Cardiac Efficiency and Oxygen Consumption Measured with ^{11}C-Acetate PET After Long-Term Cardiac Resynchronization Therapy

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Cardiac resynchronization therapy (CRT) is a treatment option in patients with severe heart failure and left bundle-branch block (LBBB). This study evaluated the effects of 4 and 13 mo of CRT on myocardial oxygen consumption (MVO$_2$) and cardiac efficiency as compared with mild heart failure patients without LBBB. **Methods:** Sixteen patients with severe heart failure and LBBB due to idiopathic cardiomyopathy were studied at baseline and after 4 and after 13 mo of therapy. Thirteen patients with mild heart failure without LBBB served as a comparison group. The clearance rate (k$_2$) of ^{11}C-acetate was measured with PET to assess MVO$_2$. Stroke volume was derived from the dynamic PET data according to the Stewart–Hamilton principle and, furthermore, cardiac efficiency using the work metabolic index. **Results:** After 4 mo of CRT, stroke volume index (SVI) increased by 50% ($P = 0.012$) and cardiac efficiency increased by 41% ($P < 0.001$). Global k$_2$ remained unchanged but regional k$_2$ demonstrated a more homogeneous distribution pattern. The parameters showed no significant changes during therapy. Under CRT, cardiac efficiency, SVI, and the distribution pattern of regional k$_2$ did not differ from mild heart failure patients without LBBB. **Conclusion:** CRT improves cardiac efficiency for at least 13 mo, as demonstrated by a higher SVI, whereas MVO$_2$ remains unchanged. Cardiac efficiency, SVI, and the MVO$_2$ distribution pattern reach the level of patients with mild heart failure without LBBB. The unfavorable hemodynamic performance in heart failure with LBBB is effectively restored by long-term CRT to the level of an earlier disease state.

Key Words: heart failure; bundle-branch block; pacing; cardiac output

In the early 1990s, cardiac resynchronization therapy (CRT) was originally initiated as a bridging therapy for advanced heart failure patients with left bundle-branch block (LBBB) awaiting heart transplantation (1,2). Various trials demonstrated CRT—predominantly performed as biventricular pacing—to be effective with respect to clinical symptoms, exercise tolerance, quality of life, and patient outcome (3–6). Currently available devices also include a cardioverter–defibrillator function, which provides substantial mortality benefits by preventing sudden cardiac death (7). In the 2002 guideline update for implantation of pacemakers and antiarrhythmic devices, CRT was classified as a class IIA indication with an A level of evidence (8).

CRT studies with PET demonstrated no changes in myocardial oxygen consumption (MVO$_2$) but a more homogeneous distribution pattern of MVO$_2$, myocardial perfusion, and glucose metabolism (9–11). However, no data are currently available on the long-term effects of CRT on cardiac efficiency and MVO$_2$. Previous studies on cardiac efficiency addressed either short-term effects after the onset of CRT (12) or effects after discontinuation of long-term CRT for 2 or 24 h (13,14).

This study was initiated to evaluate the long-term effects of CRT on cardiac efficiency and MVO$_2$. The study should further clarify whether the functional response to CRT is a continuously ongoing process or completed after a certain period. Moreover, the comparison with mild heart failure patients without LBBB—that is, the comparison with an early disease state—served to evaluate the extent of the functional restoration induced by CRT.

MATERIALS AND METHODS

Study Population

Sixteen patients with severe heart failure and LBBB (Table 1), scheduled for CRT, and 13 patients with mild heart failure without LBBB (Table 2) were studied. In all subjects the cause of heart failure was idiopathic cardiomyopathy. A significant stenosis of the coronary arteries (narrowing > 50%) was excluded angiographically. The patients with severe heart failure and LBBB, who were all in New York Heart Association (NYHA) class III, showed a QRS width > 160 ms, a left ventricular ejection fraction ≤ 30%,

