson’s modified biplane method, based on three measurements. LV mass and volume measurements were corrected for body surface. Endocardial border detection was enhanced by use of second harmonic imaging.

Pulsed Doppler measurements were obtained with the transducer in the apical four-chamber view, with the Doppler beam aligned perpendicularly to the plane of the mitral annulus. The sample volume was placed between the tips of the mitral leaflets. Five consecutive beats during quiet respiration were used for calculating the Doppler variables.

Assessment of colour M-mode flow propagation recordings was performed in the apical four-chamber view and with the M-mode cursor aligned in parallel with the LV inflow. Adjustments were made to obtain the longest column of flow from the mitral annulus to the apex of the left ventricle. The M-mode cursor was positioned through the centre of the inflow to avoid boundary regions. Vp (velocity flow propagation) was measured as the slope of the first aliasing velocity (41 cm/s) from the mitral annulus in early diastole to 4 cm distally into the ventricular cavity [14]. This method has a reproducibility index of 0.93–0.97, superior to most other indices of diastolic function [15].

Diastolic filling was classified on the basis of the mitral inflow Doppler parameters and colour M-mode flow propagation. Normal filling was indicated by an E-wave (peak early mitral inflow velocity) DT’ (deceleration time) ≥ 140 ms and < 240 ms, an E/A ratio [E-wave/A-wave (peak atrial filling velocity) ratio] between 1 and 2, and a Vp ≥ 45 cm/s. Abnormal filling was defined as an E-wave DT’ > 240 ms and an E/A ratio < 1. Pseudonormal filling
was indicated by $E$-wave DT $\geq 140$ ms and $< 240$ ms with a $V_p < 45$ cm/s. An $E$-wave DT $< 140$ ms was suggestive of a restrictive filling pattern. The cut-offs were chosen on the basis of recent recommendations [14,16].

**Tissue Doppler imaging**

Tissue Doppler imaging was obtained from the four- and two-chamber apical views and the apical long-axis view during end-expiration apnoea. The peak systolic strain rate was assessed as a mean of the values obtained from three consecutive heart cycles.

The peak systolic strain rate in each segment was assessed as the lowest value between the R-wave in the ECG and closure of the aortic valve. Timing of the aortic valve closure was defined by a curved anatomical M-mode recording placed through the aortic valve leaflets in the apical long-axis view. Strain rate was measured in the centre and basal one-third of each myocardial segment. The sample point was enlarged to $9 \times 9$ pixels, and Doppler scanning frame rates were kept between 140 and 160 frames/s. The left ventricle was divided into 16 segments equal to the wall motion score analysis and the tissue Doppler measurements for each segment were assessed [17]. The intra- and inter-observer variability of the strain rate measurements was $9 \pm 7$ and $18 \pm 14$ % respectively. The S.D. of the absolute difference in strain rate for one observer was $0.08$ s$^{-1}$ [17].

**BP**

At each visit, seated BP was measured at trough levels after 15 min of rest with sphygmomanometry using an appropriate cuff. BP was measured three times, after which a mean was calculated.

**Fructosamine, HbA$_1c$ (glycated haemoglobin) and urinary albumin excretion**

Fructosamine was estimated in all cases at the Medical Research Laboratories, Institute of Experimental Clinical Research, Aarhus University Hospital, Aarhus, Denmark, using a commercially available kit (Pentra fructosamine; ABX) based on the tetrazolium method. The intra-assay CV (coefficient of variance) was $< 5$ %. All HbA$_1c$ measurements were done by the Department of Clinical Chemistry, Aarhus University Hospital, Aarhus, Denmark, using routine HPLC. The intra-assay CV was also $< 5$ %.

The UACR (urinary albumin creatinine ratio) was determined by an immunoturbidimetric method (Roche Diagnostics).

The changes in blood glucose metabolism were purely observational since the antidiabetic treatment was unaltered by the investigators. This was attended to by the patient’s general practitioner or endocrinologists unrelated to the project. If case-optimized treatment was necessary, increased dosing of the drugs was performed. No patients changed the type of treatment (i.e. metformin to insulin).

**Statistical analysis**

All values are expressed as means $\pm$ S.D., unless otherwise indicated. Student’s $t$ test was used for continuous variables and $\chi^2$ test for categorical variables. Serial changes in LV systolic and diastolic function were assessed with repeated measurements ANOVA, Simple (Spearman) linear regression analysis was used to determine any correlations. $P < 0.05$ was considered statistically significant.

