Chapter 7

Right Ventricular Function And Survival Following Cardiac Resynchronization Therapy

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Cardiac resynchronisation therapy (CRT) reduces mortality among patients with advanced heart failure, impaired left ventricular (LV) systolic function and QRS duration ≥120 ms.[1] However, long-term death rates remain high in CRT recipients.[2] Identification of potential CRT candidates who are unlikely to derive survival benefit from this therapy, therefore, remains an important goal. Characterisation of patients who will have a poor outcome despite CRT may in fact allow the development of more targeted treatment approaches in this population.

Right ventricular (RV) function is recognised as a cardinal prognostic marker in patients with heart failure and reduced LV systolic function.[3] Its impact on all-cause mortality following CRT independent of confounding factors has not been evaluated, however. Furthermore, evidence on the effect of CRT on RV contractile function is limited.[4] The aims of this evaluation were therefore to: (1) assess the prognostic importance of RV function among CRT recipients, and (2) characterise RV function changes following CRT and its determinants.

METHODS

Patient population

The study population comprised of 905 consecutive patients from the ongoing registry of CRT recipients at the Leiden University Medical Centre.[5] Patient data were collected prospectively in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Centre, Leiden, the Netherlands) and retrospectively analysed. Indication for CRT was heart failure with LV ejection fraction (LVEF) ≤35%, and QRS duration ≥120 ms.[6] Heart failure aetiology was considered ischaemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery on coronary angiography) and/or history of prior myocardial infarction or revascularisation.

According to the institutional protocol, prior to CRT implantation, all patients underwent extensive clinical and echocardiographic evaluation.[7] Clinical evaluation was performed in particular for identification of comorbid conditions, medications and functional status, which was quantified by the New York Heart Association (NYHA) functional class. In addition, 12-lead electrocardiography and 6-min walk test were performed. Renal function was determined with estimated glomerular filtration rate calculated using the Cockcroft-Gault formula. Transthoracic echocardiography was undertaken according to a standardised protocol (see below), which included the assessment of LV and RV function. The same protocol was repeated at 6 months' follow-up to evaluate the changes in LV and RV function after CRT. Clinical long-term follow-up was performed to determine the incidence of all-cause mortality.

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system equipped with a 3.5 Mhz transducer (Vingmed Vivid7 and E9, General Electric Healthcare, Horten, Norway). Two-dimensional grey-scale, pulsed, continuous and colour Doppler data were acquired in the parasternal and apical views, the latter including dedicated imaging of the RV. Images were recorded digitally in cine-loop format and analysed offline with commercial software EchoPAC (110.0.0, GE-Vingmed, Horten, Norway).

LV end-systolic and end-diastolic volumes were measured from the apical 2-chamber and 4-chamber views and LVEF calculated using the biplane Simpson's technique.[8] RV function was evaluated by tricuspid annular plane systolic excursion (TAPSE), which was displayed by applying an M-mode algorithm to the lateral tricuspid annulus in the RV apical view. This approach to the assessment of RV function was chosen as a widely available and highly feasible one, which is recommended as a routine part of RV evaluation.[9] RV impairment was defined as TAPSE≤14 mm, as this cut-off has demonstrated important prognostic value in heart failure patients.[10] RV systolic pressure and mitral regurgitation (MR) severity were estimated according to current guidelines.[11,12] LV dyssynchrony was assessed by septal-to-lateral delay on colour tissue Doppler imaging as previously described.[13] In addition, LV diastolic function was assessed by measuring transmitral E and A wave velocities using pulsed wave Doppler at the level of the mitral leaflet tips, and E′ by offline analysis using colour tissue Doppler imaging at the septal mitral annulus. The E/E′ ratio was then calculated. Echocardiographic measurements were performed blind to patient outcome.