TABLE 1
Characteristics of Patients with Severe Heart Failure and LBBB

Patient no.	Sex	Age (y)	QRS width (ms)	NYHA class	LVEF (%)	LVEDD (mm)
1	F	64	180	3	16	84
2	M	62	200	3	25	88
3	M	68	180	3	14	93
4	F	69	176	3	25	75
5	M	71	200	3	20	83
6	F	63	235	3	22	74
7	F	74	192	3	18	86
8	M	62	220	3	19	112
9	M	58	186	3	30	62
10	F	70	184	3	23	69
11	M	74	180	3	18	79
12	F	57	220	3	26	62
13	F	65	160	3	20	85
14	F	48	186	3	25	79
15	M	53	184	3	10	89
16	F	32	180	3	25	94
Mean ± SD		62 ± 11	191 ± 19		21 ± 5	82 ± 13

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter.

a left ventricular end-diastolic diameter > 60 mm, and sinus rhythm. At the time of study enrollment they were clinically stable and on individually optimized heart failure medication (amiodarone, $n = 2$; angiotensin-converting enzyme (ACE) inhibitors, $n = 13$; angiotensin receptor blockers, $n = 3$; β-blockers, $n = 15$; digoxin, $n = 13$; diuretics, $n = 16$; and nitrates, $n = 2$). During the study the heart failure medication was not changed substantially. An adjustment of β-blocker dose to its optimal dosage occurred in 4 patients in whom this level could not be reached before CRT.

Those 13 patients with mild heart failure without LBBB at an earlier state of disease served as a comparison group. Heart failure was in 7 cases of infective and in 6 cases of unknown origin. The patients showed a QRS width ≤ 120 ms, an average left ventricular end-diastolic diameter of 68 mm, a slightly reduced ejection fraction (47%), and sinus rhythm. The NYHA class ranged from I to III (class I, $n = 2$; class II, $n = 10$; class III, $n = 1$). The medication consisted of amiodarone ($n = 2$), ACE inhibitors ($n = 12$), β-blockers ($n = 7$), digoxin ($n = 9$), and diuretics ($n = 6$).

The study protocol was approved by the local Ethics Committee of the Ruhr-University of Bochum, Germany, and the German Federal Office for Radiation Protection. All patients gave their written informed consent.

Biventricular Pacemaker Implantation

Before definite pacemaker implantation all patients had undergone a hemodynamic test in the electrophysiologic laboratory to differentiate responders from nonresponders (15). Only responders with a pulse pressure increase of ≥10% above baseline (85% of the patients screened) were included. The average pulse pressure increase was 15 ± 9 mm Hg. The device implantation was performed as described in detail earlier (16,17).

PET

The PET scans were acquired with an ECAT-951 R or an ECAT EXACT HR+ PET scanner (CTI/Siemens Medical Systems) after a bolus injection of 370 MBq ^{11}C-acetate at rest. In the CRT group, scans were performed before pacemaker implantation (11 ± 15 d), 4 mo (122 ± 32 d), and 13 mo (403 ± 36 d) under CRT.

Blood pressure and heart rate were assessed oscillometrically immediately before the tracer injection. ^{11}C-Acetate was injected as a bolus (<2 s) followed by 20 mL sodium chloride. Data processing was performed using a reversible 1-tissue compartment model (18,19). The modeling procedure resulted in 20-segment parametric polar maps of the acetate clearance (rate constant, k_2). The acetate clearance was used as a measure of MVO_2 (given in 1/min). To obtain a measure of global MVO_2, the acetate clearance rates (k_2) of all 20 segments of each measurement were averaged. For regional analysis the segments were assigned to the

TABLE 2
Characteristics of Comparison Group: Patients With Mild Heart Failure Without LBBB

Patient no.	Sex	Age (y)	QRS width (ms)	NYHA class	LVEF (%)	LVEDD (mm)
1	M	55	100	3	28	66
2	F	55	120	2	47	62
3	M	64	120	2	38	74
4	F	56	80	1	52	60
5	M	23	80	2	48	53
6	M	53	100	2	48	74
7	M	29	100	2	49	62
8	M	49	100	2	38	96
9	M	17	80	1	60	60
10	F	40	120	2	48	66
11	M	65	120	2	50	72
12	M	49	120	2	52	82
13	M	57	80	2	50	63
Mean ± SD		47 ± 15	102 ± 17		47 ± 8	68 ± 11
P vs. LBBB group	NS	0.005	<0.0001	<0.0001	0.0008	0.005

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; NS = not significant.

anterior, lateral, inferior, or septal wall and averaged. Then the coefficient of variation of regional k_2 was determined. The apical segments were excluded from regional analysis. 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 resynchronization group, 900 of 960 segments were analyzed and in the comparison group 235 of 260 segments were analyzed.

