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Restrictive left ventricular filling pattern and its effect on the clinical course of systolic heart failure in patients receiving carvedilol

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Abstract

Background: *To analyze differences in brain natriuretic peptide (BNP) levels depending on mitral flow pattern (MFP) and to assess the effects of carvedilol on changes in MFP, left ventricular function and exercise capacity.*

Methods and results: *The study population consisted of 73 patients with symptomatic heart failure in NYHA classes II and III and LVEF < 40% without prior beta-blockade. In all patients at baseline, before carvedilol, and then at 3 and 12 months after initiation of treatment, the following parameters were assessed: HR, serum BNP, echocardiographic parameters, and exercise capacity with gas monitoring during cardiopulmonary stress test. Before carvedilol there was a positive correlation between BNP and E/A ($r = 0.17$; $p = 0.05$). BNP was significantly higher in patients with restrictive MFP (rMFP) as compared with nonrestrictive MFP (nrMFP) (541.5 ± 206.7* vs. *412.6 ± 207.2; $p = 0.009$), and lower VO_{2peak} in rMFP as compared with nrMFP (12.5 ± 3.7* vs. *16.5 ± 4.7; $p = 0.001$). After initiation of carvedilol, the patients with rMFP had reduced E/A (2.9* vs. *1.4; $p = 0.003$), and rMFP was changed to nrMFP in 60.8% of patients. Respective BNP concentrations were 342.16 ± 284.31* vs. *326.40 ± 264.6; NS. In patients with rMFP VO_{2peak}, %N increased significantly from 42.4 ± 10.2 to 52.4 ± 14.4; $p = 0.012$.*

Conclusions: *In patients with systolic congestive heart failure, the presence of rMFP is related to higher BNP levels and reduced VO_{2peak}. Chronic treatment with carvedilol replaces rMFP with nrMFP and improves exercise capacity in some patients.* (Cardiol J 2008; 15: 329–337)

Key words: restrictive filling pattern, heart failure, carvedilol

Introduction

In recent decades, left ventricular diastolic dysfunction has been increasingly frequently studied [1–3]. So far, left ventricular remodelling has been discussed from the viewpoint of systolic function. In recent years a number of reports have been published focusing on the importance of diastolic impairment in patients with dilated cardiomyopathy [4–7]. Marked diastolic dysfunction in patients with systolic heart failure is an unfavourable prognostic factor [8].

Experimental and clinical studies have demonstrated that prolonged heart failure is associated with altered left ventricular filling pattern (MFP, mitral flow pattern) on pulsed-wave Doppler [9–12].

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In most patients with systolic congestive heart failure (CHF), altered diastolic filling pattern ranges from impaired relaxation to restrictive MFP (rMFP) [11].

Several studies in patients with idiopathic cardiomyopathy and ischemic cardiomyopathy have shown that restrictive filling pattern rather than systolic function is a predictor of cardiovascular events [4, 11, 13, 14].

The assessment of left ventricular filling pattern provides important prognostic information in patients with systolic dysfunction, and according to some investigators it may be a useful tool for monitoring the tolerance and effectiveness of pharmacological treatment [7, 14, 15]. A change from restrictive to non-restrictive filling pattern adds important prognostic information [16]. Xie et al. [4] documented a close relationship between restrictive filling pattern and the functional status of the patient, confirming that the parameter is a non-invasive indicator of heart failure severity. Another study showed that restrictive filling pattern, and especially short deceleration time (DT < 140 ms), is an indicator of left ventricular dysfunction that is independent of left ventricular dimensions and ejection fraction, and is associated with reduced exercise capacity on spiroergometry [5].

Mitral flow profile then adds valuable hemodynamic and prognostic information in patients with systolic dysfunction [7, 17].

Clinical studies reporting the efficacy of beta-adrenergic blocking agents in patients with impaired diastolic function are scarce and mainly concern patients with preserved systolic function [18]. Capomolla et al. [19] evaluated the effects of carvedilol on diastolic function and mitral regurgitation in patients with ischemic heart failure and idiopathic cardiomyopathy. They demonstrated that chronic treatment with carvedilol in patients with CHF inhibits progression and dilatation of the left ventricle and results in partial regression of filling abnormalities.

