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Clinical research

Effect of cardiac resynchronization therapy on global and regional oxygen consumption and myocardial blood flow in patients with non-ischaemic and ischaemic cardiomyopathy

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Aims We studied the effects of cardiac resynchronization therapy (CRT) on global and regional myocardial oxygen consumption (MVO_2) and myocardial blood flow (MBF) in non-ischaemic (NICM) and ischaemic dilated cardiomyopathy (ICM).
Methods and results Thirty-one NICM and 11 ICM patients, all of them acute responders, were investigated. MVO_2 and MBF were obtained by ^{11}C-acetate PET before and after 4 months of CRT. In NICM global MVO_2 and MBF did not change during CRT, while the rate pressure product (RPP) normalized MVO_2 increased ($P = 0.03$). Before CRT regional MVO_2 and MBF were highest in the lateral wall and lowest in the septum. Under therapy, MVO_2 and MBF decreased in the lateral wall ($P = 0.045$) and increased in the septum ($P = 0.045$) resulting in a more uniform distribution. In ICM, global MVO_2, MBF, and RPP did not change under CRT. Regional MVO_2 and MBF showed no significant changes but a similar tendency in the lateral and septal wall to that in NICM.
Conclusion CRT induces changes of MVO_2 and MBF on a regional level with a more uniform distribution between the myocardial walls and improved ventricular efficiency in NICM. Based on the investigated parameters, CRT appears to be more effective in NICM than in ICM.

Introduction

Congestive heart failure is a major health care problem with increasing prevalence and considerable economic consequences.[1] New medical treatment options have gone along with a significant prognostic improvement. Cardiac resynchronization therapy (CRT) has been introduced in patients with poor left ventricular function and conduction delays, predominantly left bundle branch block (LBBB), for improving symptoms and prolonging survival.[2,3] The rationale of CRT is to correct the unfavourable LBBB associated ventricular activation

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and contraction sequence and to improve cardiac output and efficiency by these means.

Meanwhile, multiple trials have demonstrated improvements in New York Heart Association (NYHA) functional class, exercise capacity, and quality of life, under this therapy.[4,5] However, these studies did not separately examine patients with non-ischaemic dilated cardiomyopathy (NICM) and ischaemic dilated cardiomyopathy (ICM). An echocardiographic analysis of patients enrolled in the MIRACLE trial demonstrated that CRT caused significant reverse left ventricular remodelling with improvement in left ventricular size and function to a greater extent in NICM than in ICM.[6]

With regard to these mechanical and morphological effects of CRT, we hypothesized that chronic CRT could also lead to changes of: (i) myocardial blood flow (MBF) at rest; (ii) myocardial oxygen consumption (MVO_2); and (iii) ventricular efficiency. Therefore, this study investigated effects of CRT on a global and on a regional level of perfusion and metabolism in NICM and ICM patients.

Methods

Patient characteristics

Within the 18 months inclusion period, 42 consecutive patients were studied (*Table 1*); 31 patients with NICM and 11 patients with ICM. One patient had atrial fibrillation, the others were in sinus rhythm. All patients were in NYHA functional class III. In the NICM patients, a significant coronary artery disease narrowing $>50\%$ had been excluded angiographically. The ICM patients had known coronary artery disease, 10 of them history of myocardial infarction, and six coronary revascularization surgery. Before the study, all patients were on their individually optimized heart failure medication which accounted for the different aetiologies of cardiomyopathy. In detail, 99% of the NICM patients took angiotensin converting enzymes, or angiotensin receptor blockers, 16% amiodarone, 87% beta-blockers, 87% digoxin, 97% diuretics, 19% nitrates; in the ICM collective, 97% received angiotensin converting enzymes, or angiotensin receptor blockers, 18% amiodarone, 90% beta-blockers, 64% digoxin, 91% diuretics, and 63% nitrates. During the study, heart failure medication was not changed qualitatively. An up-titration of beta-blocker dose to its optimal dosage occurred in seven NICM and in four ICM patients in whom this level could not be reached before CRT.