Device implantation

The LV lead was inserted transvenously into the coronary sinus and advanced where possible to the posterolateral cardiac vein under the guidance of venography. The RV and right atrial leads were positioned at the RV apex and right atrial appendage respectively. Implanted devices included Contak Renewal, Contak TR or Contak CD (Guidant USA), Insync Marquis, Insync III, Insync Sentry or Protecta (Medtronic Inc. USA), Atlas HF (St Jude Medical USA) and Lumax (Biotronik, Germany), while LV leads included Attain (Medtronic Inc. USA), Corox (Biotronik, Germany) and Easytrak (Guidant USA).

Outcomes

Long-term follow-up was performed by case record review, telephone contact with patient primary healthcare providers, and through the national death registry. The primary endpoint was all-cause mortality.

Statistical analysis

Continuous variables are presented as mean±SD (where normally distributed) or median (IQR) and compared between groups at baseline using analysis of variance or the Kruskal-Wallis test as appropriate. Categorical data are summarised as frequencies and percentages, and compared using the χ^2 test. For survival analysis, rates of survival were estimated using the Kaplan-Meier technique and tested between groups using the log-rank test. To reduce type I error, pair-wise comparison among multiple groups was undertaken with Bonferroni's adjustment to the threshold significant p value.[14] The proportional hazards assumption was checked for continuous variables by visual inspection of scaled Schoenfeld residuals[15] and confirmed by the method of Grambsch and Therneau,[16] and for categorical variables by visual inspection of log-log plots. Cox proportional hazards models were fitted to evaluate the predictive value of patient characteristics for the primary endpoint. Predictors associated with a p value <0.2 on univariate analysis were entered into a multivariate analysis using backward elimination to identify independent predictors of the primary endpoint. Results are expressed using HRs. Model fit was evaluated by visual inspection of the cumulative hazard of Cox-Snell residuals and by the Harrell's C-statistic.[17] The incremental value of successive predictors of the primary endpoint was assessed by the likelihood ratio test for the nesting model containing the covariate of interest. Covariates for this analysis were those demonstrating independent predictive value in the Cox model.

For repeated-measures analysis of TAPSE, mixed effects modelling was employed. The significance of predictor variables of interest was evaluated by including them in a mixed model as part of an interaction term with subjects' visit time (ie, baseline vs follow-up). If this predictor-time interaction term was significant, it implied that the candidate predictor variable's influence on TAPSE was time-dependent. Post hoc testing was then performed to determine whether the candidate predictor variable's influence on TAPSE was significant at baseline and follow-up visit. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant. All analyses were undertaken using STATA software, V.12 (Stata Corp, College Station, Texas, USA).

RESULTS

Patient population

Nine hundred and five consecutive patients who successfully underwent CRT were evaluated. In a total of 57 (6%) patients, TAPSE was deemed non-evaluable owing to image quality. Baseline clinical and echocardiographic characteristics of

the remaining 848 patients are displayed in table 1. One hundred and thirty-seven (16%) patients had atrial fibrillation (AF) at the time of implantation and 42 (5%) were upgrade procedures from RV pacing. Six hundred and fifty-two (77%) patients were in NYHA class III or IV at implantation; the remaining were in NYHA class II.

Significant RV dysfunction (as defined by a TAPSE≤14 mm10) was observed in 286 (34%) patients. Comparisons between patients with TAPSE≤14 mm and >14 mm are summarised in table 1. Patients with significant RV dysfunction exhibited a greater prevalence of ischaemic cardiomyopathy, diabetes mellitus and AF. Furthermore, functional status, exercise capacity, renal function and LV systolic and diastolic function were poorer, while RV systolic pressure was higher among patients with RV impairment. Individuals with RV impairment also exhibited less LV dyssynchrony than those with more preserved RV function.

Survival analysis

Over the course of a median follow-up time of 44 months (IQR 29–65 months), 288 deaths occurred. Death rate was observed to be significantly higher among CRT recipients with impaired baseline RV function (figure 1). The Kaplan-Meier curves of those with impaired versus preserved baseline RV function diverged early during follow-up, and continued to diverge over time. One-year death rates among those with impaired and preserved baseline RV function were 18% (95% CI 14% to 23%) and 3% (95% CI 2% to 5%), respectively. At 2 years, these death rates were 27% (95% CI 22% to 33%) and 8% (95% CI 6% to 10%), while at 5 years' follow-up, death rates were 50% (95% CI 44% to 58%) and 21% (95% CI 18% to 25%), respectively.

