

# Effects of cardiac resynchronization therapy on right ventricular function during rest and exercise, as assessed by radionuclide angiography, and on NT-proBNP levels

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**Aim.** We carried out this study to investigate mid-term effects of cardiac resynchronization therapy (CRT) on right ventricular (RV) function and neurohormonal response, expressed by N-terminal pro-brain natriuretic peptide (NT-proBNP), in heart failure patients stratified by baseline RV ejection fraction (RVEF).

**Methods and Results.** Thirty-six patients with nonischemic dilated cardiomyopathy underwent technetium-99m radionuclide angiography with bicycle exercise immediately after CRT implantation (during spontaneous rhythm and after CRT activation) and 3 months later. Plasma NT proBNP was assessed before implantation and after 3 months. At baseline, RVEF was impaired ( $\leq 35\%$ ) in 14 patients, preserved ( $>35\%$ ) in 22. At 3 months, RVEF improved during rest and exercise ( $P = .02$ ) in patients with impaired RV function, while remaining unchanged in patients with preserved RV function. Rest and exercise RV dyssynchrony decreased in both groups at follow-up ( $P < .05$ ). A similar mid-term improvement in left ventricular (LV) function and NT-proBNP was observed in patients with impaired and preserved RVEF. In the former, the decrease in NT-proBNP correlated with the improvements both in LV and RV dyssynchrony and functions.

**Conclusion.** CRT may improve RV performance, during rest and exercise, and neurohormonal response in heart failure patients with nonischemic dilated cardiomyopathy and baseline RV dysfunction. RV dysfunction should not be considered per se a primary criterion for excluding candidacy to CRT. (J Nucl Cardiol 2019;26:123–32.)

**Key Words:** Heart failure • technetium-99m • radionuclide angiography

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### Abbreviations

CRT	Cardiac resynchronization therapy
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro-brain natriuretic peptide
RV	Right ventricular
RVEF	Right ventricular ejection fraction

**See related editorial, pp. 133–135**

## INTRODUCTION

Right ventricular (RV) dysfunction is an independent predictor of mortality in patients with chronic heart failure.<sup>1</sup> While the effects of cardiac resynchronization therapy (CRT) on left ventricular (LV) function and dyssynchrony have been widely investigated,<sup>2</sup> data on the impact of CRT on RV structure and contractility are relatively scarce and often obtained with heterogeneous methodologies.<sup>3–8</sup> Moreover, the role of RV function as a determinant of response to CRT is still debated.<sup>9,10</sup> Of note, assessment of RV contractility may be challenging by echocardiography, and cannot be performed by cardiac magnetic resonance in most CRT recipients.

It is known that physical exercise may place RV under greater hemodynamic load and stress than LV.<sup>11,12</sup> Previous data on endurance athletes showed a correlation between exercise-induced reduction in RV ejection fraction (RVEF) and increase in markers of myocardial injury and strain (i.e., cardiac troponin and B-type natriuretic peptide).<sup>11,13</sup> In heart failure patients, RV function may be a relevant factor limiting exercise tolerance. So far, the effects of CRT on RV function under exercise conditions have not been well characterized.

In this prospective study, we investigated mid-term effects of CRT on (i) RV function and dyssynchrony, as assessed by Tc<sup>99m</sup> radionuclide angiography, at rest and during exercise, and (ii) neurohormonal response, expressed by N-terminal pro-brain natriuretic peptide (NT-proBNP), in heart failure patients stratified by baseline RVEF.

## METHODS

### Study Design

Thirty-six consecutive heart failure patients with nonischemic dilated cardiomyopathy and sinus rhythm, referred to our Institution for CRT implantation according to standard indications,<sup>14</sup> were prospectively enrolled. Coronary artery disease had been excluded before CRT implantation by

coronary angiography. LV volumes were assessed before implantation by echocardiography from the apical four-chamber view, and ejection fraction was derived according to biplane Simpson's method. All patients underwent Tc<sup>99m</sup> radionuclide angiography, at rest and during exercise, within 4 days of CRT implantation and after 3 months. Pharmacological treatment was kept constant during the present study, unless specific medical need arose, as in any prospective study. CRT was switched off between implantation and baseline radionuclide examination. At baseline, resting and exercise radionuclide images were recorded during spontaneous rhythm and 10 minutes after CRT activation, whereas at 3 months, images were recorded during CRT only. Bicycle exercise was performed at a fixed workload of 25 W to allow for adequate exercise and comprehensive image recording during stress condition in all patients. Exercise radionuclide images started to be acquired when at least a 10-beat increase in heart rate had been achieved. The study protocol was approved by the local Ethics Committee, and all patients provided written informed consent for participation.

