Influence of myocardial viability on responsiveness to cardiac resynchronization in ischemic dilated cardiomyopathy: a prospective observational cohort study

İskemik dilate kardiyomiyopatide kardiyak resenkronizasyon yanıtlarına miyokart canlılığının etkisi: Bir prospektif gözlemsel kohort çalışması

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ABSTRACT

Objective: To understand whether patients with post-ischemic dilated cardiomyopathy and myocardial viability (MV) could benefit from cardiac resynchronization therapy (CRT) in terms of clinical, echocardiographic and neuro- hormonal parameters compared to patients without MV.
Methods: One hundred and four consecutive patients were enrolled in a prospective observational cohort study. Using dobutamine stress echocardiography, 2 groups were identified: group A of 51 patients with MV and group B of 53 patients without MV. All patients were implanted with biventricular pacing devices combined with an internal cardioverter-defibrillator. Clinical, echocardiographic and neuro-hormonal parameters were evaluated at baseline and at six month follow-up. Analysis of variance for repeated measures on each variable suggestive of remodeling was performed. We considered responder every patient with: decrease of > 15% in left ventricular volumes and/or improvement in left ventricular ejection fraction of > 5% in addition to NYHA class improvement.
Results: All the variables improved in both groups (time effect). Comparing the two groups (group effect), the following variables were significantly better in group A: N-terminal pro-B-type natriuretic peptide (p=0.02), NYHA class (p=0.003), reverse remodeling (RR) (p=0.007), dP/dt (p=0.005), left ventricular ejection fraction (p=0.009), 3rd sound (p=0.01), and left ventricular end-systolic volume after the first week (p=0.035). RR occurred at the first week after CRT only in Group A and was maintained for all the time of this study. The maximum difference of the decrease of left ventricular volumes between the two groups occurred after the first week (p<0.001).
Conclusion: Patients with MV responded better than patients without MV with a significant improvement after the first week from CRT.
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Key words: Cardiac resynchronization therapy, dilated cardiomyopathy, ventricular remodeling

ÖZET

Amaç: Post-iskemik dilate kardiyomiyopatili ve miyokart canlılığı (MV) olan hastaların, klinik, ekokardiyografik ve nöro-hormonal parametreler açısından, MV olmayan hastalarla karşılaştırıldığında kardiyak resenkronizasyon tedavisinden (KRT) yarar görüp-görmeyeceklerini anlamak.
Yöntemler: Prospektif, gözlemsel kohort çalışmaya 104 ardışık hasta dahil edildi. Dobutamin stres ekokardiyografi kullanarak, 2 grup tespit edildi: A grup 51 MV'li hasta ve grup B 53 MV'siz hasta. Tüm hastalara internal kardiyoverter-defibrilatörle kombine biventriküler pacing cihazı konuldu. Klinik olarak, ekokardiyografik ve nöro-hormonal parametreler başlangıç ve altı aylık takipte değerlendirildi. Remodeling düşündüren her değişken hakkında tekrarlayan ölçümler için varyans analizi yapıldı. Aşağıdakileri olan her hasta "cevap veren" olarak düşünüldü: NYHA sınıflamasında düzelmeye ilaveten, sol ventrikül völümlerinde > %15 azalma ve/veya sol ventrikül ejeksiyon fraksiyonunda > %15 düzelme.
Bulgular: Tüm değişkenler her iki grupta da (zaman etkisi) düzeldi. İki grup karşılaştırıldığında (grup etkisi), aşağıdaki değişkenler A grubunda anlamlı olarak daha iyi: N-terminal pro-B-tip natriüretik peptid (p=0.02), NYHA sınıf (p=0.003), tersine remodeling (TR) (p=0.007), dP/dt (p=0.005), sol ventrikül ejeksiyon fraksiyonu (p=0.009), 3. ses (p=0.01) ve ilk haftadan sonra sol ventrikül sistol sonu völümü (p=0.035). Tersine remodeling

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KRT'den sonra ilk haftada sadece A grubunda meydana geldi ve bu çalışmanın tüm süresinde devam etti. İlk haftadan sonra, iki grup arasında maksimum SVSSV'de azalma farkı oluştu (p<0.001).
Sonuç: Kardiyak resenkronizasyon tedavisinden ilk hafta sonrasında, MV'li hastalar MV'siz hastalara göre daha iyi önemli bir düzelme gösterdiler. *(Anadolu Kardiyol Derg 2012; 12: 132-41)*
Anahtar kelimeler: Kardiyak resenkronizasyon tedavisi, dilate kardiyomiyopati, ventriküler remodeling

Introduction

Heart failure represents a major cause of mortality and morbidity in developed countries, with a growing epidemiologic importance (1, 2). Death is mainly attributed to arrhythmias in patients in New York Heart Association (NYHA) class II, progressive ventricular dysfunction in patients in NYHA class IV, and both causes in patients in NYHA class III (3).

Recently published studies have reported that cardiac resynchronization therapy (CRT) can improve clinical outcomes in patients in NYHA class III to IV despite optimized medical therapy with QRS duration greater than 120 msec. Both American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines recommended CRT (class IA) in patients with left ventricular (LV) ejection fraction (EF) less than or equal to 35%, sinus rhythm, and NYHA functional class 3 or ambulatory class 4 symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than 120 msec (4, 5). Several trials have demonstrated that CRT significantly improves hemodynamics, symptoms, exercise tolerance and quality of life in patients with idiopathic or ischemic dilated cardiomyopathy (6-8). Reduction in mortality was due to fewer deaths both from worsening heart failure and from sudden death (9).