Prior to definite pacemaker implantation, all patients had undergone a haemodynamic test in the electrophysiological laboratory in order to differentiate responders from non-responders.[7–10] Only responders with a pulse pressure increase of $\geq 10\%$ above baseline were included (*Table 1*). The device implantation was performed as described in detail earlier.[11,12]

Except for the aetiology of cardiomyopathy, the two groups did not differ significantly in their baseline clinical characteristics (*Tables 1* and *2*). The different group sizes resulted from the inclusion criteria and the duration of the observation period.

Table 1 Patient characteristics

	NICM	ICM	*P*
Number	31 (13 f, 18 m)	11 (11 m)	
Age, years	61.3 ± 8.8	64.0 ± 7.3	0.51
PR, ms	212.9 ± 39.9	222.0 ± 55.8	0.89
QRS, ms	186.1 ± 19.2	182.3 ± 20.3	0.84
Haemodynamic testing			
Increase in pulse pressure, mm Hg	14.7 ± 8.1	11.4 ± 7.2	0.12
Increase in pulse pressure, %	30.1 ± 20.0	20.9 ± 10.3	

Values are as mean ± SD.

Table 2 Haemodynamic and clinical data

	NICM			ICM		
	Baseline	Follow-up	*P*	Baseline	Follow-up	*P*
HR, L/min	71 ± 12	70 ± 12	0.93	72 ± 17	69 ± 11	0.42
SBP, mmHg	103 ± 22	118 ± 22	0.0045	112 ± 16	113 ± 17	0.82
DBP, mmHg	67 ± 11	72 ± 12	0.1	73 ± 13	69 ± 11	0.37
RPP, mmHg/min	7282 ± 1857	8266 ± 1961	0.028	7903 ± 1734	7809 ± 1347	0.79
LVED, mm	83.9 ± 12.0	74.9 ± 11.7	<.0001	77.5 ± 9.8	73.4 ± 10.2	0.08
EF, %	22.1 ± 7.1	28.0 ± 10.1	0.01	22.6 ± 5.1	26.3 ± 6.1	0.13
VO_{2max}, mL/kg/min	13.6 ± 2.7	15.6 ± 2.7	0.006	13.0 ± 4.3	14.5 ± 3.6	0.23
6 min walk, m	338 ± 70	382 ± 110	0.018	294 ± 50	404 ± 50	0.026
NYHA class (I/II/III)	0/0/31	2/18/11	<.0001	0/0/11	0/5/6	0.0065

Values are mean ± SD. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVED, left ventricular end-diastolic diameter; EF, left ventricular ejection fraction; VO_{2max}, peak oxygen uptake.

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The study protocol was approved by the local Ethics Committee of the Ruhr University Bochum and the German Federal Office for Radiation Protection (Bundesamt für Strahlenschutz). The study complied with the Declaration of Helsinki. All patients gave their written informed consent.

PET imaging and data analysis

A ^{11}C-acetate positron emission tomography (PET) study had been performed prior to pacemaker implantation (11 ± 12 days) and $\sim$4 months (115 ± 24 days) under CRT with an ECAT-951 R scanner (CTI/Siemens Medical systems, Knoxville, TN, USA). Blood pressure and heart rate were assessed oscillometrically immediately before tracer injection. ^{11}C-acetate PET processing was performed using a reversible one-tissue compartment model.[13,14] The modelling procedure resulted in 20-segment parametric polar maps of acetate uptake (K1; perfusion) and acetate clearance (k2; index of MVO_2).[15] To obtain global MVO_2 and MBF, the individual values of all segments of each measurement were added and than averaged. For regional analysis the segments were assigned either to the anterior, lateral, inferior, or septal wall. Then the segmental values of the myocardial walls were averaged. By these means, four regional values of each parameter were obtained for every patient. The apical segments were excluded from analysis. Although there is great variability in the coronary artery blood supply to myocardial segments, the segments which were summarized according to our polar maps, the anterior wall can be assigned to the left anterior descendens (LAD), those of the lateral wall to the left circumflex artery (LCX), those of the inferior wall to the right coronary artery (RCA), and those of the septum to the RCA and the LAD.

