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Left ventricular diastolic function in patients with impaired glucose tolerance and heart failure with low left ventricular ejection fraction

Ewa Straburzyńska-Migaj, Andrzej Szyszka, Romuald Ochotny, Olga Trojnarska and Andrzej Cieśliński

1st Department of Cardiology, University School of Medical Sciences in Poznań, Poland

Abstract

Background: *According to epidemiological studies, impaired glucose tolerance (IGT) is, in common with diabetes, related to an increased risk of cardiovascular disease, including heart failure (HF). Diastolic left ventricular function is one of the indices of HF severity, and a restrictive filling pattern is related to increased mortality and a need for heart transplantation. The aim of the study was to evaluate left ventricular diastolic function in patients with IGT and HF due to left ventricular systolic dysfunction.*

Material and methods: *In 61 patients with HF and left ventricular ejection fraction (LVEF) < 45%, of mean age 50.5 ± 8.0 years, echocardiography with Doppler measurement of diastolic function parameters and oral glucose tolerance test (OGTT) were performed. Restrictive filling pattern (RFP) was diagnosed with E/A > 2 or between 1 and 2 and DTE ≤ 130 ms.*

Results: *IGT was diagnosed in 25 patients and normal glucose tolerance (NGT) in 36 patients. There were no significant differences in baseline clinical characteristics and LVEF between the two groups. In patients with IGT RFP was significantly more frequent (60 vs. 33%; p = 0.039) and the patients were in a higher NYHA class than those with NGT. In a multivariate regression analysis 2-h glucose level during OGTT was a significant predictor of E/A ratio independent of NYHA class, diuretic dose and LVEF.*

Conclusion: *Diastolic dysfunction and functional status according to NYHA class is worse in patients with HF due to left ventricular systolic dysfunction and IGT than in patients with NGT.*

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left ventricular diastolic function, impaired glucose tolerance, heart failure

Introduction

The influence of glucose metabolism on the cardiovascular system has recently become a subject of intense study [1–4]. According to epidemiological studies, impaired glucose tolerance (IGT) is, like diabetes, related to an increased risk of cardiovascular disease, including heart failure (HF) [5–8]. Hyperglycaemia plays an important role in the development and progression of micro- and macroangiopathy in diabetes mellitus. Diabetes is also an independent risk factor for HF [9]. Over the years

Address for correspondence:
Dr med. Ewa Straburzyńska-Migaj
1st Department of Cardiology
University School of Medical Sciences in Poznań
Długa 1/2, 61–848 Poznań, Poland
Tel: +48 61 854 91 46, fax: +48 61 854 90 94
e-mail: ewa.migaj-straburzynska@sk1.am.poznan.pl
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confirmation has been given of the existence of a diabetic cardiomyopathy, with impaired contractility leading to congestive HF [10, 11]. It has been indicated that impaired diastolic filling related to impaired diastolic function is the first abnormality in the presence of normal systolic left ventricular function [12, 13].

According to new observations, the interrelationships between diabetes and HF are more complicated and multi-factorial [3]. Recent studies indicate the presence of reciprocal interrelationships between HF and diabetes. Patients with chronic HF are at higher risk of developing type 2 diabetes mellitus. Of the increasing number of HF failure patients about 30% have diabetes [3, 11]. Mortality in this group is higher in comparison to non-diabetics and the HF is more advanced [14–16]. Less is known about HF patients with other glucose metabolism abnormalities.

Left ventricular diastolic dysfunction is one of the markers of HF severity. A restrictive filling pattern of the left ventricle (RFP) as assessed by echocardiography is related to increased mortality and the need for heart transplantation [17, 18]. The complex mechanisms underlying diastolic dysfunction have been closely investigated. We were unable to find an analysis of the possible influence of IGT on diastolic function indices in patients with HF and low left ventricular ejection fraction (LVEF).

The aim of the study was to determine the extent to which IGT influences left ventricular diastolic function in patients with HF and low LVEF.