Reports on the effects of chronic beta-adrenergic blockade on diastolic function in patients with systolic heart failure, and the outcomes based on MFP and associated neurohormonal changes, especially BNP levels, are scarce [20].

The purpose of the present study was to:

— analyze differences in brain natriuretic peptide (BNP) levels depending on mitral flow patterns in patients with symptomatic systolic heart failure;
— assess the effects of 12-month treatment with carvedilol on changes in mitral flow pattern, left ventricular function and exercise capacity.

Methods

The study population consisted of 73 patients (68 men and 5 women) aged from 30 to 69 years (54.8 ± 7.19) with symptomatic chronic heart failure due to ischemic heart disease (58 patients) and idiopathic cardiomyopathy (15 patients). The patients received treatment in the Department of Coronary Heart Disease and Out-patient Cardiac Department Institute of Cardiology CMUJ in Cracow in 2000–2004.

Patients with left ventricular ejection fraction (LVEF) < 40% on echocardiography were recruited. Exclusion criteria were as follows: fixed atrial fibrillation, unstable angina pectoris, myocardial infarction, stroke, percutaneous transluminal coronary artery (PTCA) or coronary artery bypass grafting (CABG) within the previous 3 months, contraindications to beta-blockade, significant aortic or mitral valve defects except functional mitral regurgitation related to heart failure, renal failure and uncontrolled diabetes mellitus. Prior to inclusion 12 patients (16%) had undergone PTCA within one coronary artery, 6 patients (8%) CABG, 3 patients (4%) received a DDD pacemaker, and one patient an implantable cardioverter-defibrillator.

For at least 3 months prior to the study the patients had been receiving angiotensin converting enzyme (ACE) inhibitors, diuretics and/or digoxin but not beta-blockers. Of these patients, 25 (34%) were in NYHA class II and 48 (66%) in NYHA class III. Arterial hypertension World Health Organization stage III was diagnosed in 68.4% and diabetes mellitus type 2 in 17.4%. Coronary angiography, performed in 70 patients, revealed significant lesions in 80%.

The study protocol was approved by the Local Ethics Committee. All patients gave their informed consent.

All patients at baseline, before carvedilol, and then at 3 and 12 months after initiation of treatment, underwent a panel of studies including assessment of functional capacity according to NYHA. BNP levels, echocardiograms and cardiopulmonary stress test (CPX) parameters were obtained at baseline and at 3 and 12 months.

Blood for measurements of BNP after overnight fasting and 30 min rest in the morning was collected from the antecubital vein in EDTA (Sarsted, Germany) and centrifuged and the plasma was stored at –30°C. Measurements were done in the Laboratory of Radioligands in Cracow (head: Prof. Marek Stępniewski). BNP was measured using an immunoenzymatic method and reagents provided by Immuno Biological Laboratories (Hamburg, Germany) (normal values up to 100 pg/mL).

The degree of beta-blockade was identified from heart rate in ECG at rest (HR_s).

Echocardiograms according to the Clinical Echocardiographic Guidelines of the Polish Cardiac Society [21] were obtained to measure cavity sizes, ejection fraction, segmental wall motion abnormalities and mitral flow parameters. M-mode echocardiography in parasternal long-axis projection was performed to measure left ventricular end-systolic dimensions (LVESd). 2D echocardiography was performed to calculate left ventricular end-diastolic and end-systolic volume (LVEDV, LVESV) adjusted for body surface. Left ventricular ejection fraction was calculated using the modified Simpson's method, averaging three consecutive measurements [22]. The size of the left atrium and right ventricle was measured and the presence of regurgitation was checked. Right ventricular pressure was calculated from tricuspid regurgitation fraction.

Contractility was measured in each segment separately using the wall motion score index (WMSI) [23].