### Tc<sup>99m</sup> Radionuclide Angiography with Fourier Phase Analysis

Radionuclide angiography was performed as previously described.<sup>3,15</sup> In detail, modified *in vivo/in vitro* red blood cell labeling using 2 to 3 mg stannous pyrophosphate was performed 15 minutes before injection of about 925 MBq Tc<sup>99m</sup>. Planar imaging was obtained in the "best septal separation" left anterior oblique view with patients in the semi-supine position by a dual-headed gamma camera (Philips Prism 2000 XP) equipped with parallel-hole, high-resolution collimator. Data were collected in frame mode, excluding extrasystolic and post-extrasystolic beats (beat length window <10%), with 32 frames acquired at rest and 24 during exercise (in 128 × 128 matrix). Imaging acquisition ended when total counts of ≥6 million at rest and ≥4 million during exercise were recorded.

A background-corrected, time-activity curve was obtained for both ventricles by a semi-automated edge-detection method with a variable region of interest, verified visually and modified manually, if necessary. LV ejection fraction (LVEF) and RVEF were computed on the basis of the relative end-diastolic and end-systolic counts.<sup>15,16</sup> Patients were stratified according to baseline RVEF during spontaneous rhythm: RVEF was considered impaired if ≤35%, preserved if >35%.<sup>8</sup> The response to CRT was defined by an absolute increase in LVEF ≥5% at mid-term follow-up.<sup>15</sup>

Phase images were generated from the scintigraphic data using a specific computer program, the Fourier phase analysis software.<sup>15–17</sup> The identical scintigraphic data used to generate RV and LV EFs were digitally processed to display the "phase" for each pixel overlaying the equilibrium blood pool and gated to the ECG R-wave. The Fourier phase program assigns a phase angle to each pixel of the phase image, derived from the first Fourier harmonic of time. The phase angle corresponds to the relative sequence and pattern of ventricular contraction during the cardiac cycle. Color-encoded phase

images with corresponding histograms were generated for each patient. Scintigrams were intensity coded for amplitude, the other parameter of Fourier first harmonic study. Phase images were generated for cardiac regions using a continuous color scale, corresponding to the phase angles from 0° to 360°. Mean phase angles were computed for RV and LV blood pools as the arithmetic mean phase angles for all pixels in the ventricular region of interest. The mode was the angle with the highest value on the histogram of phases. The earliest ventricular phase angle relates to the time of onset of the ventricular contraction, the mean ventricular phase angle reflects the mean time of the onset of the ventricular contraction, and the standard deviation of the ventricular phase angle relates to the synchrony of the ventricular contraction. Intraventricular dyssynchrony was expressed by the standard deviation of the phase histogram for each ventricle, while interventricular dyssynchrony was calculated as the absolute difference between LV and RV mean phase angles.<sup>15–17</sup> The reproducibility of radionuclide measures of biventricular contractility and dyssynchrony in our center was previously determined.<sup>16</sup>

### NT-proBNP Assessment

Blood samples for NT-proBNP assessment were collected before CRT implantation and after 3 months. NT-proBNP was measured by using a two-site sandwich assay based on solid-phase Radial Partition Immunoassay (RPIA) technology (Stratus CS Acute Care pBNP TestPak, Siemens Healthcare Diagnostics). All analyses were performed by the analyzer microprocessor, and the NT-proBNP data were checked by one laboratory-skilled operator.

### Statistics

Data were analyzed using a commercially available statistical package (IBM SPSS Statistics 22). Continuous variables were tested for normal distribution using Kolmogorov–Smirnov test and presented as mean  $\pm$  standard deviation. Log-transformation of variables with a skewed distribution was performed before the analyses. One-way analysis of variance for repeated measures and 2-sided paired *t* test were performed for comparisons between baseline and follow-up, at rest and during exercise. Relations between variables were assessed using Pearson correlation coefficient. Fisher's exact test was used to compare proportions of nominal variables. *P* values  $<.05$  were considered statistically significant.

