Impact of diabetes on left ventricular diastolic function in patients with arterial hypertension

Rolf Wachter, Claus Lüers, Sibylle Kleta, Kerstin Griebel, Christoph Herrmann-Lingen, Lutz Binder, Nico Janicke, Dirk Wetzel, Michael M. Kochen, Burkert Pieske

Abstract

Aims: To analyse the effect of diabetes (DM) on diastolic function in hypertensive patients.

Methods: 439 hypertensive patients were selected for participation in this study. All participants had an echocardiographic evaluation of systolic and diastolic function. The overall degree of diastolic function and specific parameters (e.g. E/Ea ratio) were analysed.

Results: We divided the cohort (63±10 years) into those with diabetes mellitus (DM(+), n=124) and without diabetes mellitus (DM(−), n=315). The prevalence of normal diastolic function was lower in DM(+) than DM(−) (19.4% vs. 30.8%; p=0.022). The E/Ea ratio, an estimate of left ventricular end-diastolic pressure, was significantly higher in DM(+) (12.3±4.4) as compared to DM(−) (10.8±3.6, p<0.001). Sex-specific analysis revealed that the effect of DM on diastolic function was mainly limited to the male subgroup. Multivariate logistic regression analysis showed that diabetes affected diastolic function in males independent of blood pressure, left ventricular mass index, concomitant medication and prevalence of coronary artery disease.

Conclusion: Diabetes negatively affects diastolic function in patients with arterial hypertension. This effect is mainly confined to the male subgroup.

Keywords: Diabetes; Diastolic function; Heart failure; Echocardiography

1. Introduction

Type 2 diabetes mellitus (DM) is an established risk factor for cardiovascular events [1] and the development of congestive heart failure [2]. The potential existence of a diabetic cardiomyopathy was first described in 1954 by Lundbaek [3], and subsequent epidemiological studies support the notion of a distinct diabetic cardiomyopathy [4]. It is reasonable to speculate that diabetic cardiomyopathy also accounts, at least in part, for the higher incidence of heart failure in diabetics.

Diastolic dysfunction is considered a precursor of heart failure [5] and may be diagnosed non-invasively by echocardiography. Diastolic dysfunction is common in well-controlled type II diabetic patients without clinically detectable heart disease. In a recent study in 46 asymptomatic, well-controlled type II diabetic patients without diabetic complications, the prevalence of diastolic dysfunction was 60% [6]. Several mechanisms may underlie diastolic dysfunction in diabetic patients. The Strong Heart Study has shown that DM is associated with left ventricular concentric...
hypertrophy and impaired diastolic function [7]. Studies in humans and in animals demonstrated that morphological alterations can be found in diabetic hearts, including myocyte hypertrophy, perivascular fibrosis and increased quantities of matrix collagen. Recently, impaired relaxation was directly associated to myocardial accumulation of advanced glycation end products in an animal model of type 2 diabetes [8].

Though the pathophysiological role of DM in the development of diastolic dysfunction, diabetic cardiomyopathy and heart failure has been demonstrated, little is known about the interaction of DM with other established risk factors, such as hypertension.

Therefore, the aim of the present study was to analyse the interaction of DM and hypertension with respect to the development of diastolic dysfunction. The effect of sex on this interaction was also analysed.

2. Methods

467 patients with hypertension, but without overt heart failure, were invited by their General Practitioner to participate in this study, which is part of the MedVIP program of the University of Goettingen and was funded by the German Federal Ministry of Education and Research. Patients were included if they had been diagnosed to be hypertensive by their treating physician or if they were on anti-hypertensive therapy. Patients were classified as diabetic if this diagnosis was made by their treating physician or if they were on antihyperglycemic therapy. For the purpose of this study, patients who were diagnosed with diabetes before the age of 40 and who became insulin-dependent within less than a year were classified as type 1 diabetics, all other patients were classified as type 2 diabetics. Glycated haemoglobin was measured by a HPLC method (Biorad, Variant II HbAlc program, reference value <6.2%). This method is anchored to the Diabetes Control and Complication trial (DCCT) reference. HbAlc was analysed in 110 of the 124 diabetic patients (89%).

Coronary artery disease (CAD) was defined as angiographic evidence of coronary artery disease, a history of revascularisation or a history of myocardial infarction. The study complies with the Declaration of Helsinki and was approved by the local Ethics committee; all patients gave written informed consent.