Material and methods

The study included 61 patients who had been referred to the Department of Cardiology of the University School of Medical Sciences, Poznań, for evaluation of HF. These were consecutive patients with a mean age of 50.5 ± 8.0 years (28–69 years) with stable HF, NYHA class I–IV (mean 2.3 ± 0.8), and LVEF below 45% (11–44%; mean 26.8 ± 8.2%). Patients were excluded if they had had a recent (< 3 months) myocardial infarction, unstable angina or coronary revascularisation, or if they had a history of pulmonary disease, severe renal insufficiency or other organ disorders which would significantly alter their physical capacity. All the patients were maintained on their current HF therapy with stable doses for at least two weeks before the study. Fifty six (92%) patients received angiotensin-converting enzyme inhibitors, 45 (74%) received furosemid, 45 (74%) beta-blockers, 34 (56%) digoxin and 27 (44%) spironolactone.

M-mode, two dimensional and Doppler echocardiography were performed in all patients with a Hewlett-Packard Sonos 5500 echocardiographic device and a 2.5/3.5 MHz transducer. Left ventricular volumes: end-diastolic (LVEDV) and end-systolic (LVESV), and LVEF were measured from the apical four-chamber view using a modified Simpson's rule algorithm. Mitral inflow was measured from the apical four-chamber view with a sample volume positioned between the tips of the mitral leaflets to derive the following variables: peak early (E) and late (A) transmitral filling velocities, E/A ratio and the deceleration time of the E wave (DTE). A placing sample volume to record simultaneously mitral and aortic flow isovolumetric relaxation time (IVRT) was measured.

Restrictive filling pattern was defined either by E/A ratio > 2 or E/A ratio between 1 and 2 with DTE ≤ 130 ms.

The oral glucose tolerance test (OGTT) was performed in all patients based on routine methods used in the laboratory of SPSK No. 1 Hospital, Poznań. IGT was diagnosed with a fasting glucose level < 6.1 mmol/l and a level of 7.8 to 11.1 mmol/l two hours after the glucose load [19].

The results are given as a mean and standard deviation and proportions (%). The Mann-Whitney and chi-square analyses were used to evaluate the significance of differences between the groups. To determine correlations between variables the Spearman rank test was used. A multivariate regression analysis was performed to determine the relationship of E/A with NYHA class, furosemid dose and LVEF. Furthermore, a multivariate regression analysis was performed to determine the relationship between NYHA class and parameters significantly related in univariate analysis. A p value of < 0.05 was taken to be statistically significant. The statistical software Statistica 5.0 was used for all analyses.

Results

Twenty five (41%) patients had IGT and 36 (59%) had normal glucose tolerance (NGT). The clinical characteristics of both groups are presented in Table 1. There were no significant differences between the groups in age, body mass index (BMI), duration of HF symptoms, creatinine level, furosemid dose, treatment and proportion of ischaemic cardiomyopathy or hypertension. However, in the patients with IGT the HF symptoms were more severe as indicated by a higher NYHA class (there was a significantly greater proportion of NYHA III

Table 1. Clinical characteristics of patients with impaired glucose tolerance (IGT) and normal glucose tolerance (NGT)

	IGT (n = 25)	NGT (n = 36)	p
Age (years)	51.6 ± 9.4	49.7 ± 6.9	NS
Body mass index [kg/m^2]	29.0 ± 5.0	26.9 ± 5.3	0.1
Heart rate [1/min]	75 ± 14.6	76 ± 11	Ns
NYHA class	2.6 ± 0.6	2.1 ± 0.8	0.01
NYHA III + IV (%)	15 (60%)	10 (28%)	0.01
Creatinine [μmol/l]	90.1 ± 21	84.4 ± 16	NS
Furosemid dose [mg]	81.9 ± 45	66.7 ± 33	NS
Ischaemic heart disease (%)	12 (48%)	12 (33%)	NS
Hypertension (%)	15 (60%)	18 (50%)	NS
ACE inhibitors (%)	22 (88%)	34 (94%)	NS
Beta-adrenolytics (%)	20 (80%)	25 (69%)	NS
Furosemid (%)	21 (84%)	24 (67%)	NS
Left ventricular ejection fraction (%)	26.7 ± 8.6	26.9 ± 8.0	NS
Left ventricular end-diastolic volumes [ml]	194 ± 88	197 ± 100	NS
Left ventricular end-systolic volumes [ml]	256.2 ± 105.4	262 ± 113	Ns
E [cm/s]	84.3 ± 23.9	76.7 ± 25	NS
Deceleration time of the E wave [ms]	153.7 ± 74	173 ± 60	NS
A [cm/s]	58.0 ± 31	71.0 ± 21	NS
E/A ratio	2.1 ± 1.5	1.2 ± 0.9	0.075
Isovolumetric relaxation time [ms]	68.0 ± 34	80.0 ± 31	0.084