## RESULTS

Patient characteristics at baseline are presented in Table 1. All patients received a CRT device with defibrillation capabilities. LV lead position was anterior/anterolateral in 4 (11%) patients, and posterior/posterolateral in 32 (89%) patients. Atrioventricular and interventricular delays were optimized by echocardiography after CRT implantation and were not

changed during follow-up. Bicycle exercise was well tolerated without any complications, and the study protocol was completed by all patients. No arrhythmias were detected during the examinations. A similar rest-to-exercise increase in heart rate was reached during each bicycle test ( $17 \pm 6$  beats/min during spontaneous rhythm at baseline and during CRT at 3 months,  $17 \pm 7$  beats/min during CRT at baseline).

### Effects of CRT on Radionuclide Angiography Variables and NT-proBNP in the Entire Study Population

In the entire study population (Table 2), RVEF did not significantly change at baseline between spontaneous rhythm and CRT activation. At 3 months, there was an increase in RVEF at rest as well as during exercise ( $P = .011$  and  $P = .038$  vs CRT at baseline, respectively). Accordingly, RV dyssynchrony decreased over follow-up under both conditions ( $P \leq .001$ ). At baseline, RVEF and RV dyssynchrony worsened during exercise compared to that at rest. At 3 months, no significant differences in RVEF were observed between rest and exercise, although RV dyssynchrony was still higher during exercise. LVEF increased over 3 months at rest and during exercise ( $P \leq .001$  vs CRT at baseline). LV dyssynchrony was improved by CRT acutely under rest conditions ( $P = .002$ ), and decreased further at follow-up ( $P = .007$  vs CRT at baseline). No significant rest-to-exercise changes in LVEF were observed at each time point, although LV dyssynchrony increased during exercise at baseline (under CRT) and 3 months. Interventricular dyssynchrony was low at baseline, and decreased further under CRT during exercise. A significant reduction in NT-proBNP was observed at follow-up ( $P < .001$ ).

### Effects of CRT in patients with impaired or preserved RV function

By stratifying the patients according to RVEF, 14 patients (39%) had impaired RVEF, while 22 patients (61%) showed preserved RVEF during spontaneous rhythm at baseline. Baseline clinical characteristics were not statistically different between the 2 groups, except for QRS duration, which was higher in the group with preserved RV function (Table 1). Figure 1 shows rest and exercise values of all radionuclide angiography variables at each time point (spontaneous rhythm, CRT baseline, CRT 3 months) in patients with impaired and preserved RV functions, respectively. During spontaneous rhythm, RV dyssynchrony was higher in patients with impaired RVEF ( $P = .009$  and  $P = .041$  at rest and exercise, respectively), while LV variables and

**Table 1.** Baseline characteristics of the entire study population and of the subgroups of patients with impaired and preserved RV functions

	<b>Entire population (n = 36)</b>	<b>Patients with impaired RV function (n = 14)</b>	<b>Patients with preserved RV function (n = 22)</b>
Age (years)	62 ± 11	59 ± 12	65 ± 10
Male (n, %)	30 (83%)	12 (86%)	18 (82%)
New York Heart Association class	2.5 ± 0.6	2.6 ± 0.6	2.4 ± 0.6
QRS duration (ms)	158 ± 27	146 ± 22	166 ± 28*
Left bundle branch block (n, %):	35 (97%)	14 (100%)	21 (95%)
LV end-diastolic volume (mL)	243 ± 62	252 ± 44	233 ± 77
LV end-systolic volume (mL)	178 ± 48	191 ± 36	165 ± 57
LV ejection fraction (%) by echocardiography	26 ± 4	25 ± 3	28 ± 5
SPAP (mmHg)	31 ± 18	39 ± 19	27 ± 17
GFR (mL/min/1.73 m <sup>2</sup> )	64 ± 21	55 ± 21	69 ± 20
LV lead position (n, %):			
Anterior/anterolateral	4 (11%)	2 (14%)	2 (9%)
Posterior/posterolateral	32 (89%)	12 (86%)	20 (91%)
Optimized atrioventricular delay (ms)	105 ± 49	97 ± 32	111 ± 58
Interventricular delay configuration (n, %):			
Simultaneous	10 (28%)	4 (29%)	6 (27%)
LV preactivation	24 (67%)	10 (71%)	14 (64%)
RV preactivation	2 (5%)	0	2 (9%)
Concomitant therapy (n, %)			
Loop diuretics	34 (94%)	13 (93%)	21 (95%)
Angiotensin-converting enzyme inhibitors or Angiotensin receptor antagonists	36 (100%)	14 (100%)	22 (100%)
β Blockers	35 (97%)	14 (100%)	21 (95%)
Antialdosteronics	25 (69%)	9 (64%)	16 (73%)

GFR, glomerular filtration rate; LV, left ventricular; RV, right ventricular; SPAP, systolic pulmonary artery pressure (by echocardiography)

\* *P* < .05 vs patients with impaired baseline RV function

interventricular dyssynchrony were similar in both groups.

