Interplay Between Right Ventricular Function and Cardiac Resynchronization Therapy : An Analysis of the CARE-HF Trial (Cardiac Resynchronization–Heart Failure)

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Objectives

The aim of this study was to investigate the impact of cardiac resynchronization therapy (CRT) on right ventricular (RV) function and the influence of RV dysfunction on the echocardiographic and clinical response to CRT among patients enrolled in the CARE-HF (Cardiac Resynchronization-Heart Failure) trial.

Background

Cardiac resynchronization therapy prolongs survival in appropriately selected patients with heart failure but the benefit might be diminished in patients with RV dysfunction.

Methods

Of 813 patients enrolled in the CARE-HF study, 688 had tricuspid plane systolic excursion (TAPSE) measured at baseline, and 345 of these were assigned to CRT. Their median (interquartile range) age was 66 (58 to 71) years, left ventricular (LV) ejection fraction was 24% (21% to 28%), and TAPSE was 19 (16 to 22) mm. Baseline LV function and size and QRS duration were similar among TAPSE tertiles, but those in the worst tertile (TAPSE <17.4 mm) were more likely to have ischemic heart disease.

Results

Overall, CRT improved LV but not RV structure and function with little evidence of an interaction with TAPSE. During a median (interquartile range) follow-up of 748 (582 to 950) days, 213 deaths occurred. Patients with lower TAPSE had a higher mortality, regardless of assigned treatment ($p < 0.001$). Greater inter-ventricular mechanical delay, New York Heart Association functional class, mitral regurgitation, and N-terminal pro–B-type natriuretic

peptide, lower TAPSE, and assignment to the control group were independently associated with higher mortality. Reduction in mortality with CRT was similar in each tertile of TAPSE.

Conclusions

Right ventricular dysfunction is a powerful determinant of prognosis among candidates for CRT, regardless of treatment assigned, but did not diminish the prognostic benefits of CRT among patients enrolled in the CARE-HF trial. (Care-HF CArdiac Resynchronization in Heart Failure; NCT00170300)

Key Words

- chronic heart failure;
- prognosis;
- resynchronization;
- right ventricle

Abbreviations and Acronyms

- CRT, cardiac resynchronization therapy;
- IHD, ischemic heart disease;
- LV, left ventricle;
- LVEF, left ventricular ejection fraction;
- MR, mitral regurgitation;
- RV, right ventricle;
- TAPSE, tricuspid annular plane systolic excursion;
- TR, tricuspid regurgitation

Right ventricular (RV) dysfunction indicates a poor prognosis in patients with heart failure (1 and 2). Cardiac resynchronization therapy (CRT) improves left ventricular (LV) function, symptoms, and prognosis in patients with symptomatic heart failure, LV systolic dysfunction, and a prolonged QRS duration (3). However, uncertainty exists both about the effects of CRT on RV function (4, 5, 6, 7, 8 and 9) and how RV dysfunction affects the response to CRT (4, 5, 6, 7, 8, 9 and 10). However, observational studies measure outcome with but not the response to an intervention. A control group is required to distinguish treatment effects from the natural history of the disease (11). A post-hoc analysis of the REVERSE (REsyncronization reVErses Remodeling in Systolic left vEntricular dysfunction) trial, including 450 patients with chronic heart failure and mild symptoms, suggested that those with RV dysfunction (tricuspid annular plane systolic excursion [TAPSE] ≤14 mm) had a diminished response to CRT (n = 61), with less reverse LV remodelling and a poorer symptomatic response (12).

We investigated the impact of CRT on RV function and the influence of RV dysfunction on the echocardiographic and clinical response to CRT among patients enrolled in the CARE-HF (Cardiac Resynchronization−Heart Failure) trial (13).

Methods

The CARE-HF trial was a randomized trial of 813 patients (3) who had symptoms of heart failure despite guideline-indicated treatment who were in sinus rhythm and had LV systolic dysfunction and dilation and markers of cardiac dyssynchrony.

This analysis is based on 688 patients (85% of all patients in the CARE-HF trial) who had a measurement of lateral wall TAPSE at baseline by M-mode (13). In addition to TAPSE, echocardiographic measurements included: LV end-diastolic and end-systolic volumes, left ventricular ejection fraction (LVEF), RV end-diastolic area and end-systolic area, RV fractional shortening area, mitral regurgitation and tricuspid regurgitation (TR) by measuring the area of the jet divided by the area of the right atrium on color flow Doppler and trans-tricuspid gradient pressure. Echocardiography was repeated at 3, 9, and 18 months.