3. Echocardiography

Imaging was done in the left lateral decubitus position using a Hewlett-Packard Sonos 5500 (Hewlett-Packard, Andover, MA, USA) with a multifrequency transducer equipped with Doppler tissue imaging software. Standard views and standard techniques were employed according to the Guidelines of the American Society of Echocardiography [9–11]. Transmitral left ventricular filling velocities at the tips of the mitral valve leaflets were obtained, peak velocity of early (E) and late (A) filling and E wave deceleration time (EDCT) were measured. Isovolumetric relaxation time (IVRT) was obtained in the apical five chamber view. Pulmonary venous flow signals were recorded in the right upper pulmonary vein and the ratio of systolic to diastolic velocity (S/D) was analysed. Velocity flow propagation (Vp) was measured by colour Doppler M-mode in the middle of the mitral valve.

Doppler tissue imaging was used to derive early (Ea) and late (Aa) diastolic velocities at the septal margin of the mitral annulus.

Diastolic dysfunction was classified as follows: Normal diastolic function (1 < E/A < 2, 150 ms < EDCT < 280 ms, IVRT < 105 ms, S/D > 1, Ea > 8 cm/s, Vp > 45 cm/s), mild diastolic dysfunction (E/A < 1, EDCT > 280 ms, IVRT > 105 ms, S/D > 1, Ea < 8 cm/s, Vp < 45 cm/s), moderate diastolic dysfunction (1 < E/A < 2, 150 ms < EDCT < 200 ms, 60 ms < IVRT < 105 ms, S/D > 1, Ea < 8 cm/s, Vp < 45 cm/s) and severe diastolic dysfunction (E/A > 2, EDCT < 150 ms, IVRT < 60 ms, S/D < 1, Ea < 8 cm/s, Vp < 45 cm/s). E/Ea as an indirect index of left ventricular filling pressure was calculated in all participants. One of the authors (SK), who was blinded to all other clinical data, categorised all patients according to the degree of diastolic function.

4. Statistical analysis

Data were analysed using SAS 9.1 software (SAS Institute Inc., Cary, North Carolina). Continuous data are expressed as mean ± standard deviation, categorical data as median (25th–75th percentile). Differences between groups of patients were assessed by a two-tailed student’s t-test or χ^2-test where appropriate. Independence of differences from effects of covariates was assessed by multivariate logistic regression analysis. Diastolic dysfunction was used as the dependent variable; covariates in the model were age, coronary artery disease, diabetes, systolic and diastolic blood pressure, heart rate, body mass index and left ventricular mass index. These covariates were selected because they have been shown to affect diastolic function. In addition, treatment modalities, (use of ACE inhibitors/AT1-antagonists, beta blockers, diuretics and calcium antagonists) were used as covariates because they may also affect diastolic function.

For analysing the continuous variables of diastolic function, we used ANCOVA (analysis of variance adjusted by covariates). Covariates were age, heart rate, blood pressure, left ventricular mass index, and CAD, which all may have an impact on diastolic filling. Cochran Armitage trend test was used where appropriate. A two-tailed p value < 0.05 was considered statistically significant.

5. Results

5.1. Patient characteristics

467 patients with hypertension were recruited for this study. To avoid misleading results due to different
pathophysiology, 7 patients with type 1 diabetes were excluded. Complete assessment of diastolic function was unfeasible in 21 patients due to atrial fibrillation. Therefore, 439 patients were included in the analysis and are reported. Of these, 315 patients had hypertension without type 2 diabetes mellitus (DM(−)) and 124 patients had type 2 diabetes mellitus (DM(+)). In the diabetes group, 25 patients were treated with diet only, 54 were treated with oral glucose lowering drugs and 45 were insulin-dependent.

The major clinical characteristics of the study participants are depicted in Table 1. There were no significant differences in age, sex, systolic blood pressure, ejection fraction, interventricular septum and left ventricular posterior wall thickness, left ventricular end-diastolic diameter, LV mass index or prevalence of CAD between DM(−) and DM(+). However, some quite typical differences were apparent. Heart rate was significantly higher in diabetics. Possibly due to specific indications in diabetics, diabetic patients received more ACE inhibitors, calcium channel blockers and diuretics.