TAPSE was tested as a predictor of the incidence of mortality in univariate Cox analysis together with age, gender, ischaemic aetiology, diabetes mellitus, AF, NYHA functional class, 6 min walk distance, estimated glomerular filtration rate, QRS duration, LVEF, LV end-systolic volume, MR grade, LV dyssynchrony, E/E′, and RV systolic pressure (table 2). For the multivariate model, 6-min walk distance was omitted in favour of NYHA class as a measure of functional status in the interest of feasibility, as NYHA class was evaluable in all patients, whereas 179 (21%) patients were unable to perform the 6 min walk test. Similarly, RV systolic pressure was not included in the multivariate model in favour of TAPSE for the purposes of model parsimony (to avoid multicollinearity and model overfit) and technical feasibility (RV systolic pressure could not be measured echocardiographically in 419 (49%) patients due to the absence of clear tricuspid regurgitation Doppler signal). By this model, independent predictors of the primary endpoint were more advanced NYHA class, ischaemic aetiology, the presence of diabetes mellitus, AF, poorer renal function, bigger LV end-systolic volume, less LV dyssynchrony and reduced TAPSE. Model fit was found to be acceptable graphically by inspection of the cumulative hazard of Cox-Snell

Table 1. Patient baseline characteristics by right ventricular function dichotomised by TAPSE (threshold of 14 mm10)

	Entire cohort (n=848)	Impaired RV function (n=286)	Preserved RV function (=562)	p Value for TAPSE ≤14 mm vs >14 mm
Age, years (IQR)	67 (59–73)	67 (59–74)	67 (59–73)	0.7
Gender, female (%)	184 (22)	53 (19)	131 (23)	0.1
Ischaemic aetiology, n (%)	509 (60)	188 (66)	321 (57)	0.02
Diabetes mellitus, n (%)	177 (21)	75 (26)	102 (18)	0.005
Medications, n (%)				
Loop diuretic	701 (83)	254 (89)	447 (80)	0.001
ACE-I/ARB	757 (89)	247 (86)	510 (91)	0.05
Beta-blocker	598 (71)	197 (69)	401 (71)	0.5
Spironolactone	402 (47)	155 (54)	247 (44)	0.005
Heart rhythm, n (%)				
Sinus	669 (79)	196 (69)	473 (84)	<0.001
AF	137 (16)	74 (26)	63 (11)	
Paced	42 (5)	16 (5)	26 (4)	
QRS duration (ms)	155±33	154±32	156±33	0.3
NYHA class, n (%)				
II	196 (23)	50 (17)	146 (26)	0.002
III	580 (68)	200 (70)	380 (68)	
IV	72 (9)	36 (13)	36 (6)	
6 min walk distance (m)	309±122	284±122	321±120	<0.001
eGFR (ml/min)	71±33	65±30	74±33	<0.001
LVEF (%)	26±8	24±8	27±8	<0.001
LVESV (ml)	155 (115–200)	158 (122–200)	154 (113–200)	0.3
LVEDV (ml)	208 (161–263)	206 (165–263)	209 (160–263)	0.9
LV dyssynchrony (ms)	70 (30–100)	60 (25–90)	80 (35–100)	<0.001
E wave velocity (cm/s)	77±31	85±34	73±28	<0.001
A wave velocity (cm/s)	64±30	57±30	66±29	0.001
E/A ratio	1.1 (0.66–2.2)	1.5 (0.87–2.8)	0.93 (0.63–1.9)	<0.001
E′ velocity (cm/s)	4.3±1.8	4.1±1.7	4.4±1.8	0.02
E/E′ ratio	18 (12–27)	21 (14–32)	16 (11–25)	<0.001
MR grade, n (%)				
0	115 (14)	27 (9)	88 (16)	0.1
I	335 (40)	114 (40)	221 (39)	
II	256 (30)	89 (31)	167 (30)	
III	102 (12)	40 (14)	62 (11)	
IV	40 (4)	16 (6)	24 (4)	
RVSP (mm Hg)	38±14	40±13	37±13	0.03
TAPSE (mm)	17±5.0	11±2.3	19±3.6	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; RV, right ventricular; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

