CLINICAL STUDY

Diabetes reduces left ventricular ejection fraction-irrespective of presence and extent of coronary artery disease

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Abstract

Background: It is not clear whether diabetes reduces systolic left ventricular function (left ventricular ejection fraction, LVEF) irrespective of coronary artery disease (CAD). The aim of this study was to compare the LVEF between diabetic and non-diabetic patients with respect to the extent of CAD.

Methods and results: Consecutive patients undergoing stress myocardial perfusion SPECT (MPS) were evaluated. MPS was interpreted using a 20-segment model with a five-point scale to define summed stress score (SSS), summed rest score, and summed difference score. LVEF was measured by gated SPECT and then compared with respect to diabetic status and SSS categories. Of 2635 patients, data of 2400 was available. Of these, 24% were diabetic, mean age was 64 ± 11 y, and 31% were female. Diabetics had a significantly lower LVEF compared with non-diabetics regardless of the extent of CAD: 53 ± 13 and $55 \pm 13\%$ respectively ($P = 0.001$). Diabetics and non-diabetics did not differ significantly in the distribution of SSS categories. Diabetes was an independent predictor of decreased LVEF (odds ratio 1.6, 95% confidence interval 1.2–2.0; $P < 0.001$).

Conclusion: Diabetics had a lower LVEF than non-diabetics. This difference could be demonstrated regardless of CAD extent and might in part explain their generally worse cardiac survival compared with non-diabetics on an epidemiological level. In addition, this finding points to discussed mechanisms other than CAD lowering LVEF in diabetics.

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Introduction

The association between diabetes and congestive heart failure (CHF), as well as its influence on prognosis, is well known and has been extensively documented (1–4); it was established in the study by Framingham in 1971 in which the high prevalence of diabetes (14% of men and 26% of women) among patients with CHF was noted (5, 6). However, generally this finding was explained by increased prevalence of coronary artery disease (CAD) in diabetic patients (7, 8). However, large epidemiological studies have confirmed diabetes mellitus to be an independent risk factor for the development of heart failure (9); Rubler *et al.* (10) first described the existence of ‘diabetic cardiomyopathy’ in 1972 based on four adult diabetic patients with CHF that could not be explained by CAD, hypertension, valvular heart disease, or alcoholism. Subsequently, the term ‘diabetic cardiomyopathy’ as a diastolic and/or systolic CHF in diabetic patients in the absence of significant concomitant CAD or arterial hypertension has been defined.

In contrast to the consensus that diastolic dysfunction plays an important role regarding CHF in diabetic patients, the results regarding the systolic function were

not conclusive. Taking also into account the presence and extent of CAD, little is known about the comparison of left ventricular ejection fraction (LVEF) in diabetic vs non-diabetic patients. It is well known that LVEF is an important prognostic variable (11). Therefore, the aim of our study was to compare the LVEF of diabetic and non-diabetic patients adjusted for the presence and extent of CAD.

Subjects and methods

Study population

A large cohort of 2635 consecutive patients who underwent exercise or adenosine stress myocardial perfusion SPECT (MPS) at our institution was retrospectively evaluated. Patients with clinically relevant valvular disease were excluded from the study population. Of these 2635 patients, two were excluded for unknown diabetic status and 233 were excluded for technical reasons (LVEF could not be assessed by gated SPECT, mostly due to supraventricular or ventricular premature beats or atrial fibrillation). The final patient population consisted of 2400 patients: 1826 non-diabetic and 574 diabetic patients.

Diagnosis of diabetes mellitus was based on a known history of diabetes and/or antidiabetic drug therapy at the time of stress testing.

A detailed patient interview and chart review of former cardiac evaluations were the basis to assess the medical history of the patients.

Rest/stress MPS protocol

MPS was performed using a single-day gated rest/stress dual isotope protocol (TI-201 rest/Tc-99m sestamibi stress as described previously (12, 13)). Whenever possible, β -blockers as well as negative chronotropic calcium antagonists were withheld for 48 h and long-acting nitrates for 24 h before exercise testing; patients were instructed to avoid caffeine-containing products for 24 h prior to MPS. Ten minutes after administration of 111 MBq Thallium 201, a rest SPECT was obtained. Whenever possible, a symptom-limited exercise treadmill test using standard protocols was performed with a 12-lead electrocardiogram (ECG) recorded each minute. At near-maximal stress, a 740 MBq dose of Tc-99m sestamibi was injected, and exercise continued for at least an additional minute after injection.