and IV patients). There were no significant differences in LVEDV and LVESV or in LVEF. There was a trend toward a higher E/A and a shorter IVRT in patients with IGT in comparison with NGT patients. RFP was significantly more frequent in patients with IGT than in those with NGT (60 vs. 33%; $p < 0.039$) (Fig. 1). In the group of patients as a whole there were significant correlations between DTE and NYHA class ($r = -0.28$; $p = 0.03$) and LVEF ($r = 0.3$; $p = 0.02$), and there was a trend between DTE and glucose levels two hours after glucose load ($r = 0.28$; $p = 0.056$) (Table 2). There were also significant correlations between E/A and NYHA class ($r = 0.35$; $p = 0.03$) and furosemid dose

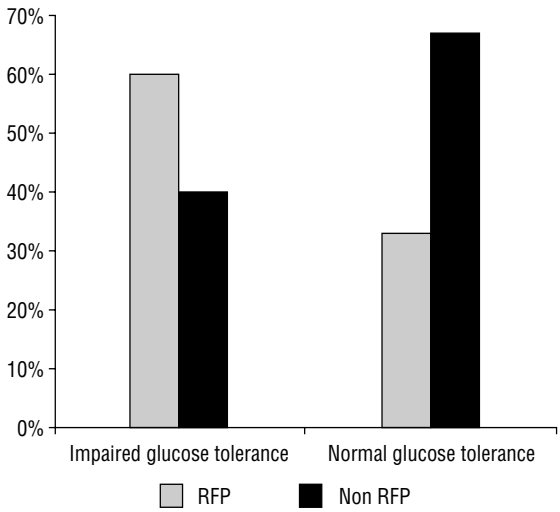

Figure 1. Restrictive filling pattern (RFP) in relation to glucose metabolism abnormalities ($p = 0.039$).

Table 2. The relation of indices of left ventricular diastolic function: E/A ratio and DTE and NYHA functional class to the studied parameters in the whole group of patients with heart failure

	E/A	DTE	NYHA
Age	NS	NS	p = 0.02
BMI	NS	NS	NS
NYHA	p = 0.03	p = 0.03	—
Furosemid dose	p = 0.03	p = 0.08	p = 0.05
HR	NS	p = 0.03	NS
Creatinine	NS	NS	p = 0.06
Glucose 2 h post load	p = 0.056	p = 0.09	p = 0.00005
LVEF	NS	p = 0.02	p = 0.00003
LVESV	NS	p = 0.09	p = 0.002
LVEDV	NS	NS	p = 0.02

DTE — deceleration time of the E wave, BMI — body mass index, HR — heart rate, LVEF — left ventricular ejection fraction, LVESV — left ventricular end-systolic volumes, LVEDV — left ventricular end-diastolic volumes

($r = 0.37$; $p = 0.03$), and there was a trend between E/A and glucose levels two hours after glucose load ($r = 0.28$; $p = 0.056$) (Table 2). In a multivariate regression analysis glucose level two hours after glucose load in OGTT was related to E/A ($p = 0.003$) independently of NYHA class (p = NS), diuretic dose ($p = 0.08$) and LVEF (p = NS). In Table 2 the results of correlations between NYHA class and clinical and echocardiographic parameters are presented. In a multivariate regression analysis performed with the inclusion of parameters significantly related to NYHA class in univariate analysis, glucose level two hours after glucose load in OGTT was independently related to NYHA class ($p = 0.01$).

Discussion

The main finding of the study is that patients with HF with low LVEF and IGT have more advanced left ventricular diastolic dysfunction and a lower functional capacity, assessed as a higher NYHA class, in comparison with patients without glucose metabolism abnormalities.