Statistical methods

Continuous data were summarized by the median (25th/75th) percentiles; categorical data were summarized by percentages. An analysis of variance model was used to look at the trend for continuous variables; the chi-squared test was used to look for trend for categorical variables (Table 1 and Table 2). Data are shown by tertile of TAPSE. The primary outcome measure of the CARE-HF trial was all-cause mortality or an unplanned hospital stay for a major cardiovascular event. All-cause mortality was the principal secondary endpoint and the primary endpoint of an extension phase (3).

Survival curves were constructed with the Kaplan-Meier method; univariate and multivariate Cox regression modeling were performed to assess the independent impact of TAPSE on clinical outcome (14 and 15). We explored whether the inclusion of 3 additional covariates—TAPSE, TR jet/right atrial diastolic area, and TR pressure gradient—added prognostic value to previous models (14 and 15). Both baseline and 3-month post-implant values were considered. Where the proportional hazards assumption was violated, Cox models with time-dependent effects were considered. Over-fitting and goodness-of-fit was also addressed.

Missing values at 3 months were imputed from baseline values to preserve the integrity of randomization.

Results

The maximum and minimum values for TAPSE in each tertile were 5.5 to 17.3 mm, 17.4 to 21.1 mm, and 21.2 to 33.4 mm, respectively; 93 patients had values ≤14 mm. Patients in the lowest tertile of TAPSE were more often men, were twice as likely to have ischemic heart disease (IHD), and had evidence of more severe heart failure (Table 1).

Cardiac resynchronization therapy reduced LV end-systolic and -diastolic volumes and increased LVEF within 3 months of implantation, with evidence of further benefit by 9 months, which was sustained at 18 months (16). Mitral regurgitation was reduced by 3 months, and the effect was sustained (Table 2). Overall, CRT did not improve RV structure and function. The effects of CRT on LV structure and function and mitral regurgitation and the lack of effect on RV structure and function were broadly similar across tertiles of TAPSE, although patients in the worst tertile had a slightly greater reduction in RVES area and TR gradient (Table 2). Results for RV structure and function were similar when patients were divided according to the presence or absence of IHD (Fig. 1).

Figure 1.

Among patients with a TAPSE measurement, 329 reached the primary endpoint (T1 = 145, T2 = 99, T3 = 85), and 213 died (Fig. 2). The median (interquartile range) follow-up, censored for death, was 748 days (58 to 950) days. A higher TAPSE at baseline was associated with a lower risk of the primary outcome (chi-square log-rank test: 27.1; $p < 0.001$) and better survival (chi-square log-rank test: 12.4; $p < 0.001$), regardless of treatment assigned. However, the effect of CRT on outcome was similar across tertiles of TAPSE (Figs. 2A and 2B). Analysis confined to the 93 patients with a TAPSE ≤14 mm also showed similar improvement in outcome, both for the primary endpoint (hazard ratio: 0.57, 95% confidence interval: 0.34 to 0.94, $p = 0.029$) and all-cause mortality (hazard ratio: 0.62, 95% confidence interval: 0.34 to 1.11, $p = 0.11$). Patients with worse TAPSE were more likely to die of heart failure. Caution should be applied to interpretation of CRT effects on mode of death in subgroups, due to the small number of events (Fig. 2B).

Figure 2.

Adding measures of RV function to a published multivariable model (14) eliminated IHD as a predictor of mortality, replacing it with TAPSE measured at 3 months after randomization (Table 3). The following variables, as in the original published model, remained independently associated with higher all-cause mortality: less interventricular mechanical delay at baseline; New York Heart Association functional class IV at baseline; assignment to the control group; more severe mitral regurgitation at 3 months; and higher N-terminal pro–B-type natriuretic peptide at 3 months (14) (Table 3). The model did not suffer from over-fitting (17). The proportional hazards assumption was not violated (overall chi-square test = 4.2, $df = 6$, $p = 0.64$) (18). In univariate analyses, LV volumes and LVEF measured at 3

months were more strongly related to prognosis than measurements at baseline, but none contributed independent prognostic information on a multivariable analysis.