Tissue Doppler Imaging (TDI) that measures regional wall motion velocities is one of the most used methods to accurately quantify regional left ventricular function. Some studies have demonstrated a relation between LV dyssynchrony on pulsed wave TDI and improvement in symptoms and/or LVEF after CRT (10-12). Penicka et al. (13) used pulsed wave TDI (with an integration of interventricular and LV dyssynchrony) and reported a sensitivity of 96% with a specificity of 77% to predict response to CRT.

Some new biochemical markers, as B-type natriuretic peptide (BNP), were used to demonstrate CRT effectiveness. BNP and its N-terminal fragment (NT-proBNP) are neurohormones synthesized and secreted mainly from ventricular myocardium. The increase of ventricular wall stress may stimulate their release. High levels of NT-proBNP are associated with high cardiac filling pressure and can predict systolic and/or diastolic heart failure (14-17).

The responsiveness to CRT is better in patients with idiopathic dilated cardiomyopathy than in those with ischemic dilated cardiomyopathy (18, 19). However, few medical studies showed that the response to CRT may be related to extent of viable myocardium and inversely related to the extent of scar tissue (20, 21).

The aim of this study was to evaluate the influence of myocardial viability (MV) (22, 23) on responsiveness to CRT in patients with ischemic dilated cardiomyopathy.

Methods

Study design

The aim of this prospective observational cohort study was to evaluate the influence of MV on responsiveness to CRT. The dobutamine stress-echo (DSE) was used to distinguish patients with 10 or more viable sectors (considering both sectors at rest and after DSE) (24-27).

Ischemic patients with very large MV were compared to ischemic patients with poor MV and variables suggestive of reverse remodeling (RR) during the follow-up were analysed.

Study population

From September 2006 to June 2010 we enrolled 104 consecutive patients with ischemic dilated cardiomyopathy and no indication of myocardial revascularization because of complex coronary anatomy, patient's refusal and comorbidities.

Inclusion criteria were: 1) last heart failure event more than 6 weeks before; 2) optimal medical therapy; 3) NYHA class III or IV; 4) QRS duration ≥120 msec; 5) end-diastolic left ventricular diameter indexed ≥ 30 mm; 6) LVEF ≤35%. All the enrolled patients fulfilled the inclusion criteria. Exclusion criteria were: 1) acute coronary syndrome or coronary artery revascularization (angioplasty or by-pass) less than 6 months before; 2) severe comorbidities limiting the life expectancy to less than 12 months; 3) atrial fibrillation; 4) serum creatinine level more than 2.5 mg/dL; 5) poor quality echocardiographic examination.

All patients gave oral and written informed consent. The study was approved by the local ethics committee and was conducted according to the Helsinki declaration.

Study protocol

Using DSE, the presence and extent of MV were investigated and two groups were identified: Group A, with MV: 51 pts, 33 males and 18 females; mean age: 70.9±5 years; BSA=1.8±0.9 m^2 (10 or more viable sectors were present, considering both sectors at rest and after DSE) and Group B: 53 pts: 34 males and 19 females; mean age: 72.3±5 years; BSA= 1.8±0.1 m^2 (<10 viable sectors were present). The two groups were homogeneous as regards demographic and clinical features (Table 1).

We analyzed clinical, echocardiographic and laboratory parameters before the implantation and at one week, three months and six months after CRT.

Study variables

The following clinical and echocardiographic variables were evaluated: QRS duration, left ventricular end-systolic volume (LVVs), interventricular (VV) delay, pre-ejection aortic time, presystolic mitral regurgitation, Q-left time (TDI), Q-right time (TDI), Q-PL (M-Mode), LVEF, dP/dt, pulmonary artery systolic pressure

Table 1. Baseline characteristics of the patients

Variables	Group A (n=51)	Group B (n=53)	*p
Mean age, years	70.9±5.2	72.3±5.4	NS
Male, n (%)	33 (64.2)	34(64.7)	NS
BSA, m^2	1.8±0.9	1.8±0.1	NS
Diabetes mellitus, n (%)	24 (47)	28 (52.8)	NS
Hypertension, n (%)	28 (54.9)	28 (47.1)	NS
Myocardial infarction, n (%)	43 (84.3)	47 (88.6)	NS
COPD, n (%)	8 (15.6)	10 (18.8)	NS
≥2 vessels coronary artery disease, n (%)	43 (84.3)	42 (79.2)	NS
PCI/CABG, n (%)	37 (72.5)	40 (75.4)	NS
ACE-inhibitor, n (%)	36 (70.5)	34 (64.1)	NS
ARB, n (%)	15 (29.4)	19 (35.8)	NS
Digitalis, n (%)	14 (27.4)	18 (33.9)	NS
Furosemide, n (%)	45 (88.2)	47 (88.6)	NS
Amiodarone, n (%)	18 (35.2)	22 (41.5)	NS
Beta-blocker, n (%)	43 (84.3)	46 (86.7)	NS
Aldosterone inhibitor, n (%)	32 (62.7)	34 (64.1)	NS
Nitrates, n (%)	42 (82.3)	40 (75.4)	NS
VAS	40.7±14.1	42.2±13.9	NS

Data are presented as mean±SD and numbers (percentages)
*unpaired t test and Chi-square test
ARB - angiotensin receptor blockers, BSA - body surface area, CABG - coronary artery bypass graft, COPD - chronic obstructive pulmonary disease, PCI - percutaneous coronary intervention, VAS - quality of life visual analogue scale

(sPAP), number of viable segments, NT- proBNP, serum creatinine, NYHA functional class, 3rd heart sound, and Quality of Life Visual Analogue Scale (VAS) test. Six variables were considered predictive of RR: LVEF, dP/dt, NT-proBNP, VAS, LVVs, pre-systolic MR. RR was defined according to a decrease in at least 15% of LVVs.