To find out associated left ventricular diastolic dysfunction, routine mitral flow parameters were assessed. E wave, A wave, E/A ratio, DT and isovolumetric relaxation time (IVRT) were measured in patients with sinus rhythm in 4-chamber projection using the spectral pulsed wave Doppler technique with the sampling volume placed on the tips of mitral leaflets [24]. In patients with normal mitral flow pattern the retrograde pulmonary venous blood flow was also analyzed [22]. Echocardiography was performed using an Acuson Aspen device with 4 MHz probe and simultaneous VHS recording.

Based on Doppler mitral flow parameters [25] the following subgroups were identified:

— rMFP group — with restrictive mitral flow pattern (23 patients), if E/A was > 2 or between 1 and 2, but DT was < 140 ms;
— nrMFP group — with nonrestrictive mitral flow pattern (50 patients), if E/A was < 1 or between 1 and 2, but DT was > 140 ms.

Exercise capacity and gas exchange parameters were identified from a spiroergometric test (CPX) on a treadmill using the modified Naughton's protocol. The test was conducted in patients who were clinically stable for at least 2 weeks and on current pharmacological regime. Before CPX, spirometry at rest was performed. Maximal oxygen consumption (VO_{2peak}) was measured when the amount of oxygen used did not increase despite higher workload. In patients who terminated the test before the plateau due to increasing dyspnea or fatigue, VO_{2peak} was averaged from the values measured in the last 30 s of the test and expressed as values adjusted for body mass (ml/kg/min) and as a percentage of the normal value [26–28].

The following exercise stress test parameters were analyzed: heart rate at rest (HR_s), exercise time (t_{max}) and workload (WAT). At peak exercise the following parameters were identified: heart rate (HR_m), peak oxygen consumption expressed as kg/min (VO_{2peak}), and percentage of the normal value (VO_{2peak}%N), ventilatory equivalent for oxygen (VE/VO_2), ventilatory equivalent for carbon dioxide (VE/VCO_2), partial oxygen pressure ($PETO_2$), and partial carbon dioxide pressure in exhaled air ($PETCO_2$). In some patients, it was impossible to define the anaerobic threshold.

At 3 and 12 months, changes in dosage of CHF agents, heart transplantation and death were recorded.

Statistical analysis

Statistical analyses were made using the STATISTICA package. Changes in the variable between measurements in the whole group, taking into account a factor dividing the population into subgroups, were analyzed using ANOVA with repeated measurements and Scheffe's test. Relationships between the two variables in the subgroups were studied using Pearson's linear correlation (r) or Spearman's (r_s) correlation. A p value of 0.05 was considered statistically significant.

Results

Clinical characteristics are summarized in Table 1. Mitral flow was analyzed in 73 patients at baseline. Nonrestrictive mitral flow pattern (nrMFP) was found in 50 (68.5%) patients, and restrictive MFP (rMFP) in 23 (31.5%) patients. Mean enalapril doses in both groups at baseline were 14.9 ± ± 7.3 mg/daily, mean diuretic dose (furosemide) was 39.1 ± 19.2 mg/daily, and mean carvedilol at 3 months was 25.0 ± 13.5 mg/daily. The dosage did not change significantly at 12 months.

At 3 months rMFP was seen less frequently (19.2%) and at 12 months only in 14% of patients (Table 2).

At 12 months rMFP changed to nrMFP in 14 patients (60.8%), whereas in 5 patients (21%) baseline rMFP remained unchanged. Among patients with nrMFP at baseline, rMFP was found only in 6 patients (12%). There was a positive correlation between HR_s and E/A ($r = 0.55$; $p = 0.049$).

Before initiation of carvedilol, patients in the rMFP group were in a significantly worse NYHA class, had significantly higher HR_s, higher BNP

Table 1. Clinical characteristics of patients before carvedilol treatment.