Discussion

This analysis shows that CRT has little effect on RV function and that the severity of RV dysfunction is a weak determinant of the effects of CRT on LV structure or function. Although a marker of a worse overall prognosis, RV dysfunction was not an important determinant of the relative benefits of CRT.

As far as we are aware, this is the first study to investigate the effect of CRT on RV function in a randomized controlled trial. Cardiac resynchronization therapy might be expected to improve RV function by lowering left atrial and pulmonary artery pressures due to improvements in LV function and mitral regurgitation (19, 20, 21 and 22). However, pacing leads might interfere with tricuspid valve function and RV apical pacing might impair RV function (23). However, we identified no substantial improvement in right heart function with CRT when compared with pharmacological therapy alone, in contrast to several (7 and 19), but not all (24), observational studies, although we might have missed subtle changes that can be measured by newer echocardiographic techniques, such as tissue Doppler or RV strain (24 and 25).

At baseline, LV systolic dysfunction was similar across tertiles of TAPSE, but those with worse TAPSE had more severe mitral regurgitation, higher pulmonary artery pressure, more severe TR and higher plasma concentration of N-terminal pro–B-type natriuretic peptide. The extent to which RV dysfunction reflects pulmonary hypertension or intrinsic RV dysfunction is uncertain and likely to vary over time and among individual patients (26). However, the high prevalence of IHD in patients with worse TAPSE suggests that RV ischemic damage might be common (7, 19, 20, 21, 22, 24, 25 and 26). Poor baseline RV function was associated with a trend to smaller improvements in LV function in response to CRT, consistent with a previous report (12). However, this trend was accounted for by the high prevalence of IHD in patients with RV dysfunction. Patients with IHD are more likely to have myocardial scar, which will impair the beneficial remodeling response to both pharmacological interventions and CRT (27 and 28).

There is growing evidence, reinforced by this analysis, that RV rather than LV dysfunction might be the more important determinant of prognosis (1 and 26). Both lower TAPSE and higher TR gradient estimated at baseline were associated with an adverse prognosis, and this relationship was strengthened when re-estimated at 3 months after randomization. Interestingly, after measures of RV dysfunction were added to the prognostic model, the presence of IHD was no longer an independent predictor of outcome. This could also reflect the importance of RV damage due to ischemia (29). Whether, RV dysfunction or etiology is the more important driver of an adverse prognosis is uncertain. The strong statistical association between worse TAPSE and higher prevalence of IHD suggests that one might just be a surrogate for the other in such models.

Several observational (6 and 10) studies have suggested that patients with RV dysfunction receive less prognostic benefit from CRT. The problem with observational studies is that they are unable to distinguish between outcome with treatment and response to it (11). This analysis confirms previous reports showing that, in patients who receive CRT, those with poor RV function will have a worse outcome. However, the change in prognosis (i.e., the

response to treatment) is similar in patients with and without RV dysfunction. This contradicts assertions that CRT is ineffective in patients with substantial RV dysfunction (6 and 10). Whether the severity of RV dysfunction should influence the choice between CRT and CRT with defibrillator is uncertain. Patients with RV dysfunction are more likely to die of heart failure rather than suddenly. However, sudden death still represents a substantial proportion of deaths in patients with RV dysfunction, which might be reduced by implantation of CRT with defibrillator.

Study limitations

The current hypothesis was not defined prior to conducting the study. Ideally, the results should be confirmed in a prospective trial of patients with both RV and LV dysfunction, but it is not clear whether this would receive ethical clearance. Alternatively, data might be available from another randomized trial that could be analyzed, retrospectively. A study of the size and duration of the CARE-HF trial is unlikely to have missed substantial effects of CRT on RV function but more modern imaging technologies might identify subtler effects. On the other hand, the study was not adequately powered to investigate the effects of CRT on outcomes, such as mode of death in subgroups of patients.

Conclusions

Right ventricular dysfunction is a powerful determinant of prognosis among candidates for CRT, regardless of treatment assigned, but does not diminish the prognostic benefits of CRT among patients enrolled in the CARE-HF trial.

These data illustrate the difference between “outcome with” and “response to” CRT, urging caution in the interpretation of observational data, and might help clinicians make appropriate clinical choices for their patients.