Primary end-point of the study was a better response to CRT in group A compared to group B. We considered responder every patient with: decreases of >15% in LVVs and/or improvement in LVEF of > 5% in addition to NYHA class improvement.

Secondary end-point was a better response of following parameters in patients with a large quote of MV (Group A): NT proBNP levels, dP/dt, pre-systolic MR, VAS score.

NT -proBNP assessment

Serum was separated by centrifugation at 1500=g and stored at -70°C until analysis; all samples from the same patient were analyzed in the same batch. NT-proBNP (in pmol/L) was measured by the commercially available electrochemiluminescence immunoassay on an Elecsys 1010 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Normal value was less than 400 pmol/L.

Standard echocardiography

All patients were examined using a HP Sonos 5500 ultrasound system (Hewlett-Packard Imaging Systems, Andover, MA). Left ventricular volumes and LVEF were calculated by modified biplane Simpson rule from the apical four-chamber and two-chamber views. Left ventricle was divided into 16 segments, in accordance with the guidelines of the American Society of Echocardiography (28). We performed atrioventricular (AV) optimization before VV optimization (29, 30). We used interactive aortic outflow method as follows: 1) obtaining continuous wave Doppler velocity-time integral (VTI) of aortic valve outflow at varying AV delays. 2) starting with AV delay of 200 msec; progressively shortening the AV delay by 20 msec until AV delay reaches 60 msec. 3) Selecting the AV delay at which the VTI (a proxy for LV stroke volume) is the largest.

Dobutamine echocardiography

MV was identified using DSE. Standard M-Mode, 2-D and Doppler echocardiographic study, parasternal long axis and short axis views (at the level of the papillary muscles), apical two- and four-chamber views were recorded at baseline and at each stage of the dobutamine protocol. 5, 10 and 20 µg/kg/min was administered for at least 5 min each before imaging. Dobutamine was discontinued before the target dosage of 20 µg/kg/min was reached when one of the following criteria occurred: systolic blood pressure ≥180 mmHg; diastolic blood pressure ≥100 mm Hg; severe hypotension (systolic blood pressure <90 mmHg); significant arrhythmias, signs of ischemia (worsening of regional wall motion, angina), or significant patient discomfort. Digitized cycles of each view were stored for later side-by-side display in a quad screen format to facilitate the comparison of images at rest and during different rates of dobutamine infusion. Images were also recorded on videotape. Echocardiograms were read by investigators unaware of the clinical and angiographic findings in each patient. The standard 16-segment model was used for semiquantitative wall-motion analysis. Wall motion was described as normal, hypokinetic, akinetic or dyskinetic. At rest hypokinetic and normokinetic sectors were considered viable. During dobutamine echocardiography, MV was defined if at least 2 near sectors, with altered contraction in basal condition, had increased their thickness and if there was an improvement of wall motion score index superior to 20%.

Tissue Doppler imaging

All patients underwent 2D-Doppler and tissue Doppler imaging (TDI) echocardiographic evaluation at baseline, and one week, three months and six months after the CRT implantation, to evaluate inter and intraventricular delay. The basal and medium sectors of the left ventricle were studied by pulsed-wave TDI, by placing the sample volume on each sector, to evaluate longitudinal myocardial function. Gain and filter settings were adjusted as needed to eliminate background noise and to allow for a clear tissue signal.

During the study the TDI technique was utilized as follows: In the apical 4-chambers and long-axis view, cardiac asynchrony was assessed from time interval between onset of QRS complex and peak of regional velocity of myocardial systolic shortening as surrogate of regional electromechanical coupling time. Regional

activation was measured at LV basal-medium lateral (LV L), basal-medium septal (LV S), and basal-medium posterior (LV P) segments and RV basal lateral (RV L) segment. Intraventricular asynchrony was calculated as difference between the longest and shortest regional electromechanical coupling time in 3 LV basal-medium zones (LV L, LV S, and LV P). Left ventricular asynchrony was defined as a delay ≥60 ms (31, 32). Interventricular asynchrony was calculated as difference between regional electromechanical coupling time in RV L segment and most delayed from 3 LV segments (longest regional electromechanical coupling time).

The myocardial velocity waves were defined by three positive waves: S1 (the first wave representing the isovolumic contraction phase), S2 (after S1, during mechanical systole), and S3 (during isovolumic relaxation phase). In CAD patients, these peaks might be different, especially in the presence of clear post-systolic motion, than we considered the time interval from the start of the QRS complex to the peak of S2. Each parameter was measured and averaged over three consecutive beats.

Three highly experienced sonographers performed all echocardiograms. All TDI time intervals were measured by one single observer. For testing reproducibility of TDI time intervals, a second observer who was blinded to the patient's data performed the measurements again on the same data in all patients.