Heart failure etiology	Idiopathic cardiomyopathy	15 (21%)
	Ischemic cardiomyopathy	58 (79%)
Hypertension III degree acc. to WHO classification		50 (68,4%)
Hypercholesterolemia		53 (73%)
Previous myocardial infarction	With Q wave	45 (52.3%)
	Without Q wave	11 (12.8%)
NYHA functional class	II	25 (34.9%)
	III	48 (66%)
Mitral flow pattern	Restrictive	23 (31.5%)
	Nonrestrictive	50 (68.5%)
Coronary angiography (n = 70)	Normal coronary arteries	14 (20%)
	1-vessel disease	11 (19.6%)
	2-vessel disease	15 (26.9%)
	Multivessel disease	30 (53.4%)

Table 2. Changes in the occurrence of restrictive (rMFP) and nonrestrictive mitral flow pattern (nrMFP) during therapy.

Mitral flow pattern	Before beta-blockade	At 3 months	At 12 months
rMFP	23 (31.5%)	14 (19.2%)	10 (14.0%)
nrMFP	50 (68.5%)	59 (80.8%)	61 (86.0%)
All	73	73	71

Table 3. Selected parameters in rMFP and nrMFP groups assessed before beta-blockade and at 12 months after initiation of carvedilol therapy.

	Before beta-blockade		p	At 12 months		p
	rMFP ($\bar{x}$ ±SD)	nrMFP ($\bar{x}$ ±SD)		rMFP ($\bar{x}$ ±SD)	nrMFP ($\bar{x}$ ±SD)	
NYHA class	2.86 ± 0.36	2.5 ± 0.52	0.001	1.6 ± 0.6	1.8 ± 0.5	NS
BNP [pg/ml]	541.5 ± 206.7	412.6 ± 207.2	0.009	342.16 ± 284.3	326.40 ± 264.6	NS
HR_s [l/min]	91.3 ± 17.31	83.4 ± 17.4	0.043	69.7 ± 9.1	68.6 ± 13.2	NS
LVEF (%)	26.6 ± 5.8	30.0 ± 6.2	0.010	35.0 ± 9.0	37.8 ± 8.3	NS
LVESd [mm]	60.1 ± 8.8	54.7 ± 9.1	0.008	55.8 ± 11.7	53.0 ± 8.8	NS
LVEDd [mm]	70.8 ± 7.0	67.7 ± 7.3	0.050	66.7 ± 9.3	65.6 ± 8.5	NS
LA [mm]	48.1 ± 6.6	43.0 ± 6.1	0.001	45.4 ± 6.3	40.9 ± 5.1	0.001
WMSI	2.4 ± 0.3	2.3 ± 0.4	0.030	2.2 ± 0.3	2.2 ± 0.2	NS
E/A	2.9 ± 1.2	1.0 ± 0.4	0.001	1.4 ± 0.9	1.2 ± 0.7	NS
DT [ms]	185.8 ± 89.04	265.8 ± 75.96	0.001	196.9 ± 76.7	249.9 ± 100.8	0.03
IVRT	108.54 ± 30.36	117.5 ± 18.14	NS	110.7 ± 31.9	94.6 ± 26.5	NS

rMFP — restrictive mitral flow pattern; nrMFP — nonrestrictive mitral flow pattern; NYHA — New York Heart Association; BNP — brain natriuretic peptide; HR_s — heart rate at rest; LVEF — left ventricular ejection fraction; LVESd — left ventricular end-systolic diameter; LVEDd — left ventricular end-diastolic diameter; LA — left atrium; WMSI — wall motion score index; E/A — E/A ratio; DT — deceleration time; IVRT — isovolumetric relaxation time

levels, larger LVESd and LVEDd, lower LVEF, larger left atrium and higher left ventricular mass index, as compared with nrMFP patients. Table 3 summarizes the differences in clinical parameters at baseline and after treatment, in both groups.