By comparing at each time point in both groups (Figure 1), immediately after CRT activation, no changes in RVEF and RV dyssynchrony vs spontaneous rhythm were observed. An acute improvement in LVEF occurred only in patients with preserved RV function. After 3 months, in patients with impaired RV function, RVEF improved at rest (*P* = .02 vs spontaneous rhythm and CRT baseline) and during exercise (*P* = .023 vs spontaneous rhythm and *P* < .001 vs CRT baseline). In patients with preserved RV function, no significant variations in RVEF were observed at follow-up. Rest and exercise RV dyssynchrony decreased at 3 months with no significantly different delta values vs spontaneous

rhythm between the two groups (−16° ± 23° vs −8° ± 12° at rest, −18° ± 24° vs −11° ± 18° during exercise in patients with impaired and preserved RV functions, respectively, *P* = ns). Over mid-term follow-up, in both groups, there was a similar improvement in LVEF (6 ± 8% vs 8 ± 8% at rest, 5 ± 8% vs 7 ± 8% during exercise in patients with impaired and preserved RV functions, respectively, *P* = ns) and LV dyssynchrony (−17° ± 26° vs −25° ± 32° at rest, −15° ± 19° vs −17° ± 27° during exercise in patients with impaired and preserved RV functions, respectively, *P* = ns). Interventricular dyssynchrony decreased in both groups at 3 months during exercise. All radionuclide angiography variables were similar at 3 months in patients with impaired and preserved RV functions, except for RVEF

and RV dyssynchrony at rest, which were still more compromised in the former ( $P = .013$  and  $P = .025$  between the groups, respectively). According to LVEF changes, 7 (50%) patients with impaired RV function and 14 (64%) patients with preserved RV function were identified as CRT responders at 3 months ( $P = ns$  between the groups). In the entire population, 15 (42%) patients were found to be nonresponders. RV and LV variables in these patients, at baseline and follow-up, are presented in Table 3. In this subgroup, despite no improvement in RVEF, RV dyssynchrony decreased at 3 months both at rest and during exercise.

By comparing rest and exercise at each time point (Figure 1), a slight decrease in RVEF and worsening in RV dyssynchrony were observed during exercise, at baseline and follow-up, in patients with preserved RV function. In patients with impaired RV function, RVEF did not change between rest and exercise at each time point, whereas RV dyssynchrony increased during exercise at baseline. No significant rest-to-exercise change in LVEF was observed in both groups. A reduction in interventricular dyssynchrony during exercise occurred under CRT (at baseline and 3 months) in patients with preserved RV function.

As shown in Figure 2, NT-proBNP was similar at baseline in patients with impaired and preserved RV functions, and decreased in both groups with comparable delta values over a 3-month follow-up ( $-469 \pm 862$  vs  $-470 \pm 1060$ ,  $P = ns$ ).

### Correlations

In patients with impaired RV function ( $n = 14$ ), RVEF during spontaneous rhythm at baseline was inversely correlated with RV dyssynchrony at rest ( $r = -0.72$ ,  $P = .003$ ) and during exercise ( $r = -0.56$ ,  $P = .037$ ). Over a 3-month follow-up, the improvement in RVEF was found to correlate with the decrease in RV dyssynchrony ( $r = -0.52$ ,  $P = .05$  at rest), and with the increase in LVEF ( $r = 0.53$ ,  $P = .05$  at rest;  $r = 0.55$ ,  $P = .042$  during exercise). Significant correlations were found between the decrease in NT-proBNP and the improvement in RVEF ( $r = -0.55$ ,  $P = .044$  at rest), RV dyssynchrony ( $r = 0.75$ ,  $P = .003$  during exercise), LVEF ( $r = -0.70$ ,  $P = .006$  at rest;  $r = -0.62$ ,  $P = .019$  during exercise), and LV dyssynchrony ( $r = 0.60$ ,  $P = .023$  at rest;  $r = 0.81$ ,  $P < .001$  during exercise). In patients with