Cardiac output was assessed according to the Stewart–Hamilton principle as described previously in detail (20). In brief, a region of interest was placed in the right ventricular cavity. A time–activity curve was generated and the downslope of the ventricular activity curve fitted to a monoexponential function with forward extrapolation to correct for recirculation (Fig. 1). The equation to determine cardiac output (CO) is:

$$CO \times c(t) = dc/dt \qquad \text{Eq. 1}$$

or

$$CO = \text{injected dose}/\!\!\int c(t)dt, \qquad \text{Eq. 2}$$

where c(t) is the right ventricular tracer concentration at time t measured with PET and corrected for recirculation. The integral c(t)dt is the area under this curve. Stroke volume index (SVI, in mL/m^2) was calculated as cardiac output/heart rate, indexed to body surface area. Cardiac efficiency was determined using the concept of work metabolic index given by:

$$WMI = SVI \times SBP \times HR/k_2, \qquad \text{Eq. 3}$$

where SBP is systolic blood pressure, and HR is heart rate.

Statistical Analysis

Data are given as mean value $\pm$ SD. Comparisons of hemodynamic, PET data (k_2, coefficient of variation of regional k_2, SVI,
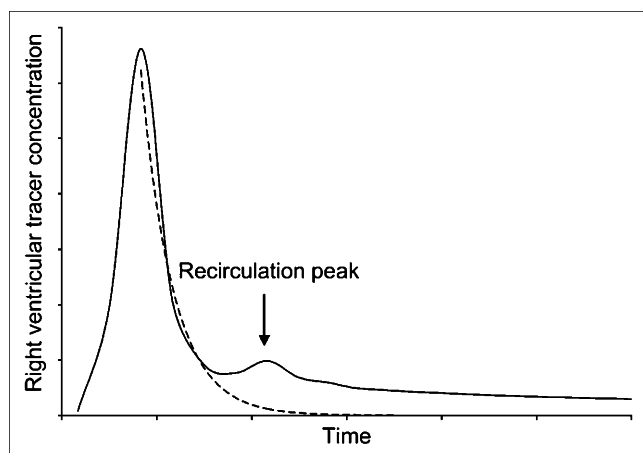

FIGURE 1. Right ventricular activity concentration curve after bolus injection. Dotted line represents monoexponential fit to downslope of activity concentration curve with forward extrapolation to correct for recirculation. Cardiac output is calculated as injected dose divided by area under concentration curve corrected for recirculation.

cardiac efficiency) in the CRT group were performed with ANOVA for repeated measures followed by a post hoc Bonferroni analysis. For comparisons of the measurements in the CRT group with the comparison group, the unpaired 2-tailed t test with a Bonferroni–Holmes correction was used. Comparison of proportions was performed by χ^2 analysis. $P < 0.05$ was considered significant.

RESULTS

Hemodynamic Data

Heart rate, systolic blood pressure, and diastolic blood pressure of the CRT group did not change from baseline to 4 mo of CRT and showed no further changes at the 13-mo measurement point (Table 3). The comparison with the mild heart failure patients revealed that (a) the systolic blood pressure of the CRT patients was lower ($P = 0.02$) before therapy, that (b) the diastolic blood pressure of the CRT patients was always lower (baseline vs. comparison group, $P = 0.004$; 4-mo CRT vs. comparison group, $P = 0.02$; 13-mo CRT vs. comparison group, $P = 0.001$), and that (c) the heart rate showed no significant differences.

MVO$_2$ and Coefficient of Variation of Oxygen Consumption

Global k_2 did not change significantly under CRT. However, before and after 4 mo of therapy, k_2 was lower than that in the comparison group with mild heart failure ($P = 0.012$ and $P = 0.023$, respectively), but not after 13 mo of therapy (Table 3; Fig. 2A).