If exercise stress was not possible or sufficient, a pharmacologic one (adenosine 140 μ g/kg per min for 6 min) was used either combined with physical stress or alone. Tc-99m sestamibi was injected after 3 min of adenosine infusion.

During both types of stress, blood pressure and ECG were monitored according to the standard protocols (13, 14).

Image acquisition

SPECT was performed using triple-head gamma cameras (IRIX3, PRISM3000, PHILIPS, CH) equipped with a low-energy ultra high-resolution collimator. A 40 and 20% symmetrical energy window was used to acquire the 72 and 169 keV peak of thallium, respectively, and a 15% symmetrical energy window to acquire the 140 keV peak of technetium. One hundred and twenty images (64 $\times$ 64 matrix) were acquired with 15 s per projection for stress and 20 s for rest images. Poststress images were gated with eight frames per heartbeat. Transaxial, sagittal, and coronal tomograms were reconstructed using a low-pass filter during back projection. Imaging was performed using standard protocols (12, 15). No attenuation or scatter correction was used. Instead supine and prone images were taken.

Analysis of perfusion SPECT

Semiquantitative visual interpretation was performed using a 20-segment model (each segment representing 5% of the myocardium), as described previously (13, 16). MPS was read by two experienced readers, a cardiology

and a nuclear medicine physician. Radioisotope uptake in each segment was graded using a five-point scale (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, and 4 = apparent absence of detectable tracer uptake in a segment). A summed stress score (SSS) was obtained by adding the scores of the 20 segments on the stress images, a summed rest score (SRS, reflecting in part the extent of scar and thus prior myocardial infarction) in a similar way by adding the scores of the 20 segments on the rest images. To assess the extent and severity of ischemia, a summed difference score (SDS, as degree of defect reversibility and extent of ischemia) was calculated by subtracting SRS from SSS. A SSS < 4 was considered as a normal, SSS 4–8 mildly abnormal, SSS 9–13 moderately abnormal, and SSS > 13 severely abnormal perfusion (17). A transient ischemic dilatation (TID) – ratio of more than 1.22 was considered positive. TID is a marker of potentially balanced and/or potentially severe ischemia.

LVEF evaluation

LVEF was calculated by using the widely validated Quantitative Gated SPECT (QGS, Cedars Sinai, Inc., Los Angeles, CA, USA) software (18). By this algorithm, the left ventricle is segmented into short axis images with eight frames per cardiac cycle. Endocardial and epicardial surfaces and valve plane for every gating interval were determined. LVEF was derived from calculated LVEDV and LVESV. LVEF assessment by MPS is well validated and reproducible (19, 20).

LVEF $\geq$ 50% was considered as normal and < 50% as reduced (21).

Statistical analysis

Continuous variables are described as the mean $\pm$ s.d. for the equally distributed and as median for the non-equally distributed variables.

Categorical and ordinal variables were compared using a χ^2 test. Continuous variables were compared using the *T*-test, Mann–Whitney *U* and one-way ANOVA with Bonferroni correction as appropriate.

A multivariate linear regression model was built to evaluate the influence of all significantly different variables of Tables 1 and 2 on LVEF. In addition to diabetes, SRS (as a surrogate marker of prior myocardial infarction/scar) and SDS (as a marker of ischemia) were part of the model to correct for the presence and extent of CAD.

A multivariate analysis (bivariate logistic regression) was performed to evaluate the independent predictors of decreased LVEF. The same variables as in the multiple linear regression model were incorporated into the logistic regression model. *P* value, odds ratio, and confidence interval (CI) were calculated for each variable.

Table 1 Baseline characteristics.