**Table 2.** Radionuclide angiography variables of biventricular function and NT-proBNP levels in the entire population ( $n = 36$ ) at different time points: during spontaneous rhythm, immediately after CRT activation (CRT baseline), and after 3 months

Variable	Spontaneous rhythm	CRT baseline	CRT 3 months
RV ejection fraction (%)			
Rest	39 ± 9	37 ± 8	41 ± 8 <sup>†</sup>
Exercise	36 ± 10 <sup>#</sup>	35 ± 8 <sup>#</sup>	39 ± 9 <sup>†</sup>
RV dyssynchrony (°)			
Rest	36 ± 19	33 ± 17	25 ± 11* <sup>†</sup>
Exercise	47 ± 21 <sup>#</sup>	51 ± 21 <sup>#</sup>	34 ± 17* <sup>†#</sup>
LV ejection fraction (%)			
Rest	22 ± 6	23 ± 6	30 ± 10* <sup>†</sup>
Exercise	22 ± 6	24 ± 6	28 ± 10* <sup>†</sup>
LV dyssynchrony (°)			
Rest	59 ± 27	48 ± 20*	37 ± 19* <sup>†</sup>
Exercise	59 ± 23	55 ± 19 <sup>#</sup>	43 ± 21* <sup>†#</sup>
Interventricular dyssynchrony (°)			
Rest	20 ± 11	19 ± 11	18 ± 12
Exercise	24 ± 13	17 ± 12*	15 ± 11*
NT-proBNP (pg/mL)			
Rest	1898 ± 1005		1429 ± 1263*

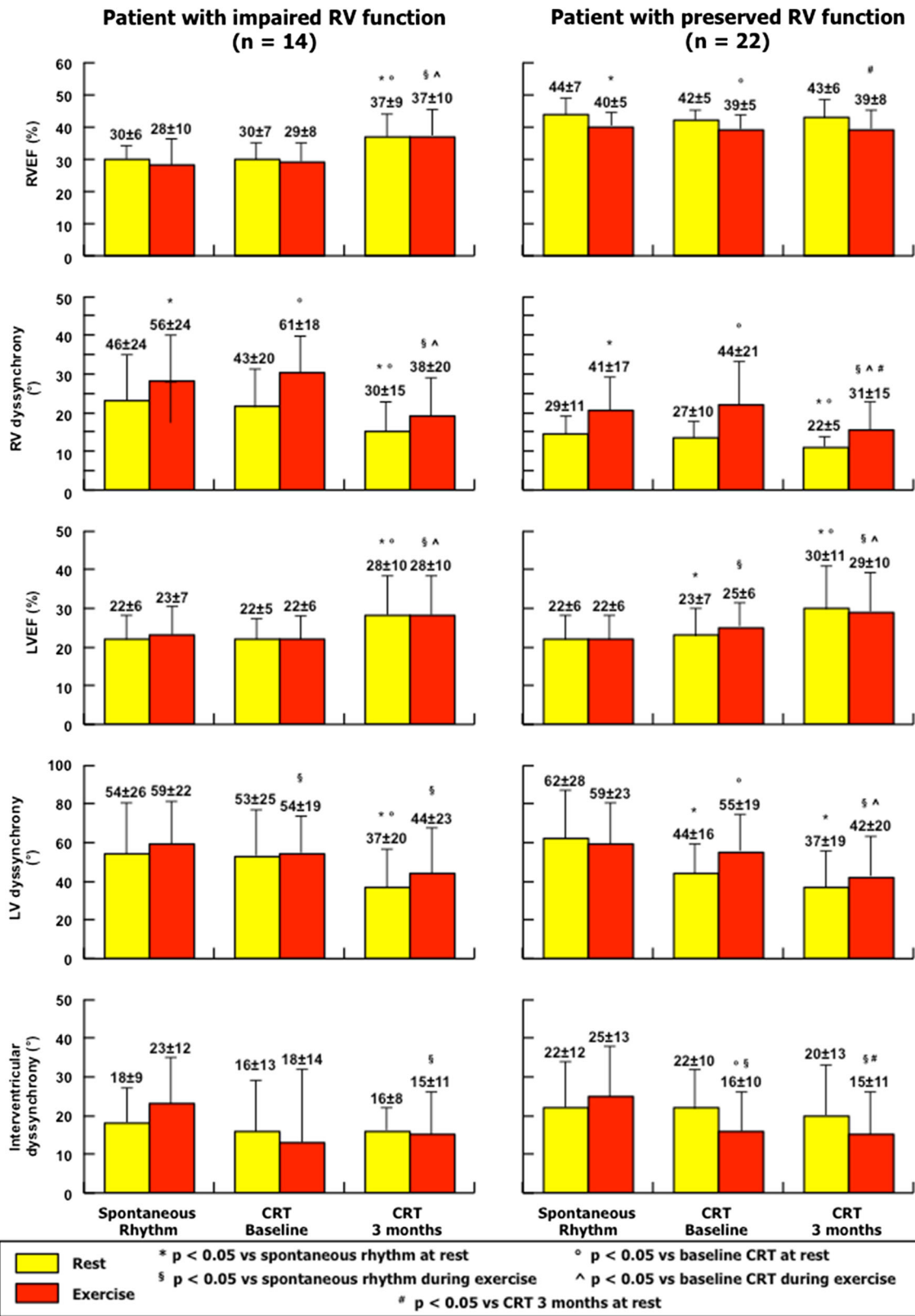
CRT, cardiac resynchronization therapy; LV, left ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricular

\*  $P < .05$  vs spontaneous rhythm

†  $P < .05$  vs CRT baseline

#  $P < .05$  vs rest





◀ **Figure 1.** Variations in biventricular function and dyssynchrony at rest and during exercise in patients with impaired and preserved right ventricular functions, respectively, at different time points: during spontaneous rhythm, immediately after CRT activation (CRT baseline), and after 3 months of follow-up (CRT 3 months). Yellow columns refer to rest, and red to exercise. *CRT*, cardiac resynchronization therapy; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *RV*, right ventricular; *RVEF*, right ventricular ejection fraction.

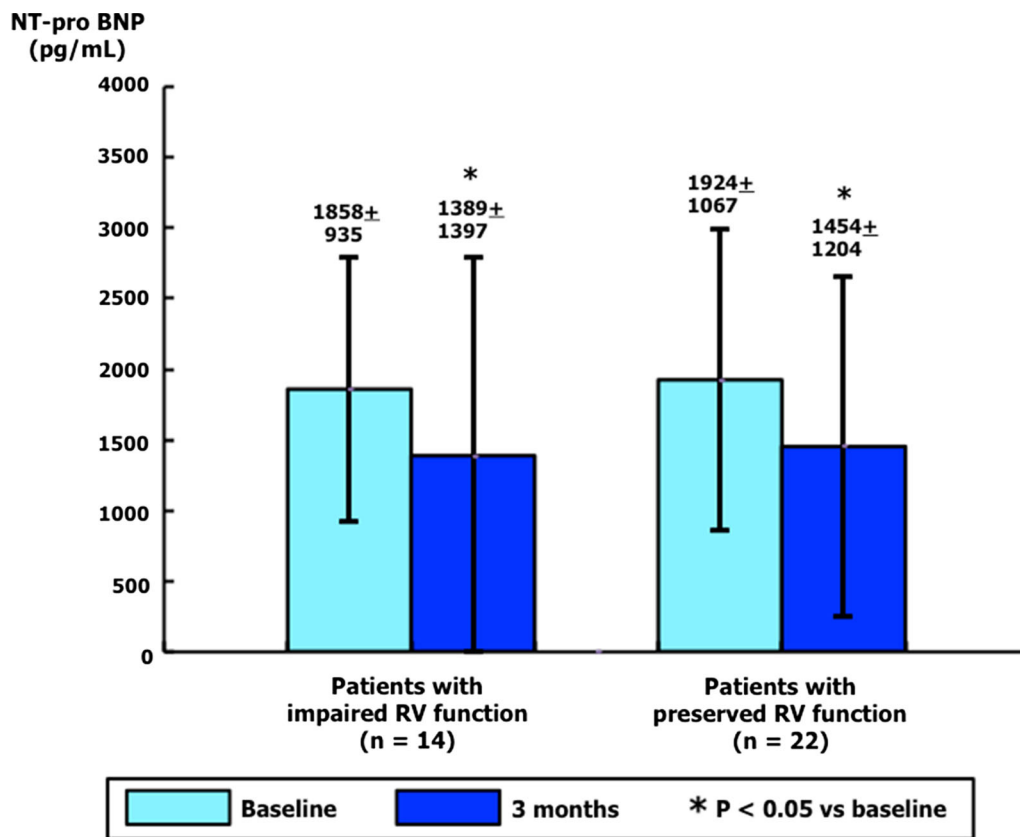
preserved RV function (n = 22), the decrease in NT-proBNP was correlated with the decrease in RV dyssynchrony during exercise ( $r = 0.50, P = .017$ ). In nonresponders, no significant correlation was found between baseline RV variables and absence of LV improvement at follow-up.