It has recently been reported that glucose metabolism abnormalities, not only associated with diabetes but also with IGT or impaired fasting glucose, are related to an increased risk of cardiovascular morbidity (CVD) [5, 6] and CVD mortality, an increased risk of death due to ischaemic heart disease, stroke and total mortality [7]. It has been demonstrated that glucose serum level is a continuous variable without definite cut-off value with reference to the risk of CVD [1]. Recent studies have revealed new data on the mechanisms of the action of hyperglycaemia on the structure and function of the cardiovascular system [1, 2]. The main factors responsible for the observed abnormalities are: endothelial dysfunction, increase in glycation and glycosilation product levels, changes in coagulation, an increase in oxidative stress, inflammation and apoptosis. It seems that IGT and post-prandial hyperglycaemia play an important role in the development and progression of atherosclerosis and are significant risk factors of cardiovascular disease. Diabetes is a disease of slow development. Vascular abnormalities in patients with type 2 diabetes are usually diagnosed at the same time as the diabetes. It could be that vascular disease appears before diabetes is diagnosed at the IGT stage of preceding glucose metabolism abnormality [6].

In one recent study it was shown by means of myocardial Doppler echocardiography that isolated type 2 diabetes mellitus causes myocardial dysfunction that becomes worse in the presence of cardiovascular disease [20]. Less is known about myocardial function in patients with IGT.

It has been documented that endothelial dysfunction, activation of an inflammatory process, oxidative stress and apoptosis also have important roles in the progression of HF symptoms [21]. It has been suggested that insulin resistance (which is associated with diabetes mellitus and IGT) in the pathogenesis of HF has a part to play [21]. In this study we have found that IGT worsens left ventricular diastolic function in patients with HF and that glucose level two hours after glucose load in the OGTT is independently related to E/A. It seems that more advanced diastolic dysfunction in patients with HF and IGT may be due, as with diabetes, to increased myocardial collagen accumulation and fibrosis with an increase in myocardial stiffness [22]. Increased glucose levels may lead to an intensification of endothelial dysfunction, a decrease in nitric oxide production and an increase in the production of free radicals, leading to microangiopathy and myocardial perfusion abnormalities and, further, to an increase in diastolic dysfunction. Diastolic dysfunction is often observed in patients with HF. The most advanced form, namely restriction, is associated with a lower exercise capacity and a worse prognosis [18, 23]. Impairment of diastolic function is due to increased filling pressure of the left ventricle, which is related to its increased stiffness. Diastolic function is dependent on, among other factors, histological changes related to collagen accumulation and an active relaxation process during the isovolumetric time. Understanding the processes influencing diastolic function would seem important as, theoretically, an improvement in diastolic properties may bring about an improvement in functional status and HF symptoms.

Patients with IGT have more advanced HF symptoms, as indicated by the higher NYHA class. As stated before, the severe diastolic dysfunction (RFP) which was observed in most of these patients is associated with a lower exercise capacity [23]. In a univariate analysis there were significant correlations between NYHA class and diastolic function indices. However, in a multivariate regression analysis glucose level two hours following glucose load in an OGTT was related independently to NYHA class. The decreased exercise capacity in patients with IGT in comparison with patients with NGT as evaluated according to NYHA class is probably due to higher vascular resistance as a consequence of endothelial dysfunction and perhaps to more pronounced skeletal muscle myopathy [21, 24].

It is proposed that OGTT be included in risk stratification in patients with known ischaemic

heart disease [25]. This may also be of value in patients with HF. From the clinical point of view observations regarding relations between IGT, diastolic dysfunction and functional status in patients with HF would appear important and may have some clinical implications. It may be supposed that this group of patients has an opportunity to achieve the greatest benefit from rehabilitation and physical training, both of which have recently been recommended for patients with heart failure.

Conclusion

In patients with heart failure and left ventricular systolic dysfunction with impaired glucose tolerance left ventricular diastolic dysfunction is more advanced and the functional status worse, as expressed by a higher NYHA class, in comparison with patients with normal glucose tolerance.

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