	Overall (n=2400)	Non-diabetics (n=1826)	Diabetics (n=574)	P
Mean age $\pm$ s.d.	64 $\pm$ 11	64 $\pm$ 11	65 $\pm$ 10	0.016
Female	736 (30.7%)	579 (31.7%)	157 (27.4%)	0.049
BMI (kg/m ²) $\pm$ s.d.	27.5 $\pm$ 4.7	27.0 $\pm$ 4.4	29.2 $\pm$ 5.0	<0.001
Typical angina	802 (33.4%)	643 (35.2%)	159 (27.7%)	0.005
Atypical angina	648 (27.0%)	514 (28.1%)	134 (23.4%)	0.058
Dyspnea	955 (39.8%)	705 (38.6%)	250 (43.6%)	0.064
Known CAD	1106 (46.1%)	857 (46.9%)	249 (43.4%)	0.412
Prior MI	776 (32.3%)	662 (33.2%)	162 (28.2%)	0.099
Dyslipidemia	1393 (58.1%)	1012 (55.5%)	381 (66.5%)	<0.001
Arterial hypertension	1556 (64.9%)	1103 (60.4%)	453 (78.9%)	<0.001
Family history of CAD	649 (27.1%)	506 (27.8%)	143 (25.0%)	0.200
Smoker	1104 (46.0%)	858 (47.0%)	246 (42.9%)	0.040
Aspirin	1900 (72.1%)	1326 (72.6%)	411 (71.6%)	0.631
Anticoagulation	212 (8.8%)	153 (8.4%)	59 (10.3%)	0.177
β -Blockers	1512 (63.0%)	1172 (64.2%)	340 (59.3%)	0.040
ACE inhibitors	487 (28.9%)	270 (21.5%)	169 (38.9%)	<0.001
ATII antagonists	401 (23.8%)	289 (21.5%)	131 (30.1%)	<0.001
Calcium antagonists	478 (20.0%)	334 (18.3%)	144 (25.2%)	<0.001
Nitrates	312 (13.1%)	238 (13.1%)	74 (13.0%)	1
Statins	1208 (53.6%)	889 (52.3%)	319 (57.6%)	0.030

BMI, body mass index; MI, myocardial infarction; CAD, coronary artery disease. Statistically significant values are in boldface.

A *P* value <0.05 was considered statistically significant.

The analyses were performed with SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline data

Table 1 summarizes the baseline characteristics of the whole patient population and the comparison of diabetic and non-diabetic patients.

Diabetic patients were older, less often female, had a higher body mass index (BMI), more often had a history of dyslipidemia and arterial hypertension, but less often were smokers. They were more often treated with statins, ACE inhibitors, ATII- and calcium

antagonists, but less often with β -blockers, compared with their non-diabetic counterparts. Of note, diabetic patients reported typical angina less frequently than non-diabetic patients. Of the 574 diabetic patients, 120 were treated with insulin, 314 with an oral antidiabetic therapy, and for the remaining 140 patients the treatment modality was not known.

Stress test and MPS results

The MPS results of diabetic and non-diabetic patients are shown in Table 2.

Non-diabetic patients had a higher resting heart rate, were more often able to undergo physical stress and complained more often of typical anginal chest pain during stress testing. Regarding overall MPS abnormality (SSS) and ischemia (SDS), there was no difference

Table 2 Results stress/myocardial perfusion SPECT.

	Overall (n=2400)	Non-diabetics (n=1826)	Diabetics (n=574)	P
Resting heart rate (bpm)	78 $\pm$ 16	76 $\pm$ 16	81 $\pm$ 16	<0.001
Sinus rhythm	2300 (95.8%)	1753 (96.0%)	547 (95.3%)	0.290
LBBB	95 (4.0%)	68 (3.7%)	27 (4.7%)	0.440
Physical stress	1528 (63.7%)	1217 (66.6%)	311 (54.2%)	<0.001
Angina during stress	592 (24.7%)	469 (25.7%)	123 (21.4%)	0.041
ST changes	459 (19.1%)	360 (19.7%)	99 (17.3%)	0.181
Antianginal therapy stopped	1037 (43.3%)	787 (43.1%)	250 (43.6%)	0.855
SSS (median)	5	5	6	0.829
SRS (median)	1	1	2	0.401
SDS (median)	2	2	2	0.710
LVEF $\pm$ s.d.	54 $\pm$ 13	55 $\pm$ 13	53 $\pm$ 13	0.001
TID	186 (7.8%)	125 (6.9%)	61 (10.7%)	0.005

bpm, beats per minute; LBBB, left bundle branch block; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; TID, transient ischemic dilatation. Statistically significant values are in boldface.

Table 3 Distribution in four SSS subgroups.

	Non-diabetics (n=1826) (%)	Diabetics (n=574) (%)	P
SSS <4	41	39	0.21
SSS 4–8	22	23	0.76
SSS 9–13	15	18	0.23
SSS >13	22	20	0.62

SSS, summed stress score.

between the groups; however, TID was less often observed in non-diabetic patients.

Overall LVEF was significantly lower in diabetic compared with non-diabetic patients, 55 ± 13 and $53 \pm 13\%$ respectively ($P=0.001$).

Test results with respect to CAD extent

All patients were stratified into four subgroups with respect to CAD extent, as defined by the SSS. Distribution of diabetic and non-diabetic patients in these subgroups was similar which is shown in Table 3. The median SSS and SDS were also similar in these four subgroups (P not significant for all comparisons).