Analysis of dichotomized data (treatment and increase/decrease in HbA$_1c$) needed a sample size estimate of 34 participants. This was to obtain a probability of 80 % that the study will detect a treatment difference at a two-sided 5 % significance level if the true difference between the variables is one S.D.

**RESULTS**

All demographic data are shown in Table 1. SBP in the overall population was reduced significantly ($P < 0.001$) by 8 mmHg within the 12 months of follow-up (Table 2),
N. H. Andersen and others

Table 2 Changes in BP, metabolic control and LV systolic function and geometry over time

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>141 ± 11</td>
<td>130 ± 12</td>
<td>133 ± 12</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83 ± 9</td>
<td>80 ± 8</td>
<td>82 ± 8</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3 ± 0.2</td>
<td>8.2 ± 0.1</td>
<td>8.2 ± 0.1</td>
</tr>
<tr>
<td>Fructosamine (µmol/l)</td>
<td>289 ± 57</td>
<td>267 ± 57</td>
<td>298 ± 64</td>
</tr>
<tr>
<td>Left atrial diameter (cm)</td>
<td>4.4 ± 0.4</td>
<td>4.4 ± 0.3</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>4.7 ± 0.7</td>
<td>4.7 ± 0.7</td>
<td>4.8 ± 0.6</td>
</tr>
<tr>
<td>LV systolic diameter (cm)</td>
<td>3.1 ± 0.6</td>
<td>3.2 ± 0.7</td>
<td>3.2 ± 0.6</td>
</tr>
<tr>
<td>Septal wall thickness (cm)</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>1.1 ± 0.3</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>222 ± 70</td>
<td>193 ± 67</td>
<td>233 ± 65</td>
</tr>
<tr>
<td>Relative wall thickness (cm)</td>
<td>0.49 ± 0.16</td>
<td>0.44 ± 0.14</td>
<td>0.47 ± 0.12</td>
</tr>
<tr>
<td>Mean peak systolic strain rate</td>
<td>1.10 ± 0.25</td>
<td>1.12 ± 0.20</td>
<td>1.25 ± 0.22*</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>36 ± 9</td>
<td>34 ± 8</td>
<td>34 ± 9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61 ± 5</td>
<td>62 ± 5</td>
<td>62 ± 5</td>
</tr>
</tbody>
</table>

whereas DBP (diastolic BP) remained unchanged \(P = \text{NS} \) (not significant; Table 2). The reduction in SBP was not significantly different between the two groups (mean reduction at final follow-up, 6 mmHg for dual blockade compared with 8 mmHg for lisinopril). The mean difference between the treatment at follow-up was 0.1 mmHg (95 % confidence intervals, –6 to 6 mmHg; \(P = 0.55 \)). Seated DBP was also unchanged at follow-up (mean reduction at final follow-up, 0 mmHg for dual blockade compared with 1 mmHg for lisinopril; \(P = 0.51 \)).

There was a tendency towards a reduction in left atrial size, LV mass and relative wall thickness after 3 months of therapy \((0.05 < P < 0.10)\), but after 12 months the mean values were similar to that at baseline (Table 2). At baseline, 38 % of patients had LV hypertrophy, which was unchanged at 3 months of follow-up. However, the number of patients with LV hypertrophy increased non-significantly to 46 % at 12 months of follow-up. Heart rate, urine albumin/creatinine ratio and body mass index also remained unchanged (results not shown).

There was no difference between the two antihypertensive treatments regarding changes in systolic and diastolic function, and all additional analyses are based on the total population.

**Systolic long-axis function**

Negative strain rates were found in all myocardial segments. The mean strain rate did not improve significantly after 3 months, but was significantly improved after 12 months of follow-up, both compared with the mean value at baseline and after 3 months. In a multiple stepwise linear regression, there was no significant correlation between the changes in SBP at follow-up and the changes in strain (strain rate compared with SBP: \(r = 0.16; P = \text{NS} \)). However, there was a significant correlation between the changes in LV mass and systolic strain rate between baseline and 12 months of follow-up \((r = 0.34, P = 0.022 \) (Figure 1).