The regional k_2 distribution among the myocardial walls, expressed by the coefficient of variation, became more homogeneous under CRT and decreased by up to 41% (baseline vs. 4-mo CRT, $P = 0.0002$; baseline vs. 13-mo CRT, $P = 0.0006$). From 4 to 13 mo of therapy no significant changes were observed. The k_2 coefficient of variation of the comparison group was similar to those under CRT but lower than that before CRT ($P = 0.0014$) (Table 3; Fig. 2B).

SVI

The SVI increased by up to 50% with CRT (baseline vs. 4-mo CRT, $P = 0.012$; baseline vs. 13-mo CRT, $P < 0.001$). During therapy the SVI showed no significant changes. Before CRT the SVI was lower ($P = 0.01$) than that in the comparison group but during CRT was similar to that of the comparison group (Table 3; Fig. 2C).

Cardiac Efficiency

Cardiac efficiency increased by up to 41% during CRT (baseline vs. 4-mo CRT, $P > 0.001$; baseline vs. 13-mo CRT, $P < 0.001$). Between 4 and 13 mo of CRT, cardiac efficiency showed no significant changes. Before CRT cardiac efficiency was lower than that in the comparison group ($P = 0.004$). During CRT cardiac efficiency was the same as that of the comparison group (Table 3; Fig. 2D).

TABLE 3
Hemodynamic, MVO₂, and Efficiency Data

Parameter	Severe heart failure with LBBB			Mild heart failure without LBBB
	Baseline	4 mo of CRT	13 mo of CRT	
Heart rate (bpm)	74 ± 13	72 ± 11	65 ± 9	69 ± 11
Systolic BP (mm Hg)	$105 \pm 27^*$	113 ± 21	113 ± 23	129 ± 25
Diastolic BP (mm Hg)	$68 \pm 10^*$	$68 \pm 14^*$	$64 \pm 12^*$	81 ± 13
k_2 (min⁻¹)	$0.081 \pm 0.015^*$	$0.082 \pm 0.016^*$	0.086 ± 0.020	0.099 ± 0.023
CV of regional k_2	$0.112 \pm 0.048^*$	$0.066 \pm 0.038^\dagger$	$0.069 \pm 0.039^\dagger$	0.063 ± 0.014
SVI (mL/m²)	$38 \pm 16^*$	$50 \pm 15^\dagger$	$57 \pm 12^\dagger$	55 ± 17
CE ($10^6 \times$ mL/m² $\times$ mm Hg)	$3.47 \pm 1.34^*$	$4.91 \pm 1.35^\dagger$	$4.85 \pm 1.29^\dagger$	4.77 ± 0.72

$^*P < 0.05$ vs. comparison group with mild heart failure.
$^\dagger P < 0.05$ vs. baseline.
BP = blood pressure; k_2 = acetate clearance rate, a measure of MVO₂ rate; CV = coefficient of variation; CE = cardiac efficiency.
Values are mean $\pm$ SD.

DISCUSSION

CRT restores left ventricular synchrony in patients with heart failure and LBBB. The coincidence of heart failure and LBBB depends on the disease state and ranges from 9.7% in NYHA class 0–I, from 32% in NYHA class II, to 53% in NYHA class III (21). Although the underlying cause of heart failure is not treated directly, echocardiography demonstrated a positive impact on left ventricular architecture with remodeling for up to 1-y follow-up (5,22). The objective of the present study was to add functional data for such an observation period.