Segments with an MBF $<50\%$ of the two segments with the maximal MBF were regarded irreversibly dysfunctional and excluded from analysis.[14] Segments outside the field-of-view of the PET scanner, or with a fractional blood volume >0.50 indicating an incorrect wall detection, were also excluded. In the NICM group, 1137 out of 1240 segments were analysed. Forty-five segments (3.6%) were disregarded due to a fractional blood volume >0.50 and 52 segments (4.2%) lay outside the field-of-view. Six segments (0.5%) were regarded irreversibly dysfunctional (five apical segments and one septal segment). In the ICM group, 343 out of 440 segments were included, 24 segments (5.5%) were rejected due to a fractional blood volume >0.50, 22 segments (5%) lay outside the field-of-view, and 51 segments (11.6%) were regarded irreversibly dysfunctional (22 apical, 14 anterior, 12 septal, and three lateral segments).

To account for changes in MVO_2 by different cardiac work at baseline and follow-up investigations, the MVO_2 was normalized with the rate pressure product (RPP). This parameter has been shown to correlate closely with acetate clearance and the MVO_2, respectively.[16–19] The normalization of MVO_2 was done by multiplication with the ratio between the median of all RPPs (7119 mmHg/min) of the baseline PET scans and the individual RPP measured immediately before the tracer application.

MBF is given in mL/min/g and MVO_2 indirectly by the acetate clearance rate in 1/min.

Statistical analysis

Data are given as mean value ± 1 standard deviation (SD). The non-parametric Mann–Whitney *U*-test for unpaired groups was used to compare global MVO_2 and MBF between the groups. Comparisons of paired parameters at baseline and under CRT were performed with the Wilcoxon signed rank test. Probability values were calculated using two-sided tests and if <0.05 considered statistically significant.

Comparisons of regional MBF (in the anterior, lateral, inferior, and septal walls) and of regional MVO_2 were analysed with ANOVA for repeated measures followed by a *post hoc* Bonferroni analysis. Statistical analyses were performed with StatView 5.0 software (SAS Institute Inc.).

Results

Haemodynamic and clinical findings

Table 2 shows the results for the NICM and the ICM patients. In the NICM group systolic blood pressure and the RPP increased significantly during CRT. Heart rate and diastolic blood pressure remained unchanged. No change of haemodynamic parameters was found in ICM.

All investigated clinical data of the NICM group improved significantly. The ICM group revealed a significant improvement in the NYHA functional class and the 6 min walk.

Global MVO_2 and MBF

The data for the global parameters are given in *Table 3*. At baseline, global MVO_2 tended to be lower in ICM than in NICM. The MVO_2 of both groups did not significantly alter during CRT. Under therapy, the RPP-normalized MVO_2 declined ($P = 0.03$) in NICM but increased insignificantly in ICM. At baseline, global MBF was lower in ICM than in NICM ($P = 0.04$) and did not alter during therapy.

Table 3 Global MBF and MVO_2

	NICM		ICM	
	Baseline	Follow-up	Baseline	Follow-up
MBF	$0.51 \pm 0.10^*$	0.52 ± 0.12	0.44 ± 0.09	0.48 ± 0.08
MVO_2	0.080 ± 0.015	0.082 ± 0.020	0.070 ± 0.018	0.074 ± 0.013
$nMVO_2$	$0.081 \pm 0.017^*$	$0.072 \pm 0.018^\dagger$	0.064 ± 0.017	0.069 ± 0.015

Values are mean $\pm$ SD. MBF in mL/min/g, MVO_2 and $nMVO_2$ in 1/min. $nMVO_2$, the RPP normalized MVO_2.
$^*P < 0.05$ vs. ICM; $^\dagger P = 0.03$ vs. baseline.

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Regional MVO_2 and MBF in non-ischaemic dilated cardiomyopathy

The results are presented in *Table 4* and *Figure 1*. The ANOVA revealed differences for MVO_2 between the myocardial walls at baseline ($P < 0.0001$) and under therapy ($P = 0.0004$). In detail, baseline MVO_2 in the lateral wall was higher than in the other myocardial walls ($P < 0.0001$ in all comparisons) and MVO_2 in the septum lower than in the anterior ($P = 0.0008$) and the lateral walls ($P < 0.0001$).

Under therapy, MVO_2 in the inferior wall was lower than in the anterior wall ($P < 0.0001$) and the lateral wall ($P = 0.007$). The other myocardial walls showed no differences. MVO_2 increased in the septal wall ($P = 0.045$) and decreased in the lateral wall ($P = 0.045$) from baseline to therapy. *Figure 2* illustrates these findings.