Pacemaker implantation and programming

All implanted biventricular pacing devices were combined with an internal cardioverter-defibrillator. Electrocatheters for the right ventricular stimulation were always located on the interventricular septum. The left ventricular pacing lead was placed in a tributary of the coronary sinus (postero-lateral vein or lateral vein). Adequate pacing and sensing properties of all leads were tested. After procedure, biventricular parameters were optimized, above all atrio-ventricular delay (12) and VV delay (sequential stimulation included from 12 to 20 msec) (33, 34). Optimum sequential CRT (defined as pre-activation of LV or RV) can reduce the extent of segments with delayed longitudinal contraction. In idiopathic dilated cardiomyopathy, the delayed longitudinal contraction tend to be located in the LV lateral and posterior walls; in contrast, in ischemic cardiomyopathy delayed longitudinal contraction is more frequent in the septum and in the inferior wall (33). Right ventricular lead preactivation was programmed in the case of septal or posterior wall delay.

Definition of goals

There is no agreement about the best end-point to evaluate the CRT response between RR or clinical status.

We considered responder every patient with: decreases of > 15% in LVVs and/or improvement in LVEF of >5% in addition to NYHA class improvement (Table 5). RR was defined according to a decrease in at least 15% of LVVs (10, 11, 35). Patients were recruited in Group A if 10 or more viable sectors were present (considering both sectors at rest and after DSE). The following clinical parameters were evaluated: NYHA functional class, 3rd heart sound, and Quality of Life Visual Analogue Scale (VAS) test (36, 37). Moreover, we evaluated NT-proBNP levels before and after CRT, in relation to MV.

Statistical analysis

The data analysis was performed using SPSS version 13.0 for Windows dedicated software (SPSS Inc., Chicago, Illinois, USA). Continuous variables of the two groups were analyzed by impaired T-test, while for categorical variables Chi-square test (or Fisher exact test when needed) was performed. Analysis of variance for repeated measures was performed on each variable suggestive of remodeling. The General Linear Model Repeated Measures procedure, that provides analysis of variance when the same measurement is made several times on each subject, was used. Each variable entered the general linear model considering the four different times at which it was collected (repeated measures), while the variable "viability" was included as factor. The course of the variables (time effect), the difference between the two groups (group effect) and the trend of the differences in the time between the two groups (group-time effect) were studied. Principle effects and interaction was analyzed. A p value <0.05 was considered statistically significant.

Results

One hundred four patients were studied: 51 with large MV (group A) and 53 with poor MV (group B). As shown in Table 2, group A patients had more viable segments than Group B (p<0.001). There was no significant difference between the two groups re-

Table 2. Electrocardiographic, echocardiographic and neurohumoral variables

Variables	Group A (n=51)	Group B (n=53)	*p
QRS duration, msec	142.0±10.4	142.7±11.2	NS
LVVs, ml	152.8±31	153.2±12	NS
VV delay, msec	85.2±18.8	92.6±16.2	0.037
Pre-Ejection aortic time, msec	150.7±5.1	149.9±9.5	NS
Mitral regurgitation, ml	53.0±14.7	50.7±12.8	NS
Q-left time, TDI, msec	208.3±54.4	150.1±52.7	0.009
Q-right time, TDI, msec	255.1±85	266.4±61.1	NS
Q-PL M-mode, msec	203.9±73.1	243.1±55.3	0.059
LVEF, %	27.0±4.3	26.7±3.6	NS
dP/dt, mmHg/sec	691.9±102.3	656.1±81.4	NS
sPAP, mmHg	44.5±8.5	46±10.2	NS
Number of viable segments, n	11.9±0.9	5.9±0.9	<0.001
NT pro-BNP, pg/ml	2287±658	2385±588	NS
Patients with creatinine 1.5-2.5 mg/dl, n (%)	14 (27.4)	15 (28.3)	NS

Data are presented as mean±SD and numbers (percentages)
*unpaired t test and Chi-square test
LVEF - left ventricular ejection fraction, LVVs - left ventricular end-systolic volume, NT-pro BNP, N - terminal pro-B-type natriuretic peptide, sPAP - Systolic pulmonary arterial pressure Q-left time, the time from the onset of the Q-wave on the surface ECG to the onset of the regional systolic motion of left ventricle (evaluated by TDI). Q-right time, the time from the onset of the Q-wave on the surface ECG to the onset of the regional systolic motion of right ventricle (evaluated by TDI). Q-PL M-mode, the time from the onset of the Q-wave on the surface ECG to the onset of the regional posterior systolic motion of left ventricle (evaluated by M-mode), TDI - tissue Doppler imaging

spect to pacemaker lead placement (postero-lateral vein: 65% vs 68%, Group A vs Group B, P=NS; lateral vein: 35% vs 32%, Group A vs Group B, P=NS). All the variables improved in both groups (time effect). Comparing the two groups (Group effect), the following variables showed a significant difference: NT-proBNP decreased (p=0.02) (Fig. 1a and Table 3, 4), NYHA class improved (p=0.003) (Fig. 1b), LVVs at the first week decreased (p=0.035) (Fig. 1c), RR (p=0.007) (Fig. 1d), dP/dt (p=0.005) (Fig. 2a), LVEF (p=0.009) improved (Fig. 2b), pre-systolic MR (p=0.032) and 3rd sound were less frequent (p=0.01) (Fig. 2c). The following variables showed significant differences in the time between the two groups (group-time effect): VAS test (p<0.002) (Fig. 2d), NYHA class (p=0.009), RR (p<0.001), dP/dt (p=0.001) and the presence of 3rd sound (p=0.003) during the six month follow-up. The 3rdsound presence significantly decreased in Group A more than in Group B (3rd sound before CRT=83% in Group A, after one week=25%, after three months=17%, after six months=15%; group effect: p=0.01; Group-time effect: p=0.003).