5.2. Differences in left ventricular filling patterns

We found a high prevalence of asymptomatic diastolic dysfunction: 318 of the 439 patients (72.4%) were characterised with diastolic dysfunction (270 mild, 46 moderate, 2 severe). Patients with moderate/severe diastolic dysfunction were combined into one group for further analysis. The prevalence of diastolic dysfunction was similar in males (74.4%) and females (69.9%, \( p=0.301 \)).

Diastolic dysfunction was significantly more prevalent in DM(+) (80.6%) than in DM(−) (69.2%) \( (p=0.016) \). Moreover, diastolic dysfunction was more severe in DM(+). The prevalence of mild (65.3% vs. 60.0%) as well as moderate/severe diastolic dysfunction (15.3% vs. 12.7%)

![Fig. 1. Relative prevalence of normal diastolic function (left), mild (middle) and moderate/severe (right) diastolic dysfunction in hypertensive patients without (DM(−)) and with diabetes (DM(+)).]
function was 69.2%, 76.0%, 81.5% and 82.2% for DM(−), DM(+) on diet only, DM(+) on oral glucose lowering drugs and insulin-dependent DM, respectively (p = 0.015 for trend).

The average duration of diabetes in the whole cohort was 8.0±8.0 years. There was no significant difference in diabetes duration between males (7.9±7.4 years) and females (8.0±8.7 years) (p = 0.962). Also, no difference in diabetes duration between patients with normal diastolic function (8.5±7.4 years) and patients with diastolic dysfunction (7.6±7.9 years) could be detected (p = 0.837).

The prevalence of diastolic dysfunction was 76.7% in patients with good (HbA1c<6.5%) and 79.2% in patients with moderate (6.5%≤HbA1c<8.0%) and 92.9% in patients with poor (HbA1c≥8.0%) glycaemic control (p = 0.255 for trend). Insulin dosage in insulin-dependent diabetics (n = 45) was not different between women and men (Table 1, p = 0.798) and not different between patients without and with diastolic dysfunction (p = 0.386).

5.4. Sex-specific differences in diastic function

In this cohort of patients with arterial hypertension, sex-specific analysis revealed an effect of DM on diastolic function that was only significant in men. Participants where dichotomised as having diastolic dysfunction or normal diastolic function. In males, 30.6% of men in the DM(−)-group had normal diastolic function, compared with only 12.1% in the DM(+) group (p = 0.003). In women, 31.1% in the DM(−)-group and 27.6% in the DM(+) group had normal diastolic function (p = 0.624).

We also analysed the effects of DM on the degree of diastolic dysfunction (Table 2, upper part). Compared to male DM(+) participants, male DM(−) participants showed a lower prevalence of impaired relaxation and moderate/severe diastolic dysfunction (p = 0.008). In females, the prevalence of mild diastolic dysfunction as well as moderate/severe diastolic dysfunction was nearly identical in DM(+) and DM(−) women.

Data are shown for the whole population as well as separately for women and men.

vs. 9.2%) was higher in DM(+) vs DM(−) (p = 0.022), respectively (Fig. 1).

5.3. Diabetes duration and severity

Antihyperglycaemic treatment (as a potential indicator for severity of DM) was related to the prevalence of diastolic dysfunction. The prevalence of diastolic dys-

| Table 2 | Prevalence of different stages of diastolic dysfunction in all patients and in the subgroup of patients without evidence of CAD |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Normal diastolic function | Mild diastolic dysfunction | Moderate/ severe diastolic dysfunction | p value |
| All (n=439) | DM(−) (n=315) | 97 (30.8%) | 189 (60.0%) | 29 (9.2%) | 0.022 |
| DM(+) (n=124) | 24 (19.4%) | 81 (65.3%) | 19 (15.3%) | |
| Female (n=193) | DM(−) (n=135) | 42 (31.1%) | 83 (61.5%) | 10 (7.4%) | 0.555 |
| DM(+) (n=58) | 16 (27.6%) | 35 (60.3%) | 7 (12.1%) | |
| Male (n=246) | DM(−) (n=180) | 55 (30.6%) | 106 (58.9%) | 19 (10.6%) | 0.008 |
| DM(+) (n=66) | 8 (12.1%) | 46 (69.7%) | 12 (18.2%) | |
| All without CAD (n=325) | DM(−) (n=233) | 78 (33.5%) | 136 (58.4%) | 19 (8.2%) | 0.038 |
| DM(+) (n=92) | 19 (20.7%) | 60 (65.2%) | 13 (14.1%) | |
| Female without CAD (n=116) | DM(−) (n=84) | 39 (33.6%) | 68 (58.6%) | 9 (7.8%) | 0.704 |
| DM(+) (n=32) | 14 (27.5%) | 32 (62.7%) | 5 (9.8%) | |
| Male without CAD (n=117) | DM(−) (n=91) | 39 (33.3%) | 68 (58.1%) | 10 (8.5%) | 0.014 |
| DM(+) (n=26) | 5 (12.2%) | 28 (68.3%) | 8 (19.5%) | |