Baseline MBF revealed regional differences between the myocardial walls ($P < 0.0001$) in NICM. The lateral wall showed a higher perfusion than all other myocardial walls (anterior vs. lateral, $P < 0.0001$; inferior vs. lateral, $P = 0.0035$; lateral vs. septal, $P < 0.0001$). During therapy there were no longer significant regional differences ($P = 0.55$). MBF increased by CRT in the anterior ($P = 0.03$) and septal ($P = 0.001$) walls and decreased in the lateral wall ($P = 0.02$).

The MVO_2/MBF ratio was nearly identical for all the myocardial walls before and during therapy.

Regional MVO_2 and MBF in ischaemic dilated cardiomyopathy

The results are given in *Table 4* and *Figure 1*. The ANOVA of MVO_2 revealed no significant differences either among the myocardial walls at baseline or during therapy. Only insignificant changes occurred from baseline to follow-up. However, there was the tendency of a higher baseline MVO_2 in the lateral wall than in the septal wall and also of a balance of MVO_2 between these walls under CRT.

MBF demonstrated the same characteristics as MVO_2. The MVO_2/MBF ratio was nearly identical to that of the NICM group and remained constant from baseline to follow-up.

Discussion

We investigated 31 NICM and 11 ICM patients, all of them acute responders with similar clinical baseline characteristics, before and during 4 months of continuous CRT. The study results document that mid-term CRT did not substantially affect global MVO_2 and MBF in either group.

Transforming the measured ^{11}C-acetate clearance rates into an absolute MVO_2,[20] it amounts to 5.9 ± 0.8 in NICM and to 5.1 ± 1.0 mL/min/100 g in ICM, respectively. These data indicate a reduced MVO_2 in both groups (normal range >7.6 mL/min/100 g[21]) which reflects the overall depressed contractility due to the cardiomyopathy. Correspondingly, MBF was found to be

Table 4 MBF and MVO_2 of the myocardial walls

		Baseline				Follow-up			
Group	Parameter	Anterior	Lateral	Inferior	Septal	Anterior	Lateral	Inferior	Septal
NICM	MBF	0.49 ± 0.11	0.58 ± 0.13	0.51 ± 0.14	0.48 ± 0.08	$0.53 \pm 0.15^*$	$0.52 \pm 0.12^*$	0.52 ± 0.12	$0.54 \pm 0.12^*$
	MVO_2	0.079 ± 0.017	0.090 ± 0.018	0.078 ± 0.016	0.073 ± 0.014	0.084 ± 0.021	$0.083 \pm 0.018^*$	0.078 ± 0.020	$0.081 \pm 0.022^*$
	MVO_2/MBF	0.17 ± 0.04	0.16 ± 0.03	0.16 ± 0.02	0.15 ± 0.02	0.16 ± 0.03	0.16 ± 0.03	0.15 ± 0.03	0.15 ± 0.02
ICM	MBF	0.50 ± 0.15	0.47 ± 0.11	0.40 ± 0.09	0.43 ± 0.08	0.52 ± 0.13	0.47 ± 0.10	0.45 ± 0.10	0.49 ± 0.08
	MVO_2	0.072 ± 0.022	0.075 ± 0.019	0.064 ± 0.016	0.065 ± 0.016	0.08 ± 0.017	0.075 ± 0.015	0.070 ± 0.015	0.073 ± 0.014
	MVO_2/MBF	0.15 ± 0.03	0.16 ± 0.03	0.16 ± 0.04	0.15 ± 0.03	0.16 ± 0.04	0.16 ± 0.02	0.16 ± 0.04	0.15 ± 0.02

Values as mean $\pm$ SD. MBF in mL/min/g, MVO_2 in 1/min, MVO_2/MBF in g/mL.
$^*P < 0.05$ vs. corresponding wall at baseline.