### DISCUSSION

In CRT patients with nonischemic dilated cardiomyopathy and impaired baseline RV function, at mid-term follow-up, we observed an improvement in RVEF and RV dyssynchrony, at rest as well as during

exercise. Patients with preserved baseline RV function exhibited a mid-term decrease in RV dyssynchrony, without any significant changes in RVEF. These observations provide support to the concept that CRT may provide a favorable RV remodeling and improvement in RV performance, not only at rest but also during exercise, in heart failure patients with baseline RV dysfunction. Of note, we analyzed only patients with nonischemic dilated cardiomyopathy, in order to avoid interferences of myocardial scars with the electromechanical activation pattern of both ventricles.

The interplay between RV function and CRT in heart failure patients is still a debated issue. In a previous radionuclide angiography study, Burri et al.<sup>8</sup> found a slight increase in RVEF at follow-up in a population of CRT patients with ischemic and nonischemic cardiomyopathy. Accordingly, previous echocardiography studies described an improvement in RV size and pulmonary artery pressure,<sup>4</sup> and an increase in RV Tissue Doppler velocities<sup>5</sup> and myocardial strain<sup>6</sup> in patients undergoing CRT treatment. Our results



**Figure 2.** Variations in NT-proBNP in patients with impaired and preserved right ventricular functions, respectively, at baseline and after 3 months. *Light blue columns* refer to baseline, and *dark blue* to 3-month follow-up. *NT-proBNP*, N-terminal pro-brain natriuretic peptide; *RV*, right ventricular.

**Table 3.** Radionuclide angiography variables of biventricular function in nonresponders (n = 15) at different time points: during spontaneous rhythm, immediately after CRT activation (CRT baseline), and after 3 months

Variable	Spontaneous rhythm	CRT baseline	CRT 3 months
RV ejection fraction (%)			
Rest	35 ± 10	35 ± 9	37 ± 9
Exercise	34 ± 11	35 ± 8	36 ± 9
RV dyssynchrony (°)			
Rest	38 ± 22	36 ± 19	29 ± 13*†
Exercise	48 ± 23#	55 ± 23#	39 ± 22†#
LV ejection fraction (%)			
Rest	21 ± 6	21 ± 5	21 ± 5
Exercise	22 ± 7	22 ± 7	22 ± 7
LV dyssynchrony (°)			
Rest	50 ± 26	50 ± 24	45 ± 18
Exercise	54 ± 24	55 ± 22	52 ± 22
Interventricular dyssynchrony (°)			
Rest	19 ± 10	15 ± 10	15 ± 11
Exercise	22 ± 10	17 ± 14	14 ± 10*

CRT, cardiac resynchronization therapy; LV, left ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricular

\*  $P < .05$  vs spontaneous rhythm

†  $P < .05$  vs CRT baseline

#  $P < .05$  vs rest

extend these observations, suggesting that the improvement in RVEF by CRT seems to occur in the subgroup of patients with baseline RV dysfunction. In agreement with these findings, in the study by Bleeker et al.,<sup>4</sup> RV reverse remodeling was most evident in patients with the largest RV dilatation at baseline. A modest, albeit significant, increase in tricuspid annular plane systolic excursion was detected by Scuteri et al.<sup>18</sup> only in the group of CRT patients with baseline depressed RV function, despite no improvement in RV dimensions at a 6-month follow-up.

The mechanisms underlying the improvement in RV function under CRT are not completely known. It is likely that the improvement in LV performance may lead to a decrease in pulmonary artery pressure, thereby resulting in reduced RV afterload and increased RV function.<sup>4,5</sup> Our results showed a significant decrease in RV dyssynchrony after mid-term CRT treatment. The favorable effect of CRT on the coordination of RV contractility, together with the improvement in LV mechanical synchrony and function, may be responsible for the observed increase in global RV systolic function.<sup>6</sup> CRT effects on RV and LV synchrony and contractility may favorably impact ventricular interdependency, thereby increasing cardiac performance.