During the six month follow-up 3 deaths occurred in group A and 9 deaths in group B. Cardiovascular deaths were one in group A (cardio-embolic stroke) and 5 in group B (4 for end stage of heart failure and one for incessant and refractory ventricular arrhythmia).

Reverse remodeling

RR was found only in group A (Fig. 1d). The maximum difference in the percent decrease of LVVs between the two groups occurred after the first week from CRT (p<0.001). At the first week after CRT the mean decrease of LVVs in group A was equal to 15.9±5.4 ml and in group B-9.06±4.7 ml (p<0.001). Three and six months after CRT a further decrease of LVVs occurred in both groups, but no significant difference between the two groups was found (3 months: group A=6.04±3.3 vs group B=7.1±4.0; 6 months: group A=1.5±2.5 vs group B=2.0±2.1). RR was detected at the first week after CRT only in group A (Fig. 1c-d) and was maintained during the follow-up. In Figure 1d the decrease of LVVs (RR) in percent is reported, higher is the value more important is RR.

Clinical and echocardiographic response

During 6 months of study, we found an agreement between clinical response and echocardiographic response in 56 patients (Table 5). Fourteen patients in group A (27.4%) and 28 patients in the group B (52.8%) were non-responders (p=0.01) considering both clinical and echocardiographic parameters. The subgroup B with clinical response to CRT reached an insufficient percentage of decrease of LVVs.

Discussion

Several studies have shown that about 30% of patients fulfilling the ACC/AHA criteria for CRT implantation did not benefit from CRT (38-40).

Table 3. Echocardiographic, neurohumoral and clinical variables at baseline and during the follow-up

Group	Variables	Baseline	1st week	3rd month	6th month
A	LVEF, %	27.0±4.4	34.5±5.8	36.8±6.3	37.4±5.9
	dP/dt, mmHg/s	691.9±102.3	765.8±103.3	785.9±110.2	798.3±106.8
	NT-proBNP, pg/ml	2287±658	1738±606	1512±665	1379±597
	VAS	40.7±14.1	65.3±17.5	68.4±14.6	67.6±13.1
	LVVs, ml	152.8±31	134.7±25	128.7±25	127.0±25
	Q-left time TDI, msec	208.3±54.4	215.2±48	214.3±47	214.5±47
	Q-right time TDI, msec	255.1±85	211.5±49	210.6±49	211.8±51
	Patients with pre-systolic MR, %	64.70	19.60	27.45	23.52
B	LVEF, %	26.7±3.7	29.5±6.1	30.8±5.8	31.2±6.1
	dP/dt, mmHg/s	656.1±81.4	696.3±100.2	705.8±102.6	727.5±108.0
	NT-proBNP pg/ml	2385±588	2085±616	1893±756	1731±798
	VAS	42.2±13.9	54.2±17.9	56.0±17.2	57.1±19.7
	LVVs, ml	153.2±12	137.0±15	133.7±17	128.6±18
	Q-left time TDI, msec	150.1±52.7	147.9±44	147.5±44	146.3±44
	Q-right time TDI, msec	266.4±61.1	208.2±60	205.2±58	205.3±59
	Patients with pre-systolic MR, %	60.37	41.50	41.50	37.73

Data are presented as mean±SD and numbers (percentages)
Analysis of variance for repeated measures was performed on each variable suggestive of remodeling (see Table 4)
LVEF - left ventricular ejection fraction, LVVs-left ventricular end-systolic volume, MR - mitral regurgitation, m - months, NT-pro BNP-N - terminal pro-B-type natriuretic peptide, SD - standard deviation,VAS - quality of life visual analogue scale, w-week
Q-right or left time (TDI): Q-left time is the time from the onset of the Q-wave on the surface ECG to the onset of the regional systolic motion of left ventricle (evaluated by TDI), apart from the site of measurement and considering the longest interval. Q-right time is the time from the onset of the Q-wave on the surface ECG to the onset of the RV regional systolic motion (evaluated by TDI)