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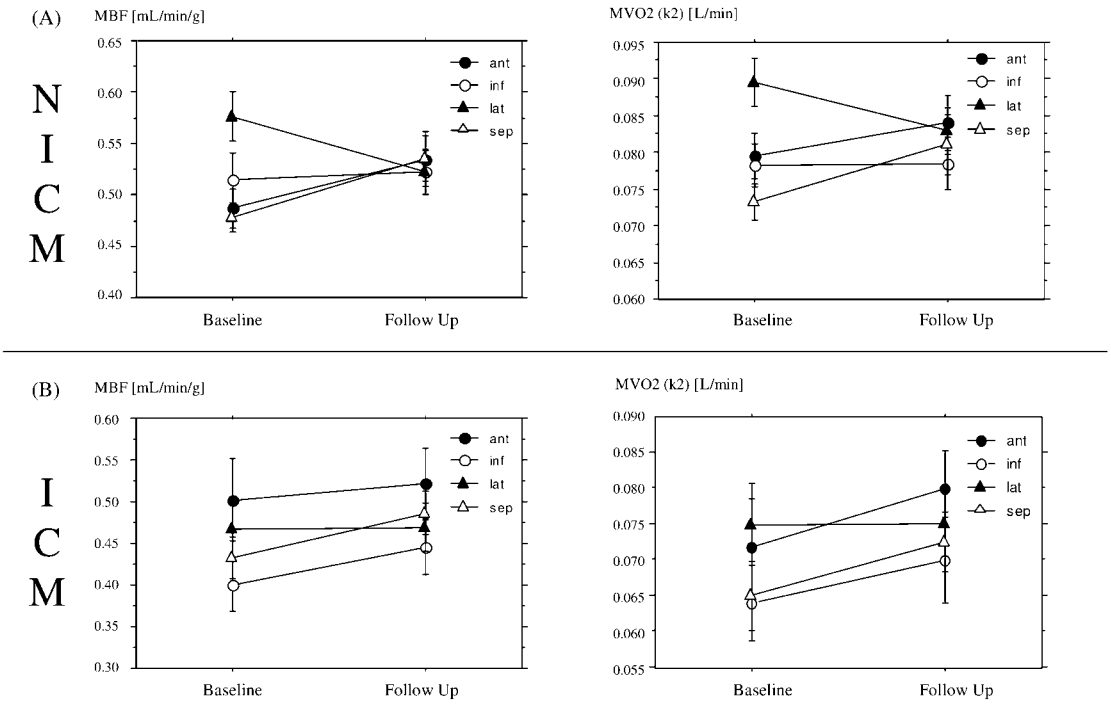

Figure 1 Regional MBF and MVO_2 in NICM (*A*) and in ICM (*B*).

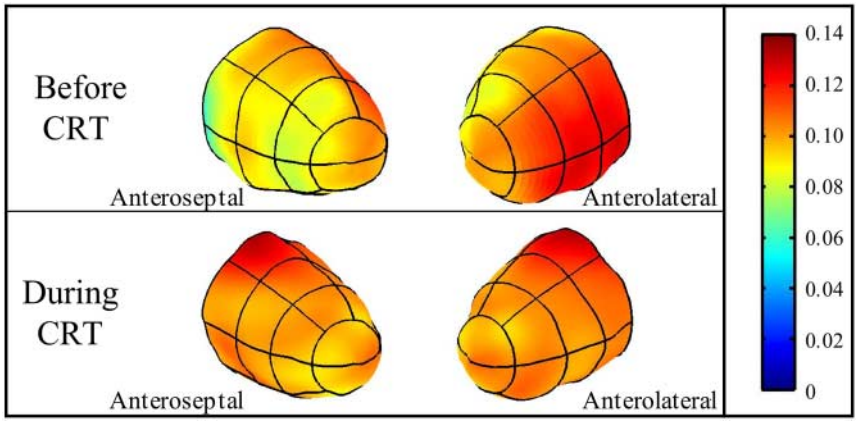

Figure 2 Anteroseptal and anterolateral view of a parametric 3-D MVO_2 (k_2) map of an NICM patient before and under CRT. Before therapy, MVO_2 is highest in the lateral wall and lowest in the septum. During CRT the differences between the myocardial walls vanish and MVO_2 is more uniform in the left ventricular myocardium. MVO_2 (k_2) is given in 1/min.

below the normal limit,[22] and consistent with perfusion values (0.49 ± 0.17 in NICM; 0.38 ± 0.15 mL/min/g in ICM) measured with the microsphere technique.[23]

Previous studies, which considered short-term effects of CRT, also demonstrated an unchanged global MVO_2 and MBF.[24–27] Obviously, the same accounts for mid-term CRT and indicates that the global state of the myocytes was not affected during the observation period.