In rMFP patients, as early as at 3 months after beta-blockade, E/A was significantly reduced (Fig. 1), similar to WMSI from 2.4 ± 0.3 *vs*. 2.3 ± 0.3, p = = 0.03, as compared with nrMFP patients. The remaining echocardiographic parameters remained unchanged at 3 months after carvedilol. BNP levels were found to be strongly associated with left ventricular diastolic function. There was a positive correlation between BNP and E/A (r = 0.17; p = 0.05)

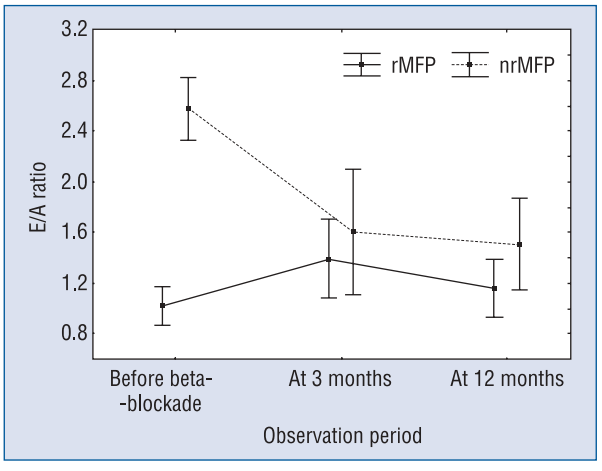

Figure 1. Changes in E/A ratio values during carvedilol therapy in patients with nonrestrictive (nrMFP) and restrictive (rMFP) mitral flow pattern.

and a negative correlation between BNP and IVRT ($r = –0.19$; $p = 0.06$). This may indicate that BNP levels are related to the severity of left ventricular diastolic impairment.

In rMFP patients at baseline, exercise time was shorter, and workload and VO_{2peak} were lower as compared with nrMFP patients, implying a negative effect of restrictive mitral flow on exercise capacity in patients with failing hearts.

In patients with initial rMFP, 3-month beta-adrenergic blockade resulted in prolonged exercise time from 480.9 s to 610.5 s, and at 12 months to 660.3 s; workload and metabolic equivalent were also increased (Table 4). At 12 months, in rMFP patients, VO_{2peak} increased by a mean of 1.95 ml/kg/min. In nrMFP patients, VO_{2peak} increased only by 0.23 ml/kg/min. VO_{2peak}%N increased significantly in rMFP patients from 42.4 ± 10.2 to 52.4 ± 14.4; $p = 0.012$ (Table 5). In nrMFP patients both VO_{2peak} and $VO_{2\,peak}$%N remained unchanged during treatment (Fig. 2). These findings indicate that the change in mitral flow profile from restrictive to non-

Table 4. Correlations between BNP and E/A, IVRT, LA, IM, RVSP before beta-blockade and at 3 and 12 months after carvedilol therapy

	BNP [pg/mL] — correlation values at study time points		
	Before beta-blockade	At 3 months	At 12 months
E/A	r = 0.17 p = 0.05	r = 0.29 p = 0.005	r = 0.16 NS
IVRT	r = –0.19 p = 0.06	r = –0.32 p = 0.002	r = –0.22 p = 0.038
LA	r = 0.20 p = 0.05	r = 0.32 p = 0.002	r = 0.12 NS
IM	r= 0.20 p= 0.04	r = 0.35 p = 0.001	r = 0.21 p = 0.042
RVSP	r = 0.24 p = 0.02	r = 0.23 p = 0.032	r = 0.29 p = 0.005

BNP — brain natriuretic peptide; E/A — E/A ratio; IVRT — isovolumetric relaxation time; LA — left atrium; IM — mitral insufficiency; RVSP — right ventricle systolic pressure

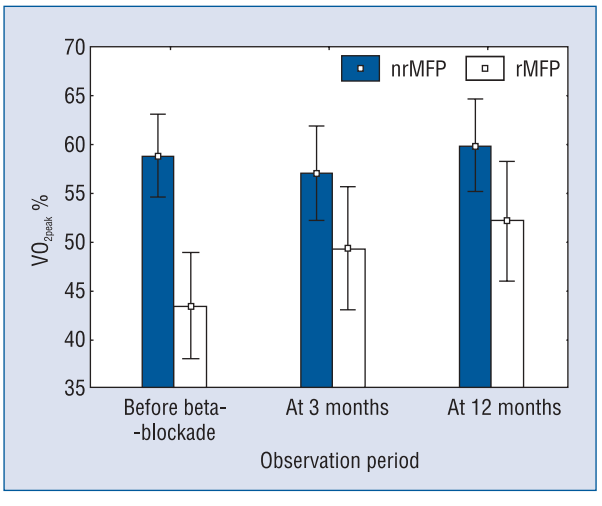

Figure 2. Comparison of peak oxygen consumption (VO_{2peak}%) changes in rMFP and nrMFP groups assessed before beta blockade and after 3 and 12 months carvedilol therapy.