The changes in HbA1c from baseline to 3 months of follow-up were not significantly correlated with systolic strain rate \((\text{HbA1c: } r = 0.23, P = \text{NS} \); fructosamine: \(r = 0.015, P = \text{NS} \)). However, there was a significant correlation between the changes in HbA1c, fructosamine and systolic strain rate between baseline and 12 months of follow-up \((\text{HbA1c: } r = 0.35, P < 0.01; \text{fructosamine: } r = 0.40, P < 0.01 \).

Patients with improved glycaemic control \((n = 24)\), defined as a reduction in HbA1c after 12 months of follow-up \((8.3 \text{ to } 7.4 \%)\), had a significantly improved strain rate over baseline \((-1.07 \pm 0.3 \text{ s}^{-1} \text{ at baseline to } -1.32 \pm 0.25 \text{ s}^{-1} \text{ at 12 months of follow-up; } P < 0.01 \)) compared with patients with increased HbA1c \((8.2 \text{ to } 9.1 \%); n = 24; -1.14 \pm 0.25 \text{ s}^{-1} \text{ at baseline to } -1.16 \pm 0.27 \text{ s}^{-1} \text{ at 12 months of follow-up; } P = \text{NS} \). The two groups had comparable baseline values of SBP, LV mass, age, and disease duration (Table 3). Similar findings were observed when the population was dichotomized according to increased or decreased levels of fructosamine during follow-up. Patients with reduced fructosamine levels had improved systolic strain rate \((-1.10 \pm 0.3 \text{ s}^{-1} \text{ at baseline to } -1.31 \pm 0.16 \text{ s}^{-1} \text{ at 12 months of follow-up; } P = 0.01 \) compared with patients with increased fructosamine levels \((-1.10 \pm 0.15 \text{ s}^{-1} \text{ at baseline to } -1.13 \pm 0.17 \text{ s}^{-1} \text{ at 12 months of follow-up; } P = \text{NS} \).

In a time-corrected repeated measurements ANOVA, including baseline, 3-month and 12-month strain rate...
results and HbA1c, fructosamine, LV mass, SBP, gender, age and study treatment, there was a highly significant relationship between systolic strain rate and HbA1c ($P < 0.001$) and fructosamine ($P < 0.05$) and also a significant relationship with LV mass ($P < 0.05$), whereas correlation with the other factors mentioned was not significant.

**Diastolic function**

Thirty patients demonstrated an abnormal diastolic filling pattern (62%) of which four patients had pseudonormal filling patterns. Eighteen patients had normal diastolic filling (38%). After 3 months of treatment, the prevalence was unchanged and, after a further 9 months, two additional patients were characterized as having diastolic dysfunction and one patient progressed to pseudonormal filling.

There was a tendency towards improved diastolic function after 3 months of treatment with significantly reduced $E$-wave DT and improved $E/A$ ratio, but these changes regressed after 12 months of treatment (Table 4).

A repeated measurements ANOVA, including the baseline, 3-months and 12-months results, yielded a model in which changes in $E$-wave DT were significantly correlated with changes in LV mass ($P < 0.05$) and DBP ($P < 0.05$), but were not correlated with changes in SBP ($P = 0.14$), HbA1c, fructosamine, albuminuria, antihypertensive therapy and time.

**DISCUSSION**

The present study provides novel follow-up data on the systolic long-axis function in hypertensive patients with Type II diabetes. The major new finding is that decreased long-axis function in Type II diabetes mellitus does not necessarily represent irreversible damage to the myocardium, but rather a changeable condition related to the glycaemic control and to changes in the LV mass. Surprisingly, the significant BP reduction by the antihypertensive therapy did not seem to be related to the long-axis function, as was expected [18], since bosoapical displacement of the left ventricle is significantly correlated with SBP in normal subjects [17].

Instead, mere fluctuations in the glycaemic control seemed to be related to changes in LV long-axis function over time. The largest improvements in systolic strain rate were attributed to patients with better glycaemic control, whereas patients with increased fructosamine levels or HbA1c did not have any changes in the reduced long-axis function.

Previously, cross-sectional data have shown a relationship between the glycaemic regulation and strain rate [8,9] and, accordingly, it has been suggested that low glycaemic levels simply reflect a better metabolic control over time and thereby less effect on the myocardium. In contrast, the present study has demonstrated that reduced glycaemic levels may have a direct impact on myocardial function.