Diabetic patients had a significantly lower LVEF than non-diabetic patients irrespective of CAD extent (Fig. 1).

Relation to antidiabetic treatment

In a subgroup analysis, we evaluated the LVEF regarding the antidiabetic treatment (Fig. 2). The LVEF turned out to be significantly lower in patients treated with insulin in comparison with non-diabetic patients and diabetic patients without insulin treatment. No difference could be shown between non-diabetic patients and diabetic patients that were not treated with insulin.

Figure 1 Comparison of LVEF in non-diabetic and diabetic patients regarding as a function of coronary artery disease (CAD) – in three of the four subgroups, a significantly higher LVEF in non-diabetic compared with diabetic patients could be shown irrespective of CAD extent. LVEF, left ventricular ejection fraction; SSS, summed stress score; MPS, myocardial perfusion SPECT.

Figure 2 LVEF difference regarding the antidiabetic treatment regimen in the diabetic patients – significant differences were only seen in the subgroup of diabetic patients treated with insulin: their LVEF was significantly lower in comparison with non-diabetic patients and diabetic patients without insulin treatment. LVEF, left ventricular ejection fraction.

Variables linked to LVEF

In the multivariate linear regression analysis, male sex, diabetes, ACE inhibitor intake, pharmacologic stress, SRS, and SDS were linked with decrease in LVEF. Typical angina and intake of a statin were linked with increase in LVEF (Table 4).

Independent predictors of decreased LVEF

In total, 545 non-diabetic patients (30%) and 211 diabetic patients (37%) had a reduced LVEF ($P=0.005$).

As shown in Table 5, male sex, diabetes, pharmacological stress, SRS, and SDS were independent predictors of reduced LVEF. In contrast, the presence of angina decreased the probability of reduced LVEF. Of note, TID (as a possible marker for balanced and/or extensive ischemia) was not a predictor of reduced LVEF.

Diabetes, therefore, independently predicted decreased LVEF irrespective of prior CAD, evidence and extent of CAD.

Discussion

This study demonstrated a significantly lower LVEF in diabetic compared with non-diabetic patients ($P=0.001$) in a large patient population. Even though the difference was small, this finding may have important epidemiological impact, since LVEF is one of the most important predictors of survival. This hypothesis is supported by data from the Mayo clinic that has demonstrated a significantly worse survival of even asymptomatic diabetic patients with an LVEF of $<50\%$ (22).

Table 4 Variables independently influencing LVEF (as assessed by linear regression analysis).

	Regression coefficient	95% CI	P
Male sex	−6.72	−7.72 to −5.72	<0.001
Typical angina	1.73	0.61 to 2.85	0.002
Diabetes	−1.62	−2.67 to −0.57	0.003
Intake of ACE inhibitor	−1.75	−2.79 to −0.71	0.001
Intake of a statin	1.35	0.42 to 2.28	0.005
Pharmacological stress	−2.27	−3.21 to −1.32	<0.001
SRS (/score point)	−1.03	−1.11 to −0.95	<0.001
SDS (/score point)	−0.46	−0.56 to −0.36	<0.001

SRS, summed rest score; SDS, summed difference score.

The major finding of this study was that the difference in LVEF held true irrespective of the presence and extent of CAD.

In the last decades, the systolic function in diabetic vs non-diabetic patients has been investigated repeatedly, although mostly in cohorts with much fewer patients and with different LVEF measurement methods; in addition, the results were not conclusive: regarding LVEF, most of the studies did not report a difference between diabetic and non-diabetic patients (23–25), despite some studies that demonstrated a slightly lower LVEF in diabetic patients (26, 27). In the studies in which a lower LVEF was shown, it was mainly attributed to the fact that CAD is more common and also more often severe in diabetic patients even though the presence and extent of CAD were not taken into account (22, 28–30). This gap has been closed with our study because LVEF was compared in patients without evidence of CAD or in comparable groups when it came to the extent of CAD.

Konduracka *et al.* (24) also did not find any difference in LVEF ($P=0.169$) in a relatively small patient cohort (185 diabetic patients and 105 non-diabetic control subjects) and raised the question whether diabetes alone was really able to precipitate myocardial dysfunction despite the well-known histological changes in the myocardium; however, they only assessed patients with type 1 diabetes without risk factors and a mean age of only 34.5 years.