Table 5. Selected cardiopulmonary stress test parameters in rMFP and rnMFP groups before beta-blockade and at 12 months after initiation of carvedilol therapy.

	Before beta-blockade		p	At 12 months		p
	rMFP ($\bar{x}$ ±SD)	nrMFP ($\bar{x}$ ±SD)		rMFP ($\bar{x}$ ±SD)	nrMFP ($\bar{x}$ ±SD)	
T_{max} [l/min]	480.9 ± 207.1	657.2 ± 291.8	0.004	660.3 ± 235.3	792.7 ± 298.4	NS
WAT	54.3 ± 29.0	80.3 ± 47.9	0.004	85.4 ± 39.3	107.6 ± 41.5	NS
VO_{2peak} [ml/kg/min]	12.5 ± 3.7	16.5 ± 4.7	0.001	14.5 ± 3.1	16.7 ± 4.6	NS
VO_{2peak} [%N]	42.4 ± 10.2	58.0 ± 15.5	0.041	52.4 ± 14.4	59.0 ± 15.6	NS
VE/VCO_2	37.86 ± 9.45	36.7 ± 7.41		37.6 ± 7.8	38.9 ± 8.57	

T_{max} — stress test duration time; VO_{2peak}, — peak oxygen consumption; WAT — workload; VO_{2peak}%N — percentage of the normal value; VE/VCO_2 — ventilatory equivalent for oxygen

restrictive improves exercise capacity in heart failure patients. When the frequency of restrictive mitral flow profile was analyzed in association with peak oxygen consumption, rMFP was seen in 64% of patients with VO_{2peak} < 14 ml/kg/min at baseline, as compared with 14.8% of patients with VO_{2peak} > > 14 ml/kg/min. At 12 months the number of patients with VO_{2peak} < 14 ml/kg/min decreased from 25 to 13, and rMFP was found in 33% of them.

At one year of follow-up there were 3 deaths, whereas at follow-up of 5 to 36 months, mean 22.81 ± ± 6.46 months, there were 5 deaths. At 3 months these patients had lower LVEF as compared with the survivors (28.3 ± 2.6 *vs*. 34.4 ± 7.6; p = 0.029) and higher E/A (2.7 ± 0.8 *vs*. 1.4 ± ± 0.9; p = 0.003) corresponding with restrictive mitral flow pattern. Moreover, those who died had a larger left atrium (48.7 ± 6.6 *vs*. 42.3 ± 3.1; p = 0.003) and higher WMSI (2.5 ± 0.1 *vs*. 2.2 ± ± 0.3; p = 0.049).

Discussion

In CHF patients, the efficacy of pharmacological treatment is usually evaluated from left ventricular systolic function as the most reliable indicator of left ventricular impairment. Left ventricular systolic dysfunction in heart failure is usually associated with diastolic dysfunction. Diastolic impairment in patients with LVEF < 45% is an additional factor of poor prognosis. Evidence shows that restrictive mitral flow pattern is the strongest indicator of poor prognosis in patients after myocardial infarction and with dilated cardiomyopathy [11, 29].

In patients with left ventricular systolic dysfunction in the course of various diseases, diastolic function is also impaired, which is associated with relaxation abnormalities, decreased compliance and disordered left ventricular geometry because of ventricular dilatation [12]. In some patients with dilated cardiomyopathy, mitral flow pattern is typical of impaired relaxation, and in others restrictive MFP is associated with increased filling and marked left ventricular stiffness [5, 6, 30–35].