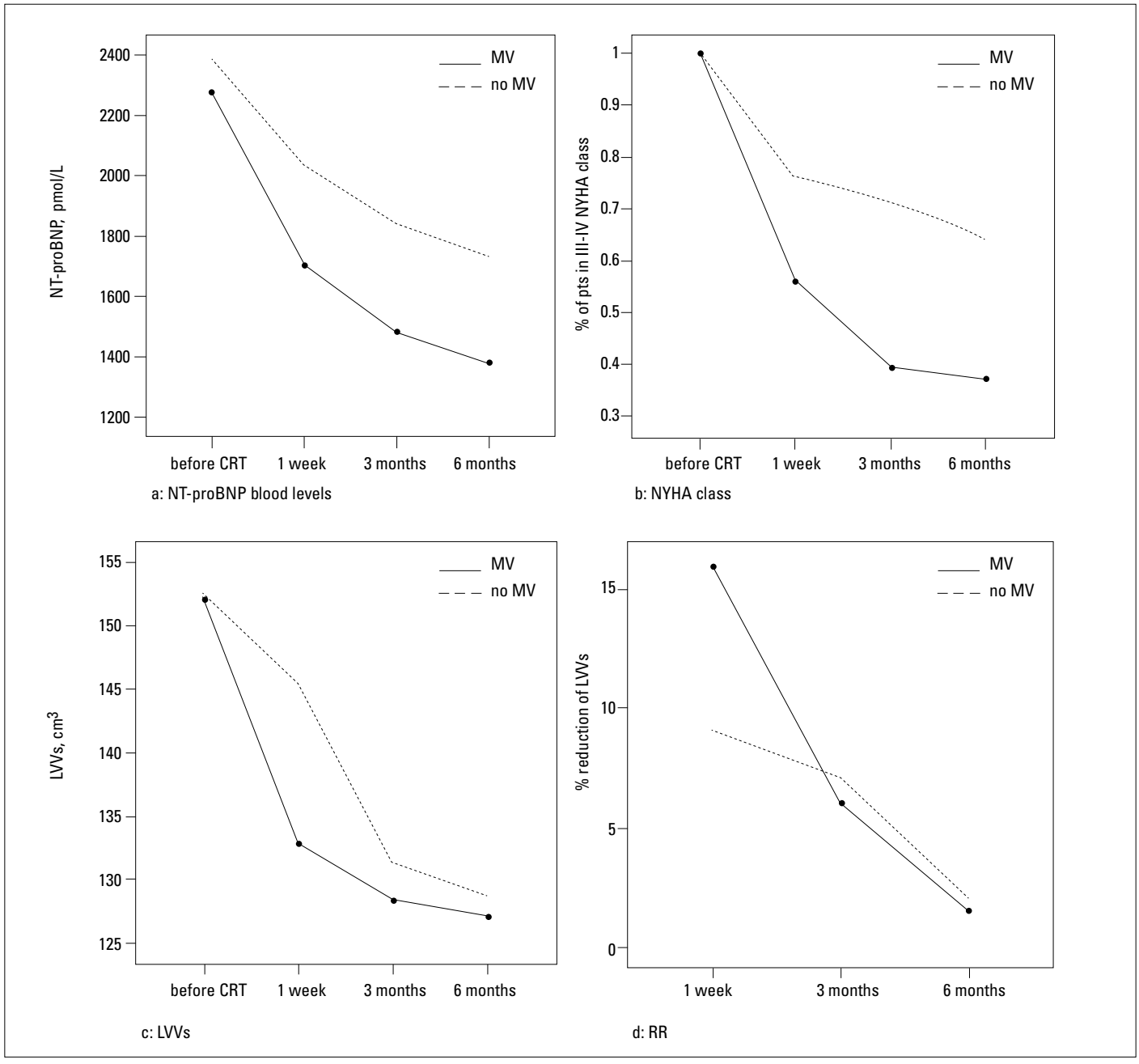

Figure 1. a: NT-proBNP levels. Time effect: p<0.0001; group effect: p=0.02; group-time effect: p=0.1
b: NYHA class. Time effect: p<0.0001; group effect: p=0.003; group-time effect: p=0.009
c: LVVs. Time effect: p<0.0001; group effect: p=0.4 (1st week p=0.035); group-time effect: p =0.64
d: RR. Time effect: p<0.0001; group effect: p=0.007 (1st week p=0.001); group-time effect: p<0.001

CRT - cardiac resynchronization therapy, LVVs - left ventricular end-systolic volume, MV - myocardial viability, NT-proBNP- N-terminal pro-B-type natriuretic peptide, pts - patients, RR - reverse remodeling as percent reduction of LVVs

Continuous line: group with myocardial viability

Broken line: group without myocardial viability

Statistic: The General Linear Model Repeated Measures was used. This procedure provides analysis of variance when the same measurement is made several times on each subject

Primary end-point of the study was to demonstrate a better response to CRT in group A compared to group B. We considered responder every patient with: decreases of >15% in LVVs and/or improvement in LVEF of >5% in addition to NYHA class improvement.

We observed a decrease in NYHA class after CRT in the majority of patients (time effect). However, the presence of MV was associated with a greater functional class improvement, with a significant difference in group effect (p=0.003) and in group time effect (p=0.009). Comparing the two groups an improvement of LVEF (p=0.009) was also observed.

The first week after CRT the decrease of LVVs was greater in group A as compared to group B (p<0.001); similarly RR was detected only in group A and persisted at the follow-up. In the present study the non-responder patients were 14 in group A

Table 4. Statistical analysis results of General Linear Model Repeated Measures procedure

Variables	Time effect		Group effect		Group-time effect		Estimation of parameters (p)		
	p	F	p	F	p	F	1 w	1 mo	3 mo
NT pro-BNP	<0.0001	80	0.02	5.3	0.1	2.1	0.013	0.018	0.019
VAS	<0.0001	10	0.013	6.3	0.002	10.2	0.010	0.001	0.004
LVVs	<0.0001	7.5	0.4	0.6	0.64	0.21	0.035	0.61	0.79
dP/dt	<0.0001	12.7	0.005	8.4	0.001	11	0.002	0.001	0.002
LVEF	<0.0001	78.9	0.009	7.1	0.11	2.5	0.004	0.003	0.027
Pre-systolic MR	<0.0001	16	0.032	4.7	0.061	3.6	0.044	0.003	0.039

Each variable entered the general linear model considering the four different times at which it was collected (repeated measures), while the variable "viability" was included as factor. The course of the variables (time effect), the difference between the two groups (group effect) and the trend of the differences in the time between the two groups (group-time effect) were studied. General Linear Model (GLM) includes repeated measurements (factorial design) ANOVA, Mauchly's test of sphericity, t-test, F test. In addition to testing hypotheses, GLM Repeated Measures produces estimates of parameters at 1 week, 3 months and 6 months