Data are shown for the whole population as well as separately for women and men.

vs. 9.2%) was higher in DM(+) vs DM(−) (p = 0.022), respectively (Fig. 1).

5.3. Diabetes duration and severity

Antihyperglycaemic treatment (as a potential indicator for severity of DM) was related to the prevalence of diastolic dysfunction. The prevalence of diastolic dys-

| Table 3 | Major echocardiographic parameters of diastolic function in patients without (DM(−)) or with (DM(+) concomitant type 2 diabetes |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Total (n=439) | DM(−) (n=317) | Female (n=193) | Male (n=246) |
| E velocity (cm/s) | 73.1±17.4 | 76.1±18.7* | 76.6±17.4 | 77.2±17.2 | 70.5±16.9* | 75.2±19.9* |
| A velocity (cm/s) | 85.5±20.8 | 91.8±21.9** | 83.3±21.8 | 95.3±21.7 | 87.6±18.5*** | 88.7±21.9*** |
| E/A ratio | 0.95±0.33 | 0.88±0.31 | 0.91±0.31 | 0.85±0.27 | 0.98±0.34 | 0.90±0.34 |
| Deceleration time (ms) | 231±66 | 229±75 | 228±66 | 215±77 | 234±67 | 241±73 |
| IVRT (ms) | 108±25 | 106±28 | 106±24 | 100±26 | 110±27 | 111±28* |
| Ea (cm/s) | 7.3±2.1 | 6.6±1.9** | 7.2±2.3 | 6.9±1.8 | 7.2±2.0 | 6.4±1.9** |
| Aa (cm/s) | 10.9±2.6 | 11.3±2.7 | 11.0±2.7 | 11.3±2.8 | 10.8±2.6 | 11.4±2.5 |
| E/Ea ratio | 10.8±3.6 | 12.3±4.*** | 11.4±3.8 | 11.9±3.8 | 10.3±3.4*** | 12.7±5.0*** |

*p<0.05 vs. DM(−). **p<0.01 vs. DM(−). ***p<0.001 vs. DM(−).

*p<0.05 vs. Female. **p<0.01 vs. Female. ***p<0.001 vs. Female.

Data are also shown separately for women and men. E velocity: Early diastolic filling velocity, A velocity: Late diastolic filling velocity, IVRT: Isovolumetric relaxation time. Ea: Tissue Doppler early diastolic filling velocity, Aa: Tissue Doppler Late diastolic filling velocity. All p values are adjusted for covariates: age, heart rate, blood pressure, left ventricular mass index, CAD.
and DM(−)-participants \( (p=0.555) \). Data in patients without evidence of CAD showed similar results (Table 2, lower part).

### 5.5. Impact of diabetes on E/Ea ratio in patients with arterial hypertension

We analysed the E/Ea ratio (transmitral early left ventricular filling velocity (E) to early diastolic velocity of the mitral annulus (Ea)), which correlates with the left ventricular end-diastolic pressure. E/Ea was significantly lower in participants without diabetes as compared to diabetics \((10.8 \text{ vs. } 12.3, p<0.001, \text{see Table 3})\).

In patients with diastolic dysfunction, E/Ea was significantly higher as compared to participants with normal diastolic function. E/Ea was higher in non-diabetic females as compared to males (Fig. 2, \( p=0.007 \)). Diabetes was associated with higher E/Ea values in men and in women, but this difference was only significant in men (Fig. 2).