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Table 1.				
Clinical<comma> Biological<comma> and Echocardiography Characteristics at Baseline in Entire Population and Divided by Tertiles of TAPSE				
Baseline Characteristics	TAPSE Tertiles (n = 688)			
T1 (n = 233)	T2 (n = 231)	T3 (n = 224)	p Value for Trend	
Clinical				
Age<comma> yrs	66(60–73)	58(51–66)	65(57–71)	0.07
Men	195(84)	150(65)	155(69)	<0.001
NYHA functional class IV	15(6)	16(7)	11(5)	0.5
BMI (kg/m2)	25(23–28)	26(23–29)	27(24–30)	0.001
Heart rate<comma> beats/min	71(62–83)	68(60–77)	69(60–76)	0.01
Systolic BP<comma> mm Hg	110(100–120)	117(105–130)	120(110–130)	<0.001
LBBB	206(88)	207(89)	206(91)	0.05
QRS duration (ms)	160(150–180)	165(154–180)	160(152–180)	0.87
Ischemic heart disease	121(52)	65(28)	44(20)	<0.001
NT-proBNP (pg/ml)	3<comma>023(1<comma>310–5<comma>979)	1<comma>792(727–4<comma>287)	1<comma>099(566–2<comma>740)	<0.001
eGFR<comma> ml/min/1.73 m2	53(42–67)	59(43–72)	64(49–77)	<0.001
Echocardiography				
LVEDV (ml)	296(246–354)	307(237–384)	295(235–385)	0.82
LVESV (ml)	225(180–273)	222(168–294)	219(167–290)	<0.001
LVEF (%)	23(20–26)	24(21–29)	25(22–29)	<0.001
LA diastolic area	23(18–29)	19(14–23)	18(15–24)	<0.001
MR jet area (mm2)	25(15–35)	23(13–32)	16(9–30)	<0.001
IVMD<comma> ms	46(26–64)	48(33–65)	51(31–72)	0.034
RVED area<comma> cm2	23(18–29)	20(16–24)	19(16–22)	<0.001
RVES area<comma> cm2	16(10–20)	11(8–14)	10(7–13)	<0.001
RV fractional shortening area<comma> %	31(23–40)	43(36–50)	47(38–54)	<0.001
TAPSE<comma> mm	14(12–16)	19(18–20)	23(22–25)	<0.001
TR jet area<comma> cm2	3.4(1.8–6.4)	2.2(1.3–4.0)	1.8(1–3)	<0.001
TR jet available	179(77)	160(69)	137(61)	<0.001
RA diastolic area<comma> cm2	16.2(10.8–21.4)	11(8.9–14.7)	10.5(8.8–13)	<0.001
TR jet area/RA area cm2	21.9(15.2–33.6)	18.9(12.5–29.6)	15.3(10.4–25.9)	<0.001
TR gradient<comma> mm Hg	33(24–42)	28(21–36)	28(21–37)	0.011
TR gradient available	141(60)	124(53)	79(37)	<0.001
Treatment				
Beta-blockers	164(70)	164(70)	172(77)	0.12
ACE inhibitors/ARB	220(94)	219(94)	212(94)	0.91
Aldosterone inhibitor	131(56)	129(55)	125(55)	0.92
Furosemide ≥80 mg/day	134(57)	89(38)	68(30)	<0.001
Digitalis	91(39)	96(41)	109(48)	0.039

Values are median (25th/75th percentiles) or n (%).

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; IVMD = interventricular mechanical delay; LA = left atrial; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; RA = right atria; RV = right ventricle; RVED = right ventricular end-diastolic area; RVES = right ventricular end-systolic area; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