The results demonstrate a long-term improvement in cardiac efficiency for up to 13-mo follow-up with CRT. This gain is based on a higher SVI without a concomitant increase in oxygen consumption, heart rate, or blood pressure. The efficiency level after 4 mo continued to persist for
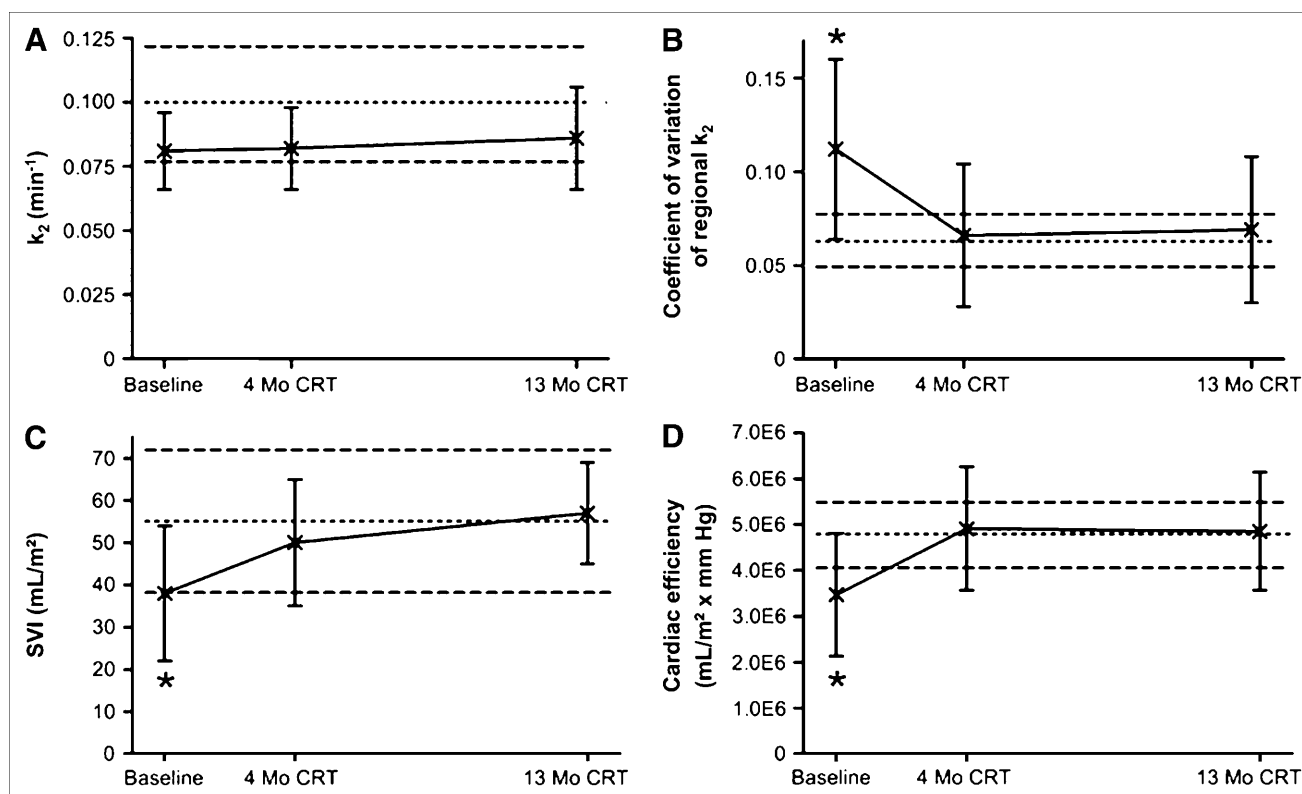

FIGURE 2. Acetate clearance rate k_2, a measure of MVO₂ rate (A); coefficient of variation of k_2 between myocardial walls (B); SVI (C); cardiac efficiency in patients with severe heart failure and LBBB ($n = 16$) at baseline, after 4 mo, and after 13 mo of CRT (D). Values are mean $\pm$ SD. $^*P < 0.05$ vs. 4 mo and 13 mo of CRT. Dotted horizontal line indicates mean value of corresponding parameter of comparison group with mild heart failure patients without LBBB ($n = 13$) and dashed lines indicate mean $\pm$ SD.