#### 5.6. Multivariate regression analysis

We performed a multivariate logistic regression analysis to assess the impact of diabetes on diastolic function. Analyses were also performed separately in women and men and are shown in Table 4.

In the overall population, age, diabetes, diastolic blood pressure, left ventricular mass index and ACE-inhibitor/AT1-antagonist therapy were independently associated with diastolic dysfunction.

In women, only age and diastolic blood pressure were independent predictors of diastolic dysfunction. Diabetes tended to be associated with diastolic dysfunction, but failed to reach significance \( (p=0.101) \).

In men, age, left ventricular mass index and diabetes were independently associated with diastolic dysfunction.

### 6. Discussion

#### 6.1. Principal findings

We observed three main effects of diabetes on diastolic function in asymptomatic hypertensive patients:

1. Patients with diabetes had a higher prevalence of diastolic dysfunction, which was also present after adjustment for age, prevalence of coronary artery disease and concomitant medication.
2. The effect of diabetes on prevalence and severity of diastolic dysfunction was more pronounced in men as compared to women.
3. In consequence, diabetes was associated with an increased E/Ea ratio (reflecting higher left ventricular filling [12]) and this impact was more prominent in men.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Odds ratio (95% CI)</th>
<th>Female Odds ratio (95% CI)</th>
<th>Male Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.078 (1.048–1.109)</td>
<td>1.094 (1.042–1.148)</td>
<td>1.079 (1.039–1.121)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>0.994 (0.959–1.034)</td>
<td>0.984 (0.941–1.033)</td>
<td>0.987 (0.906–1.089)</td>
<td>0.789</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.481 (1.089–2.014)</td>
<td>1.470 (0.928–2.330)</td>
<td>1.670 (1.048–2.661)</td>
<td>0.031</td>
</tr>
<tr>
<td>Systolic BP (per mmHg)</td>
<td>0.992 (0.977–1.007)</td>
<td>0.986 (0.963–1.010)</td>
<td>0.996 (0.974–1.018)</td>
<td>0.718</td>
</tr>
<tr>
<td>Diastolic BP (per mmHg)</td>
<td>1.053 (1.021–1.087)</td>
<td>1.098 (1.043–1.157)</td>
<td>1.025 (0.982–1.069)</td>
<td>0.258</td>
</tr>
<tr>
<td>Heart rate (per beat/min)</td>
<td>0.991 (0.968–1.014)</td>
<td>0.967 (0.930–1.006)</td>
<td>1.003 (0.970–1.036)</td>
<td>0.872</td>
</tr>
<tr>
<td>LVM (per g/m²)</td>
<td>1.011 (1.003–1.019)</td>
<td>1.005 (0.991–1.020)</td>
<td>1.014 (1.002–1.027)</td>
<td>0.026</td>
</tr>
<tr>
<td>Body mass index (per kg/m²)</td>
<td>0.962 (0.910–1.017)</td>
<td>0.978 (0.904–1.058)</td>
<td>0.967 (0.884–1.057)</td>
<td>0.458</td>
</tr>
<tr>
<td>ACE-I /ARB</td>
<td>1.716 (1.021–2.885)</td>
<td>1.697 (1.763–3.775)</td>
<td>1.805 (0.871–3.739)</td>
<td>0.112</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.788 (0.456–1.361)</td>
<td>1.143 (0.519–2.519)</td>
<td>0.516 (0.226–1.777)</td>
<td>0.116</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.717 (0.431–1.194)</td>
<td>0.569 (0.255–1.266)</td>
<td>0.896 (0.441–1.822)</td>
<td>0.762</td>
</tr>
<tr>
<td>Ca channel blockers</td>
<td>1.222 (0.675–2.212)</td>
<td>2.432 (0.922–6.149)</td>
<td>0.645 (0.281–1.483)</td>
<td>0.302</td>
</tr>
</tbody>
</table>

Data are shown for all patients and separately for women and men. CI: Confidence interval, BP: blood pressure, LVM: Left ventricular mass index, ACE-I: ACE inhibitor, ARB: Angiotensin receptor blocker, Ca: Calcium.
6.2. Effects of type 2 diabetes mellitus on diastolic function