Nevertheless, the left ventricular end-diastolic diameter documents that CRT initiated a reverse ventricular remodelling process in NICM and therefore also in ICM. In line with these morphological changes, clinical and haemodynamic parameters improved mostly in the NICM group, which also showed a better ventricular efficiency. In contrast, ICM patients demonstrated no change in efficiency.

The finding of improved efficiency by CRT is consistent with other studies which examined patients after 2 min of pacing/stimulation and NICM patients after temporary cessation of CRT.[28,29] Ukkonen *et al.*[24] found a 13% improvement of efficiency in eight patients (six of them with ICM) with ^{11}C-acetate PET. This result is similar to that of our NICM group but differs from the ICM group. The discrepancy may be caused by a greater extent of irreversibly dysfunctional and/or ischaemic segments in our ICM patients.

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Mechanisms of CRT have been found to be a reduced mitral regurgitation, a better atrioventricular co-ordination, and an improved ventricular co-ordination, which enable the ventricles to act more efficiently.[30,31] In particular, the ability of reco-ordination depends on preserved mechanical function.[32] We suppose that the response to CRT in ICM turns out to be poorer than in NICM for two reasons: (i) ICM patients had more irreversibly dysfunctional segments, which may affect mechanical function; and (ii) ICM patients showed a significantly lower MBF, which suggests that regional or even global ischaemia was likely to be present.

These considerations are further supported by the echocardiographic analysis of NICM and ICM patients enrolled in the MIRACLE trial, which demonstrated greater changes in NICM than in ICM.[6] The clinical and haemodynamic results of the ICM group, however, may be regarded as a therapeutic benefit, because they consistently indicate a trend towards an improvement.

Regional MVO_2 and MBF

As pointed out above, ventricular reco-ordination represents one of the main pillars of CRT. To assess this effect on MVO_2 and MBF the parameters were analysed on a regional level.

Before CRT, regional MVO_2 and MBF of the NICM patients were characterized by a significant imbalance between the myocardial walls with the highest values in the lateral wall and the lowest in the septum. This pattern can be explained as follows: the dys-synchronous contraction in LBBB is associated with a delayed activation of the lateral wall.[33,34] During the cardiac cycle, the contraction of the early activated segments distends the still inactivated lateral wall and increases intraventricular pressure. Consequently, the delayed activated lateral wall segments have to perform a higher work,[35] and therefore exhibit a higher MVO_2 than the other walls, as confirmed by our study. On the other hand, the low MVO_2 in the septum results from its early contraction and a reduced regional ejection fraction.[36]

Due to the close match of MBF to MVO_2,[37] which was reflected in the constant MVO_2/MBF ratios, MBF demonstrated nearly the same characteristics as MVO_2.

Previous studies have shown that CRT is able to reduce the intraventricular delay caused by LBBB.[31] By these means, an improved co-ordination and a more effective ventricular contraction is induced with a more uniform distribution of cardiac work among the myocardial walls.[30] Accordingly, the effect of resynchronization was reflected in our NICM patients by a more uniform distribution of MVO_2 and MBF between the myocardial walls. This occurred by a decrease of both in the lateral wall and an increase in the septum. The changes in the lateral wall indicate a lower regional workload due to the suspended delay. Those of the septum suggest a higher regional workload that documents a more effective integration of this wall into the cardiac cycle than under LBBB conditions. In addition, glucose metabolism has also shown a more homogeneous distribution in the myocardium by CRT.[26]

The ICM group failed to show significant changes by CRT but at least the trend of changes was similar to those of the NICM group.

In summary and in conclusion, our study provides evidence that mid-term CRT affects MBF and MVO_2 on a regional level and that it appears to be more effective in NICM than in ICM. However, it has to be considered that the ICM results are biased for reasons of patient recruitment on a small sample size. Therefore they have to be interpreted cautiously, especially in comparison with the NICM results. Nevertheless, as pointed out above, they are in line with echographic data.[6] Against this background, our study implies: (i) that NICM and ICM represent two different CRT groups which require a separated analysis with larger sample sizes concerning clinical benefits and outcome; and (ii) that studies have to clarify whether long-term CRT is able to improve perfusion and metabolism on a global level suggesting a real regression of cardiomyopathy.

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