In the present study, rMFP was found in 30% of patients at baseline, nrMFP (impaired relaxation or pseudonormalization) in 65%, and only 5% had normal mitral flow pattern.

There was a relationship between the presence of restriction and NYHA class. The correlation between NYHA class and E/A confirmed the dependence between circulatory capacity and diastolic dysfunction. According to some investigators, CHF patients with rMFP have more severe clinical symptoms of heart failure, more frequent third heart sound, increased left ventricular end-diastolic pressure, more severe ventricular dilatation, larger left atrium, higher wedge pressure and mitral regurgitation [36]. For this reason, restrictive mitral flow pattern may be a marker of hemodynamic abnormalities and usually implies increased left ventricular end-diastolic pressure and pulmonary wedge pressure [37].

In the present study, carvedilol induced significant changes in systolic and diastolic ventricular function corresponding with positive left ventricular remodelling. The significantly reduced HR_s at 3 months, as a manifestation of beta-blockade, was partly associated with insignificant improvement of left ventricular systolic function (increased LVEF, decreased LVEDd) and significant improvement of wall motion. In patients with rMFP, the significantly reduced HR_s at 3 months also resulted in E/A reduction and DT prolongation, i.e. diastolic improvement. At 12 months, diastolic function remained unchanged.

The present study shows that the most affected patients, i.e. the patients with restricted mitral flow pattern, showed improved diastolic function at 3 months. It was the first, favourable manifestation of carvedilol efficacy.

The lack of significant difference in LVEF between patients with restrictive and nonrestrictive MFP after 12-months carvedilol therapy may indicate that systolic improvement, to a considerable degree, depends on the reversibility of initial diastolic dysfunction.

The present findings are concordant with the results of Andersson et al. [38], who found that diastolic function was most markedly improved at 3 months after metoprolol, whereas LVEF increased significantly at 6 and 12 months.

Changes in left ventricular diastolic function are related to a number of factors including relaxation velocity, left ventricular wall stiffness and pressure gradient between the left ventricle and left atrium. Active myocardial relaxation is responsible for left ventricular pressure reduction and rapid filling after mitral valve opening. Relaxation affects isovolumetric diastole, early filling in mitral flow, and E/A. Deceleration time is significantly related to left ventricular wall stiffness [22].

Despite various limitations associated with the assessment of left ventricular diastolic function based on traditional parameters (E/A, DT, IVRT) related to age and heart rate, evidence shows the prognostic value of diastolic dysfunction and its correlation with heart failure progression [25]. In the present study the mean age was 56.0 ± 9.19 years,

and none of the patients was over 70. Of the left ventricular diastolic parameters studied, mainly E/A was found to be affected by beta-adrenergic blockade.

The recent SWEDIC study (Results of the Swedish Doppler-Echocardiographic Study) was designed to investigate the effect of carvedilol on diastolic function (E/A, DT, IVRT) in patients with heart failure and preserved systolic function. Carvedilol was found to significantly change E/A. The E/A ratio is considered the most useful indicator of diastolic dysfunction in CHF patients. The study showed that the beneficial effects of carvedilol, as compared with placebo, included a significantly improved E/A, which was found in patients with initial heart rate > 71 bpm [18]. The investigators concluded that the benefits of carvedilol resulted from improved early filling of the left ventricle [18].

In the present study, rMFP patients were in worse NYHA class, had larger left atrium, mitral regurgitation, and lower exercise capacity on CPX and VO_{2peak} as compared with nrMFP patients. Carvedilol for 12 months in rMFP patients reduced left atrial size and mitral regurgitation. This finding is indirect proof that improved diastolic function after beta-adrenergic blockade significantly affects left atrial function, which is concordant with the recent study on left atrial size and left ventricular diastolic function [39].

In heart failure, we observe an early rise in BNP [40, 41]. Its excessive release in CHF patients is an important element of neurohumoral activation. BNP concentrations increase in proportion to the severity of heart failure. For this reason, BNP may add prognostic information to identify patients at risk [42, 43].