In our study, diabetes was associated with a higher prevalence and severity of diastolic dysfunction as compared to participants without diabetes. Our study confirms the findings of Liu et al. [13], who showed that diabetes impairs diastolic function independent of traditional risk factors (e.g., age, left ventricular mass index). Furthermore, recent data from the echocardiographic sub-study of the LIFE trial, demonstrated adverse effects of diabetes on ventricular function in hypertensive patients [14]. In extension to this and other studies, in which only mitral inflow characteristics (e.g., E/A ratio) were analysed [14, 15], the use of tissue Doppler imaging allowed us to assess the degree of diastolic dysfunction and to differentiate between normal diastolic function and pseudo-normalisation, i.e., a stage of moderate diastolic dysfunction. Consequently, we found that not just single echocardiographic parameters, such as Ea [16] or E/A [13], but also the overall degree of diastolic dysfunction is more severely impaired in diabetic patients. This is of particular importance since the degree of diastolic dysfunction is a strong predictor of mortality [17].

In extension to a previous study [13], we were also able to show that the effect of diabetes on diastolic function was independent of different treatment modalities. In multivariate analysis, therapy with ACE inhibitors or angiotensin receptor blockers was associated with diastolic dysfunction, whereas therapy with beta blockers or diuretics was not. However, these results should be handled with caution as this was a retrospective analysis and the observed association might also be related to specific indications for blockers of the renin–angiotensin system in diabetes, such as nephroprotection or vascular protection.

6.3. Differences between women and men in the association between diabetes and diastolic function

In addition to our finding that diastolic dysfunction was more prevalent and more severe in hypertensives with diabetes, this association was more pronounced in men as compared to women.

Differences between women and men in the impact of diabetes on cardiac function and structure have previously been reported. Recently, Rutter et al. [18] described sex-related differences of glucose intolerance and diabetes on left ventricular mass. Moreover, different animal studies have shown that sex affects the development of cardiac specific phenotypes [19, 20]. Thus, male hearts seem to be more sensitive to alterations than female hearts and usually display more pronounced cardiac phenotypes than females.

There are clinical data to support our findings. If men with hypertension and diabetes have an increased risk, then therapy in men might be more effective. Indeed, antihypertensive treatment leads to a greater reduction in absolute risk in men as compared to women [21]. Therapy with an ACE inhibitor was superior to diuretic therapy as anti-hypertensive treatment in men, but not in women [22]. These results indicate that male and female hearts might react differently to metabolic (hyperglycaemia, diabetes) and therapeutic changes and differences between women and men should receive more attention in future trials.

Diabetes is a known risk factor for heart failure and cardiovascular events [23] and this association is partly mediated by its effect on LV structure. On the other hand, the risk for clinical heart failure in the Framingham study was five times higher in female diabetics (compared to non-diabetics), but only two times higher in male diabetics [2]. In our study, diastolic function was more severely affected in men than in women — an observation that is supported by a recent re-evaluation of data from the CHARM heart failure program, which showed that both diabetes and male sex were independent predictors of morbidity and mortality [24]. Our findings of sex-related effects of diabetes may partly explain the differences between women and men in age-adjusted heart failure incidence in the population [25].

6.4. Diabetes duration, severity and treatment modality

Good glycaemic control can help to maintain normal diastolic function in diabetics: In the Strong Heart Study, it was shown that the quality of glycaemic control was related to single echocardiographic parameters of diastolic function [13]. Recently, von Bibra et al. [26] extended these findings, by showing that improved metabolic control with insulin leads to an improvement in diastolic myocardial velocity in non insulin-dependent diabetics. The notion that the severity of the disease and the quality of metabolic control is related to the degree of diastolic dysfunction is in accordance with the results of our study. We observed that diastolic dysfunction worsened with the need for more intensified therapy as an indirect parameter for the severity of the disease. We also observed a trend towards a more severely impaired diastolic function with poor glycaemic control (as evidenced by elevated HbA1c values). However, as in the Strong Heart Study [13], the time since diagnosis was not predictive of diastolic dysfunction in our study.