LVEF - left ventricular ejection fraction, LVVs - left ventricular end-systolic volume, MR - mitral regurgitation, m - months, NT-pro BNP-N-terminal pro-B-type natriuretic peptide, SD-standard deviation, VAS-quality of life visual analogue scale, w-week

Q- right or left time (TDI): Q-left time is the time from the onset of the Q-wave on the surface ECG to the onset of the regional systolic motion of left ventricle (evaluated by TDI), apart from the site of measurement and considering the longest interval. Q-right time is the time from the onset of the Q-wave on the surface ECG to the onset of the RV regional systolic motion (evaluated by TDI)

Table 5. Distribution of clinical and echocardiographic variables in responders and non-responders

Variables at 6 months	Responders (n=56)	Non-responder (n=42)
NYHA Class improvement, n (%)	56 (53.8)	6 (5.7)
*RR, n (%)	37 (35.5)	0
LVEF improvement >5%, n (%)	43 (41.3)	3 (2.8)
NT pro-BNP reduction, n (%)	50 (48.0)	5 (4.8)
3rd sound disappearance, n (%)	47 (45.1)	9 (8.6)
VAS test improvement, n (%)	51 (49.0)	10 (9.6)
Pre-systolic MR disappearance, n (%)	46 (44.2)	5 (4.8)
dP/dt reduction, n (%)	47 (45.1)	5 (4.8)

*RR has been defined as decrease in at least 15% of LVVs; this parameter was reached only in group A, with a large quote of myocardial viability

We considered responder every patient with: decreases of >15% in LVVs and/or improvement in LVEF of >5% in addition to NYHA class improvement. During 6 months of study we found an agreement between clinical response and echocardiographic response in 56 patients

In brackets we reported the percentage compared to all population (104 pts)

LVEF - left ventricular ejection fraction, MR - mitral regurgitation, m - months, NT-pro BNP-N-terminal pro-B-type natriuretic peptide, RR - reverse remodeling, VAS - quality of life visual analogue scale, w-week

(27.4%) and 28 in the group B (52.8%) considering both clinical and echocardiographic parameters.

Secondary end-point was a better response for following parameters in patients with a large quote of MV (group A): NT proBNP, dP/dt, pre-systolic MR, VAS score. The results of the study confirmed our hopes: comparing the two groups NT-proBNP and pre-systolic MR decreased markedly, while dP/dt and VAS improved significantly.

Several authors observed that the responsiveness to CRT was better in patients with idiopathic dilated cardiomyopathy than in patients with ischemic dilated cardiomyopathy. In this study, we found that in the setting of ischemic dilated cardiomyopathy an important difference in the response to CRT may exist in relation to the presence of MV. The patients with a consistent amount of MV could respond better to CRT implantation (41-43).

In the present study, the effects of CRT on clinical, echo and biochemical parameters were analyzed in patients with and without MV. NT-pro BNP, a peptide strongly correlated with outcome in heart failure patients, decreased more in patients with MV, in accordance with previous studies (14-17). Importantly, NT-proBNP levels were associated with a greater decrease of LVVs when MV had been found. Therefore, the decrease in NYHA class and the observed larger decrease in NT-proBNP levels might be associated with a better prognosis in the MV patients, compared with the no MV ones. A further important finding of our study was the significant improvement of the above mentioned parameters already at the first week after CRT. A relevant effect of CRT within the first week after the implantation was reported in previous studies (33, 38, 44-47).

When the difference in the time between the patients with and without MV was evaluated (group-time effect), the functional class, the quality of life, and the LV remodeling performed better when CRT had been implanted in patients with MV. The decrease of the 3rd sound in group A more than group B showed that a clinical parameter can also be important in the valuation of the responsiveness to CRT.

Comparing the two groups (group effect) pre-systolic MR was less frequent in group A (p=0.032). However pre-systolic MR persisted at the follow-up in a little quote of patients with RR despite atrio-ventricular interval optimization. The disagreement between the RR and the presence of pre-systolic MR could be explained on the basis that the optimal AV delay varies with time, necessitating periodic re-evaluation. However, we suppose that the different quote and distribution of MV could play a role with an early displacement of papillary muscles in a very little quote of ischemic patients. Atrial contraction could also explain the phenomenon with an improvement of left ventricular end-diastolic pressure.