Only a few smaller studies have taken the presence of CAD into account, e.g. Htay *et al.* (23) evaluated the LVEF in 70 patients with diabetes mellitus type 2 and compared the results with gender-matched controls; after having excluded the presence of CAD, mean LVEF was shown to be comparable at least in men with and without diabetes ($P=0.16$) but was lower in women with diabetes compared with women without diabetes ($P=0.04$).

LVEF of patients treated with insulin was significantly lower in comparison with non-diabetic patients ($P=0.02$) and diabetic patients ($P=0.02$) without insulin treatment (even though insulin treatment did not turn out as an independent predictor of decreased LVEF). These results are in line with other observations where insulin treatment or insulin resistance was

predictive of CHF development (4, 31). In addition, Smooke *et al.* (32) showed an independently and markedly increased risk of mortality in insulin-treated diabetic patients with CHF (hazard ratio (HR) 4.30, 95% CI 1.69–10.94, $P<0.00001$), but not in non-insulin-treated diabetic patients compared with non-diabetic patients (HR 0.95, 95% CI 0.31–2.93, $P=0.395$). Witteles & Fowler (33) pointed out that there is increasing evidence that insulin resistance is also a primary etiologic factor in the development of non-ischemic CHF; indeed, insulin has profound effects on the myocardium (regarding energy metabolism, sympathetic activity, inflammation, oxidative stress, and microvascular dysfunction) (24, 34), but insulin treatment also implicates greater extent of macrovascular disease (a fact that did not seem to play a role in our study).

In this study, LVEF decreased as a function of diabetes in addition to male sex, extent of CAD (scar as shown by SRS; ischemia as represented by SDS), pharmacologic stress, and ACE inhibitor intake. Male individuals are well known to have lower LVEF than female individuals (35). The correlation of the extent of CAD and LVEF is quite obvious and pharmacologic stress is a well-known surrogate marker for overall sicker patients. ACE inhibitor intake is of course more common in patients with reduced LVEF. Interestingly, the presence of typical angina was linked to a higher LVEF. This is in line with the seemingly paradoxical finding in a large patient population where angina turned out to be a 'protective' factor (36). This may be similar to the fact that symptomatic patients seek help before they have an event as in contrast to patients with silent events, e.g. a silent myocardial infarction that results in decreased LVEF. A statin therapy demonstrated a positive correlation with LVEF. A recent meta-analysis also showed a positive effect of statin treatment on LVEF by demonstrating that use of statins in CHF patients may result in the improvement of cardiac function (37).

Looking at variables independently predicting a decreased LVEF, diabetes turned out to be an independent predictor, this in addition to male sex, pharmacologic stress, extent of scar (SRS), and ischemia (SDS). Again, patients with typical angina were less likely to have a decreased LVEF. Potential reasons have been discussed above.

Table 5 Independent predictors of decreased LVEF.

	OR	95% CI	P
Male sex	2.0	1.40–2.81	<0.001
Typical angina	0.7	0.47–0.96	0.026
Diabetes	1.6	1.14–2.13	0.006
Pharmacologic stress	1.7	1.25–2.23	0.001
SRS (/score point)	1.32	1.28–1.37	<0.001
SDS (/score point)	1.11	1.07–1.14	<0.001

SRS, summed rest score; SDS, summed difference score.

Limitations

We acknowledge the potential limitations of our study. It was a retrospective evaluation; although we recorded antidiabetic management at baseline, information on the duration of diabetes or diabetic control (such as HbA1c) was not available. As our patients were consecutive referrals to a tertiary center for further evaluation, there is certainly a referral bias.

Furthermore, we used MPS variables as surrogate markers for the presence and extent of CAD. Of course, by this method, we only pick up changes that are hemodynamically relevant and do not provide information on the coronary artery level (e.g. calcification). However, for the purpose of our study, this point should not play a relevant role.

The treatment modality in diabetic patients could not be assessed in 140/574 patients. In addition, we could not determine the type of diabetes (although we estimate more than 95% to be of type 2).

Implications

The high prevalence, morbidity, and mortality of CHF mandate early identification of risk factors and clinical signs to start appropriate and timely therapy; in addition to the high prevalence of CHF in diabetic patients, diabetes has been shown to have a prognostic impact on these patients (38, 39). Detecting and understanding LV dysfunction in diabetic patients may also help to delay or prevent the progression of CHF.

Conclusion

Diabetic patients had a lower LVEF than non-diabetic patients (even though the overall difference was small). This difference could be demonstrated regardless of CAD extent and may in part explain their worse cardiac survival compared with non-diabetic patients on an epidemiological level. In addition, this finding points to other discussed mechanisms than CAD being responsible for decreased LVEF in diabetic patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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