Despite evidence showing a possible improvement in RV performance after CRT, previous findings have highlighted an association between baseline RV dysfunction and decreased likelihood of response to CRT in terms of LV reverse remodeling and clinical improvement.<sup>8,18,19</sup> This might be explained by the observation that RV dysfunction is a marker of advanced disease in chronic heart failure.<sup>18</sup> Accordingly, death rate was previously found to be higher in CRT patients with impaired baseline RV function.<sup>20</sup> However, an analysis of the CARE-HF study showed that RV dysfunction seems not to diminish the prognostic benefits of CRT, although it is a powerful predictor of mortality among heart failure patients as candidates for CRT.<sup>21</sup> In line with these results, a recent meta-analysis showed no significant association between baseline RV function and response to CRT as assessed by LVEF.<sup>10</sup> In our study, at mid-term follow-up CRT patients with impaired and preserved baseline RV function exhibited a similar improvement in LVEF and NT-proBNP, and this was remarkably associated with a significant increase in RVEF in patients with baseline RV impairment. However, these findings should be integrated with long-term outcome data, which was beyond the aim of the current study. The percentage of mid-term CRT responders, according to LVEF increase, tended to be



lower in the group with impaired vs preserved baseline RV function (50 vs 64%, respectively), the difference not reaching statistical significance.

During exercise, we observed a worsening in RV dyssynchrony in all patients, and a slight decrease in RVEF in patients with preserved RV function, despite no significant rest-to-exercise change in LVEF. In line with these observations, although in a different clinical setting, previous studies showed that acute or prolonged intense exercise has the greatest cardiac impact on RV, reflected by a reversible increase in RV pressures and volumes and a transient impairment in RV contractility, most likely due to a high susceptibility of the RV to ventricular load increases.<sup>11–13</sup> It should be noted that assessment of RV function during exercise is still a challenging issue with current methodologies. Indeed, RV evaluation may be difficult by echocardiography, owing to the complex anatomy and geometry, and cannot be performed by cardiac magnetic resonance in most CRT recipients. Based on these considerations, exercise RV assessment was performed in the present study by means of a radionuclide methodology, which allows for a feasible and reproducible evaluation of both RV dyssynchrony and systolic function.<sup>8,16</sup>

In patients with impaired baseline RV function, we found a significant correlation between the improvement in RVEF and the decrease in NT-proBNP. This is consistent with previous investigations,<sup>11–13,22,23</sup> showing a strong association between RV dysfunction and biochemical markers of myocardial injury (i.e., cardiac troponin and BNP). BNP plasma elevation occurs in patients with RV overload and dysfunction in response to increased wall tension and stretch.<sup>24</sup> Improvement in RV function may have a favorable impact on neurohormonal balance in CRT patients. Therefore, there may be a complex interplay between prognostic factors in heart failure patients, the improvement in RV function being associated with the decreased NT-proBNP, the increased LV preload, and exercise capacity.<sup>23</sup>

### Limitations

Some study limitations need attention. A submaximal increase in heart rate was achieved during each bicycle test. Since we focused on a radionuclide methodology,<sup>25</sup> prospective echocardiographic data on RV function and systolic pulmonary artery pressure were not collected. The clinical relevance of improved RVEF in patients with baseline RV dysfunction was not assessed in terms of functional status, exercise capacity, and outcome, due to the relatively short follow-up. We did not assess the short-term changes in RV function, but rather the changes at 3-month follow-up. Moreover, the small number of patients with baseline RV

dysfunction did not allow for assessment of the prognostic impact of radionuclide functional variables through multivariate analysis.<sup>26,27</sup>

### NEW KNOWLEDGE GAINED

In patients with nonischemic dilated cardiomyopathy and impaired baseline RV function, undergoing CRT treatment, a mid-term improvement in RVEF and RV dyssynchrony, at rest as well as during exercise, may be observed by radionuclide angiography. The improvement in RVEF was correlated with the decrease in NT-proBNP, showing a favorable impact on neurohormonal balance.

### CONCLUSION

CRT may improve RV performance as assessed by radionuclide angiography, during rest and exercise, and by neurohormonal response in heart failure patients with baseline RV dysfunction. The practical implication of this study is that RV dysfunction should not be per se a primary criterion for excluding candidacy to CRT in heart failure patients who fulfill evidence-based eligibility criteria for this nonpharmacological treatment.

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### Disclosure

*None to declare.*

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