Table 2.									
Changes in Quality of Life and Cardiac Function Between Baseline and 9 Months									
TAPSE Tertiles	T1	T2	T3	p Value					
CRT	Medical	CRT	Medical	CRT	Medical	Control vs. CRT	Interaction TAPSE vs. CRT		
Number with paired results	89	75	94	92	85	93			
LVEDV (ml)	−27(−67to−3)	−1(−29to15)	−59(−98to−22)	−11(−39to7)	−49(−107to−6)	−6(−38to16)	<0.001	0.11	
LVESV (ml)	−30(−66to−10)	−7(−30to11)	−60(−95to−19)	−11(−32to7)	−46(−96to−12)	−9(−37to9)	<0.001	0.15	
LVEF (%)	4(1.3to9.2)	0.9(−0.9to3.2)	5.6(1.1to10.8)	1(−1.7to3.7)	6.2(1.6to11.9)	1.2(−0.7to4.2)	<0.001	0.12	
LA diastolic area<comma> cm2	−4.8(−8.4to1.8)	−3.7(−7.1to2.2)	−3.8(−7.7to0.6)	−1.9(−7.0to1.7)	−5.2(−9.2.07)	−2.4(−3.7to0.8)	0.01	0.24	
MR jet area (%)	−4(−13to−2)	0(−11to9)	−4(−14to1)	0(−9to5)	−3(−9to3)	2(−3to10)	0.001	0.22	
IVMD (ms)	−24(−41to−4)	0(−17to15)	−21(−38to−9)	−5(−21to10)	−24(−40to−2)	1(−9to13)	<0.001	0.13	
TAPSE (mm)	1.1(−0.1to3.7)	1.4(−0.7to4.1)	0.4(−.1to3.6)	0.8(−1.1to2.8)	−1.0(−3.5to0.1)	−.2.1(−3.6to0.8)	0.5	0.79	
RVED area (cm2)	−1(−7.4to1.1)	−0.1(−3.1to2.5)	−0.9(−3.7to1.4)	−1.6(−3.4to0.7)	−1.2(−3.5to0.7)	−0.9(−3.5to2.0)	0.34	0.1	
RVES area (cm2)	−2.9(−6.4to0.7)	−1.0(−4.4to1.9)	−0.4(−4to0.5)	−1.0(−2.8to0.7)	−0.8(−2.5to1.7)	−1.0(−2.8to0.3)	0.38	0.03	
RV fractional shortening area (%)	6(−1to15)	5(0to13)	4(−4to11)	3(−3to8)	−1(−11to5)	3(−3to13)	0.38	0.36	
Paired TR jet	41(46%)	60(80%)	45(48%)	46(50%)	47(55%)	61(66%)			
TR jet area (cm2)	−0.6(−2.3to0.8)	−0.5(−2.2to0.9)	−0.4(−1.3to1.4)	−0.4(−1.7to0.3)	0.1(−1.2to1.1)	−0.1(−1to0.5)	0.41	0.78	
RA diastolic area (cm2)	−0.9(−7.7to1.4)	−1.3(−4.3to0.9)	−0.9(−3.9to1.9)	−0.6(−4.7to1.2)	−0.5(−2.5to1.4)	−1.1(−3.8to1)	0.56	0.39	
TR jet area/RA area (cm2)	−4.5(−14.9to5.6)	−1.3(−11.5to9.1)	−2.2(−9.2to11.7)	−0.8(−14.3to4.8)	3.8(−4.2to12)	2.8(−13.4to10.8)	0.32	0.2	
Paired TR gradient	29(33%)	28(37%)	32(34%)	16(17%)	22(26%)	20(22%)			
TR gradient<comma> mm Hg	−8(−11.7to−3.4)	−1.6(−10.5to6.3)	−0.4(−5.6to3.7)	−2.8(−6.1to2.8)	0(−9.2to2.7)	−5.1(−7.5to−1.5)	0.42	0.03	

p for interaction between CRT and TAPSE level from an analysis of variance model combining TAPSE levels 2/3.

CRT = cardiac resynchronization therapy; other abbreviations as in Table 1.

Table 3.										
Multivariable Cox Regression Models With Baseline and 3-Month Data to Predict All-Cause Mortality										
Variables	HR	(95% CI)	p Value							
NYHA functional class IV	2.16	(1.28–3.63)	0.004							
NT-proBNP<comma> 3 months (pg/ml)*	1.62	(1.41–1.86)	<0.001							
MR<comma> 3 months (cm2)*	1.01	(1.00–1.02)	<0.001							
IVMD (ms)	0.98	(0.98–0.99)	<0.001							
CRT	0.57	(0.53–0.99)	0.04							
TAPSE<comma> 3 months (mm)*	0.58	(0.40–0.84)	0.004							
TAPSE (mm)* by tertile										
T2	0.76	(0.56–1.04)	0.09							
T3	0.69	(0.50–0.97)	0.03							
Missing	0.97	(0.59–1.58)	0.91							

NT-proBNP transformed by natural logarithms.

Q = quartile; other abbreviations as in Table 1.

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3-month values imputed by last observation carried forward where baseline data missing. The TAPSE by tertile replaced TAPSE continuous (mm), adjusting for same covariates. Hazard ratio (HR) for missing TAPSE gives an indication of bias.