6.5. Estimates of left ventricular filling pressures in diabetes

Consistent with recent observations in a large cohort [27], E/Ea tended to be higher in non-diabetic women as compared to non-diabetic men. Diabetes affected E/Ea ratio differently in men and women. The finding of a significantly increased E/Ea ratio only in men could indicate that diabetes leads to a more pronounced increase in left ventricular end-diastolic pressure in men. The finding of a higher left ventricular end-diastolic pressure in diabetes is consistent with invasive studies in humans [28]. In addition, abnormal E/Ea was associated with reduced exercise tolerance in otherwise asymptomatic patients [29]. Further studies are needed to clarify the clinical relevance of this
finding, especially the potential prognostic role of E/Ea in predicting morbidity and mortality.

6.6. Potential mechanisms

Several possible mechanisms for the direct adverse effects of diabetes on the heart independent of coronary artery disease are currently under discussion, including: elevated left ventricular mass, elevated central blood pressure, disturbed ventriculo-arterial coupling, and diffuse fibrosis of the myocardium [3,30]. The finding of increased E/Ea ratio as an indicator of elevated left ventricular end-diastolic pressure favours the hypothesis that reduced compliance is a major underlying pathology. Studies have shown that diabetic patients with hypertension have greater interstitial connective tissue deposition than patients with either diabetes or hypertension as isolated entities [31]. However, other mechanisms, such as increased ventricular–vascular stiffness in women [27], may contribute to these sex-related differences.

6.7. Study limitations

The diagnoses of “hypertension” and “diabetes” were made by the referring physician. Accepting these referral diagnoses may have affected the results. However, only 15 of 439 patients (3.4%) were not on anti-hypertensive therapy and none of these 15 patients had a sitting blood pressure below 140/90 mmHg upon study entry.

Some drugs (e.g. beta blockers) may be taken for indications other than hypertension and could therefore lead to misclassification. 53 patients took only beta blockers and no other anti-hypertensive drugs (6 in the diabetes group, 47 in the non-diabetes group). Only 9 patients (17.0%) had coronary artery disease as a potential differential indication for beta-blocker therapy and none of these patients had atrial fibrillation or any other indication for beta-blocker therapy. In addition, only 3 of the 9 CAD-patients on beta blockers had a blood pressure below 140/90 mmHg.

Another possible wrong classification could include diabetics who were receiving an ACE inhibitor or an AT1-antagonist for renal or vascular protection. Eleven of the diabetic patients were on ACE-inhibitor monotherapy, and two were on AT1-antagonist monotherapy. Of these patients, none had a blood pressure below 140/90 mmHg. We therefore exclude the possibility that a relevant proportion of patients were erroneously classified as hypertensives.

In our study, female hypertensives without diabetes had significantly higher E/Ea values than male hypertensives. Consequently, an alternative explanation for our finding of a larger impact of diabetes on diastolic function in males as compared to females could be that hypertension might affect diastolic function more severely in women, and there is no detectable further effect of an additional risk factor, such as diabetes.

There may also be some diabetics in the non-diabetes group, as we did not rule out the existence of so far non-diagnosed diabetes in these patients, e.g. by glucose tolerance testing. We also did not measure C-peptide levels or GAD-antibodies to differentiate type 2 from type 1 diabetes. Therefore, the differences between DM(−) and DM(+) might even be more striking if patients with so far undiagnosed diabetes or impaired glucose tolerance/impaired fasting glucose had been identified in the DM(−) group. Moreover, we did not measure glucose levels on the day of assessment of diastolic function and therefore cannot exclude that hyperglycaemia in diabetics affected our results.

The prevalence of coronary artery disease (CAD) was nearly three times higher in male participants than in female (35.8% vs. 13.5%, p < 0.001). Exclusion of patients with CAD did not significantly alter the results, but reduced the difference between male and female diabetics. One might speculate that a deleterious interaction between CAD and DM on diastolic dysfunction, which was more pronounced in men, may have influenced our results. Moreover, microvascular disease, which has a high prevalence in diabetes, may have influenced diastolic function.

Due to the design of our study, we did not have a control group without hypertension, without diabetes and without CAD. Therefore, we were only able to analyse the effects of concomitant diabetes in hypertensives and could not evaluate the effects of diabetes in non-hypertensives.

6.8. Conclusion

Diabetes further aggravates diastolic dysfunction in hypertensive patients. This effect appears to be more pronounced in men as compared to women, but may need further support from larger epidemiological trials. Our results also indicate the potential of diastolic dysfunction as a novel indicator of end-organ damage in asymptomatic patients with hypertension and diabetes.

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