up to at least 13 mo of therapy and, hence, demonstrates a long-lasting CRT effect. Previous studies with similar issues addressed either short-term effects after the onset of CRT (*12*) or effects after acute discontinuation of long-term CRT (*13,14*). After 8–13 mo of CRT, Ukkonen et al. (*13*) found a 12% and Sundell et al. (*14*) found a 24% decrease in efficiency when CRT was switched off for 2 or 24 h, respectively. The changes in efficiency demonstrated in the present study are more substantial. There are 3 potential explanations for the observed differences: (i) A different methodologic approach was used to determine stroke volume. The method in the present study has been validated in a pig model versus thermodilution but not in humans with a standard method—for example, echocardiography (*20*). To reduce a potential systematic bias, only changes but not the absolute values were considered in the comparison with other studies. (ii) The present study applied compartmental modeling for the acetate clearance, whereas Ukkonen et al. and Sundell et al. used exponential curve fitting (indicated as k_{mono}), which underestimates the acetate clearance (*23*). Considering that k_{mono} and k_2 showed merely minimal changes in all efficiency studies, only a minor effect is to be expected with respect to changes of SVI and cardiac efficiency through the different methods. (iii) Ventricular remodeling was likely to occur during the 13-mo observation period of the present study—as indicated by the decrease in LVEDD—but not between the short-term measurements of the cited studies (*13,14*). Therefore, the remodeling process may have enhanced the direct short-term effect of CRT on cardiac efficiency. Summarizing the results of all efficiency studies, they give rise to the statement that the response to CRT occurs immediately but that it is initially incomplete.

The question that arises from our results is whether CRT is able to induce a regression of disease state. With regard to morphologic studies there is evidence of a reverse remodeling process (*22*). However, the cited studies with measurements after interruption of long-term CRT reveal that the therapeutic benefit is closely related to the induced electromechanical resynchronization and reversible after cessation of therapy. MVO_2, which was reduced in cardiomyopathy (*24,25*), may serve as an indirect marker for the disease state. Transforming the measured ^{11}C-acetate clearance rates into an absolute MVO_2 (*26*), it amounts to 6.0 ± 0.8 at baseline and at 3 mo, to 6.4 ± 1.2 at 13-mo follow-up for the CRT patients, and to 7.4 ± 1.4 mL/min/100 g for the mild heart failure patients. These data indicate a reduced MVO_2 (normal range > 7.6 mL/min/100 g (*27*)) in the CRT group and no basic regression of the underlying disease during the observation period. Although not statistically different from the earlier measurements, the 13-mo MVO_2 shows a trend toward higher values that is underlined by its insignificant difference to the MVO_2 of the comparison group. This finding may indicate, therefore, that CRT eventually induces slight changes to the cardiomyopathic process. It is consistent with the hypothesis that dyssynchrony itself contributes to disease pathophysiology (*28*).

Intraventricular dyssynchrony in LBBB has been characterized with PET as having regional inhomogeneities of perfusion and metabolism. CRT reduces the intraventricular delay and balances regional perfusion and metabolism with a more homogeneous distribution pattern in the left ventricular myocardium (*9,11,13,29*). As a measure of inhomogeneity, the coefficient of variation of regional k_2 (MVO_2) significantly decreased with CRT and remained at this level. The finding also suggests, as implied by previous efficiency studies, that the process of pacemaker-induced resynchronization succeeds completely, at least after 4 mo, without any further adaptation.

Considering the improvement of symptoms and NYHA class by CRT, an additional intention of the present study was to evaluate the degree of CRT-induced changes in relation to a comparison group in an earlier state of disease—that is, with mild heart failure without LBBB (*3–5*). Parameters directly influenced by CRT are both at the 4-mo and the 13-mo follow-up on the level of the comparison group. This finding implies that (a) dyssynchrony is at least one of the leading factors that worsens cardiac function in heart failure patients with LBBB, that (b) dyssynchrony is effectively treatable with CRT, and that (c) CRT induces working conditions similar to that of patients in an earlier state of disease without LBBB.

CONCLUSION

CRT improves cardiac efficiency by a higher SVI without a concomitant increase in metabolic cost, heart rate, or blood pressure over a follow-up interval of 13 mo. MVO_2, heart rate, and blood pressure showed no changes within this period. Parameters directly influenced by CRT, comprising the distribution pattern of MVO_2, change to the level of a comparison group with mild heart failure but without LBBB. To summarize, the unfavorable hemodynamic performance in heart failure with LBBB is effectively and permanently suspended with CRT, restoring the working condition of an earlier disease state without LBBB.

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