At present, no data on human myocardium are available regarding the complex mechanism responsible for this finding. However, experimental studies support two possible mechanisms of action. First, formation of AGEs
on extracellular matrix components could lead to an accelerated increase in collagen cross-linking and thereby contribute to myocardial stiffness, as shown in experimental diabetes [19]. This phenomenon has, in experimental settings, been diminished by treatment with a cross-link breaker [20] or a neutralizing AGE-receptor antibody [21], which inhibits the impact of AGEs and cross-linked proteins on tissue in the myocardium. These issues need further elucidation.

Secondly, improved glucose metabolism could also directly result in improved cardiac function, possibly through GLUT 4 (insulin-responsive glucose transporter isoform) expression on the surface of the cardiomyocyte, which seems to exert an effect on cardiac function in experimental studies [22]. Changes in LV mass, which partly reflect changes in BP over time, were also related to systolic long-axis function. The correlation with the strain rate was, however, modest, probably due to the moderate changes in LV mass found in the present study. The improved long-axis function from LV mass reduction may be multifactorial, primarily consisting of a pure mechanical influence from lessened afterload. In addition, reduced fibrosis and diminished apoptosis of the myocytes and endothelial cells in the diabetic myocardium might be attenuated by angiotensin II inhibition [23], which was the main action of the drug therapy involved in the CALM II study.

However, this substudy actually documented an actual progression of LV hypertrophy in Type II diabetic patients, despite seemingly adequate BP control. This finding is partially explained by the design of the CALM II study, which allowed an SBP up to 160 mmHg in individuals during follow-up [11]. Moreover, the finding of increasing LV mass during follow-up also underlines the severity of the Type II diabetic disease in which LV hypertrophy may develop beyond the compensatory needs for increased workload [24]. In these cases, LV hypertrophy may be more related to metabolic factors and neurohormonal activation than to stroke work [25].

The moderate changes in LV mass were also reflected in the rather modest changes in diastolic function in the present study. There was a tendency towards improved diastolic function in relation to the significant reduction in SBP and LV mass within the first 3 months of the study. However, from the 3 months of follow-up and onwards, it seemed that the LV mass and the stiffness of the myocardium returned to the baseline status, despite the fact that the majority of patients obtained adequate BP control at 12 months of follow-up.

An interesting observation was the relationship between the minor changes in E/A ratio and the level of urinary albumin excretion throughout the study period. The co-existence of albuminuria and decreased LV compliance has been described previously in patients with essential hypertension and Type II diabetic patients [26–28]. However, the findings in the present study could indicate that these major risk factors may be more closely related than described previously.

Limitations

The lack of a controlled intervention of the blood glucose metabolism is a limitation of the present study. In addition, the dichotomized data by HbA1c were not a predefined analysis. A more effective reduction in HbA1c would have provided additional evidence of the influence of metabolic homoeostasis on LV long-axis function. This could be provided by a study based on metabolic control and type of antidiabetic agent alone.

Secondly, changes in central BP were not investigated in the present study. A significant reduction in central BP might be related to improvements in the LV contractility [29,30]. This issue needs further elucidation.

Thirdly, assessment of changes in diastolic function was not the primary scope of the present study; these findings could be influenced by under-powering.

Finally, the observer variability of strain rate measurements needs to be taken into consideration.

Conclusions

LV systolic long-axis function is significantly correlated with changes in metabolic control and LV mass in hypertensive patients with Type II diabetes mellitus. Thus there was no relationship between the reduction in SBP and systolic long-axis function. Changes in diastolic function were mainly correlated with changes in LV mass and DBP, but also to some degree related to urinary albumin excretion.

ACKNOWLEDGMENTS

We thank laboratory technicians Merete Möller and Karen Mathiassen for their great effort and excellent technical assistance. The study has been supported by LeoPharma (Denmark), The Danish Diabetes Association, The National Research Council/The University of Aarhus, The Novo Nordisk Foundation and The Sehested Hansen Foundation. The CALM II study was supported by a grant from AstraZeneca®.

REFERENCES


© 2006 The Biochemical Society
Left ventricular function during antihypertensive treatment

59


Received 15 December 2005/24 February 2006; accepted 3 March 2006
Published as Immediate Publication 3 March 2006, doi:10.1042/CS20050367