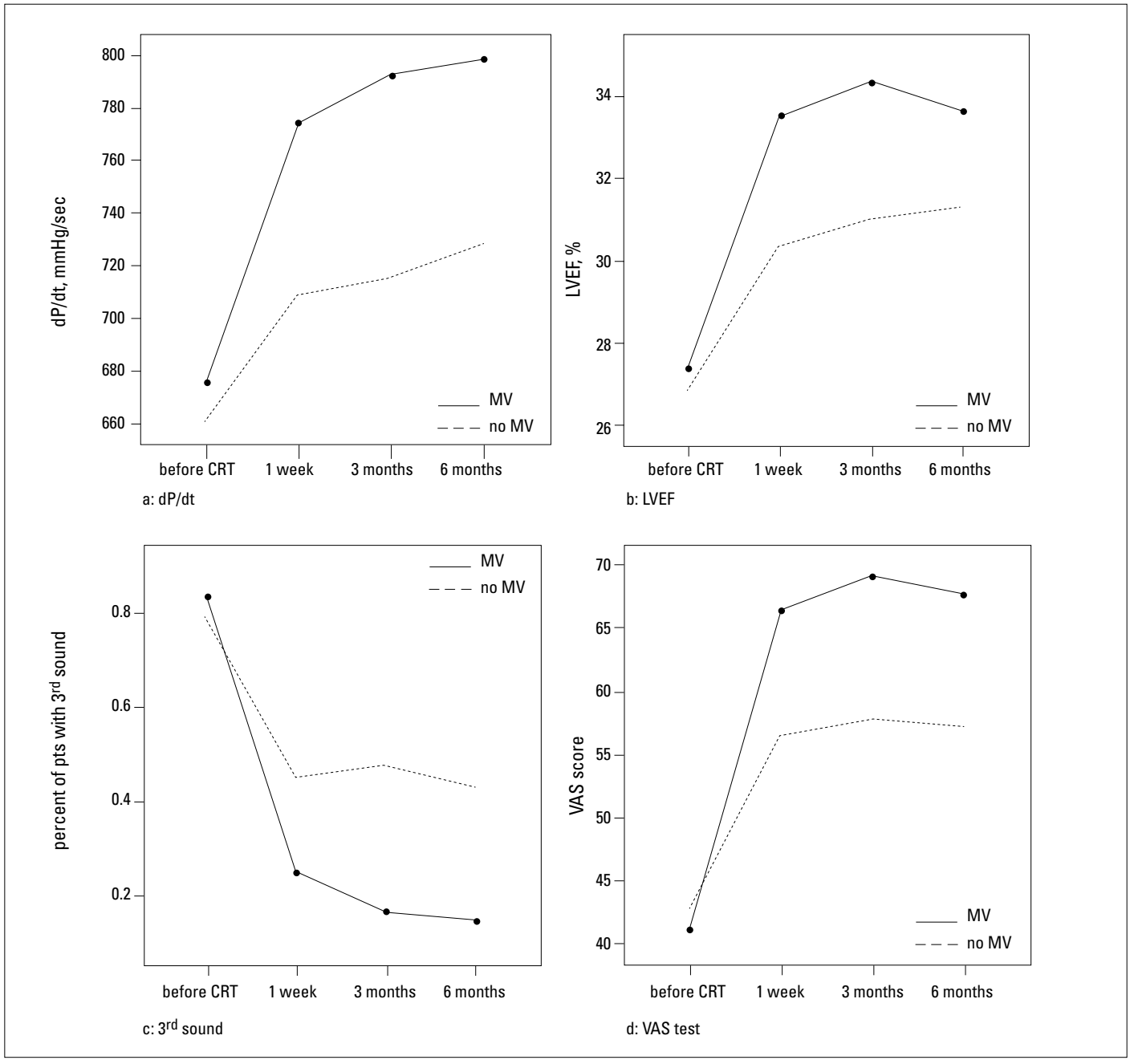

Figure 2. a: dP/dt. Time effect: p<0.0001; group effect: p=0.005; group-time effect: p=0.001
b: LVEF. Time effect: p<0.0001;group effect: p=0.009; group-time effect: p=0.11
c: 3rd sound. Time effect: p<0.0001; group effect: p=0.01; group-time effect: p=0.003
d: VAS test. Time effect: p<0.0001; group effect: p<0.013; group-time effect: p<0.002
CRT - cardiac resynchronization therapy, LVEF - left ventricular ejection fraction, MV - myocardial viability, pts- patients, VAS - Quality of Life Visual Analogue Scale
Continuous line: group with myocardial viability
Broken line: group without myocardial viability
Statistic: The General Linear Model Repeated Measures was used. This procedure provides analysis of variance when the same measurement is made several times on each subject

Group A patients showed a different distribution of the asynchrony at basal and medium segments. By sequential stimulation it was probable possible to recruit more segments in group A. This method of stimulation had already been studied before (33). Patients with ischemic dilated cardiomyopathy and a large portion of MV might have the greatest profit by sequential CRT because of the greater heterogeneity of the segments evaluated.

Study limitations

Our study has some limitations. By pulsed-wave TDI, only one region can be interrogated at a time, precluding simultaneous comparison of the segments under evaluation. Furthermore the echocardiographic parameters are influenced by differences in heart rate, loading conditions and respiration, making the measures less accurate.

In the CRT literature there is currently a consensus that using the timing of velocity data is not ideal and deformation data or information on septal stretch and fast motion during the QRS complex might provide better assessment of cardiac mechanics.

However, some studies have demonstrated a relation between LV dyssynchrony on pulsed wave TDI and improvement in symptoms and/or LVEF after CRT (48-50). Penicka et al. (13) used pulsed wave TDI (with an integration of interventricular and LV dyssynchrony) and reported a sensitivity of 96% with a specificity of 77% to predict response to CRT. A further limitation of the study could be related to the impossibility to stimulate the correct site with the longest delay; this is a possible cause of no response to CRT. Finally, the parameters that did not show the significant statistic difference could reach it with a more numerous sample and extending the follow-up.

Conclusions

Patients with MV responded better than patients without MV, in terms of RR, disappearance of the clinical cardiac 3rd sound, LVEF, dP/dt, NT-proBNP levels, NYHA class and VAS test. The best result was already found at first week after CRT. In this study 14 patients in group A (27.4%) and 28 patients in the group B (52.8%) were non-responders considering both clinical and echocardiographic parameters.

RR occurred at the first week after CRT only in group A and was maintained for all the time of this study. The subgroup B with clinical response to CRT reached an insufficient percentage of decrease of LVVs.

Further studies have to be done to confirm that ischemic dilated cardiomyopathy patients with viable myocardium could have better or similar response to CRT than idiopathic dilated cardiomyopathy patients.

Conflict of interest: None declared.

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