In the present study, BNP was markedly elevated at baseline in rMFP patients as compared with nrMFP patients. The correlation between BNP and diastolic function parameters indicates a relationship between diastolic dysfunction and elevated BNP. Higher BNP at baseline was associated with larger left atrium, mitral regurgitation, right ventricular size and elevated pulmonary arterial pressure. Recently it has been reported that severe diastolic impairment or high-grade mitral regurgitation may induce excessive BNP secretion also by atrial myocytes [44].

So far, most reports have dealt with BNP in patients with left ventricular diastolic dysfunction and normal systolic function [45]. In 2004 Toughton et al. [44] demonstrated increased BNP in patients with diastolic heart failure and left ventricular systolic dysfunction.

In the present study, 12-month treatment with carvedilol was associated with a significant decrease in BNP, especially in patients with rMFP at baseline. At 12 months, BNP levels were similar in patients with rMFP and nrMFP. This finding, and the associated improvement in diastolic function in rMFP patients, indicates that changes in BNP correspond with the degree of diastolic function improvement.

Exercise capacity in patients with heart failure depends primarily on left ventricular diastolic function, which was confirmed in the present study.

Patients with rMFP had significantly lower VO_{2peak} in comparison to nrMFP patients. Restrictive MFP was also more frequent among patients with VO_{2peak} < 14 ml/kg/min. Chronic treatment with carvedilol was associated with a significant improvement in diastolic function and an increase in VO_{2peak} by a mean of 1.95 ml/kg/min. These findings indicate a significant relationship between diastolic improvement and peak oxygen consumption in patients with restriction that is reversible by beta-adrenergic blockade, and imply that the subjects who benefit most from beta-adrenergic blockade with carvedilol are those with the poorest exercise capacity at baseline.

The mechanism of the positive effects of carvedilol on diastolic function is not clear. Short relaxation time is an unfavourable factor, especially when myocardial function is impaired. Beta-adrenergic blockade prolongs diastole more than systole, which in turn augments diastolic filling and improves myocardial function and metabolism.

According to Bergstrom et al. [18], the beneficial effects of carvedilol on diastolic function are associated with slowing down the left ventricular filling rate rather than augmenting myocardial relaxation. Ventricular filling is shifted from late to early diastole, thus normalizing its course. Sequelae of reduced heart rate are difficult to differentiate from other effects of beta blockade. However, evidence shows that beta-blockers do not only act through reduction of heart rate. Other negative chronotropic agents such as calcium channel blockers do not produce similar outcomes in CHF patients [18].

Previous studies have shown that restrictive mitral flow pattern is associated with increased mortality rate in CHF patients [11, 30]. The present study confirms this finding. Of the 5 patients who died during follow-up, 3 had rMFP at baseline, which remained unchanged despite treatment. The remaining 2 patients had nrMFP before beta-blockade. After treatment, nrMFP changed to rMFP in one patient, and nrMFP remained unchanged in one patient. The annual mortality rate among patients with restrictive MFP was 17% and was lower than that reported by Pinamonti et al. [17], i.e. 35%.

Evidence shows that rMFP which remains unchanged during treatment is an independent prognostic factor [17].

The present study shows that preserved rMFP or no changes after treatment may be an indicator of poor prognosis.

Limitation of the study

The main limitation of the study is its inhomogeneous population for evaluation of the severity of diastolic dysfunction and the influence of pharmacotherapy. Because of the small sample size, we used a simplified classification of diastolic dysfunction into restrictive and nonrestrictive mitral flow pattern. The small sample size also prevented us from evaluating changes in diastolic function with respect to the severity of systolic impairment.

Conclusions

1. Restrictive mitral flow pattern in patients with systolic heart failure is associated with higher heart rate at rest, worse exercise capacity, lower peak oxygen consumption and higher brain natriuretic peptide levels in comparison with patients with nonrestrictive mitral flow pattern.
2. A change from restrictive to nonrestrictive mitral flow pattern after treatment is the first manifestation of positive carvedilol effects preceding systolic improvement.

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