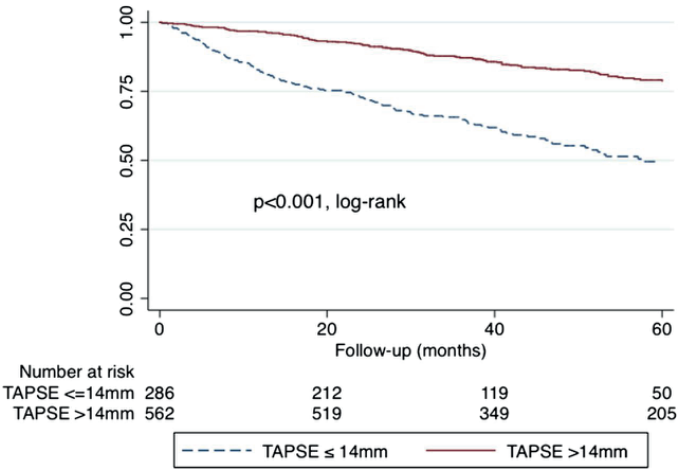

Figure 1. Survival following cardiac resynchronisation therapy and right ventricular (RV) function. Kaplan-Meier survival estimates according to baseline RV function dichotomised by a 14 mm tricuspid annular plane systolic excursion threshold.[10]

Table 2. Independent predictors of death among CRT recipients

	Univariate		Multivariate	
Parameter	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Age (years)	1.03 (1.02 to 1.04)	<**0.001**	0.991 (0.973 to 1.01)	0.3
Gender (female)	1.3 (0.98 to 1.8)	0.07	0.82 (0.53 to 1.3)	0.4
Non-ischaemic aetiology	0.644 (0.503 to 0.825)	<**0.001**	0.730 (0.535 to 0.996)	**0.047**
Diabetes mellitus	1.9 (1.4 to 2.4)	<**0.001**	1.9 (1.4 to 2.6)	<**0.001**
AF	1.8 (1.3 to 2.4)	<**0.001**	1.4 (1.0 to 2.0)	**0.045**
QRS duration (per 10 ms increase)	1.00 (0.999 to 1.01)	0.1	0.997 (0.991 to 1.00)	0.4
NYHA class	2.5 (2.0 to 3.1)	<**0.001**	1.7 (1.3 to 2.2)	<**0.001**
6 min walk distance (per 50 m increase)	0.80 (0.75 to 0.84)	<**0.001**		
eGFR (per 10 ml/min increase)	0.80 (0.76 to 0.84)	<**0.001**	0.83 (0.77 to 0.89)	<**0.001**
LVEF (per 5% increase)	0.82 (0.76 to 0.89)	<**0.001**	0.95 (0.84 to 1.1)	0.4
LVESV (per 10 ml increase)	1.04 (1.01 to 1.06)	**0.007**	1.05 (1.01 to 1.08)	**0.008**
LV dyssynchrony (per 10 ms increase)	0.97 (0.94 to 0.99)	**0.02**	0.96 (0.93 to 0.99)	**0.02**
E/E′	1.02 (1.01 to 1.03)	<**0.001**	1.01 (0.998 to 1.02)	0.1
MR grade 3 or 4	1.4 (1.1 to 1.9)	**0.02**	1.0 (0.71 to 1.5)	0.8
RVSP (mmHg)	1.03 (1.02 to 1.04)	<**0.001**		
Baseline TAPSE>14 mm	0.33 (0.26 to 0.43)	<**0.001**	0.48 (0.36 to 0.65)	<**0.001**

AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

residuals (see online supplementary appendix) with Harrell's C statistic 0.76. The incremental value of evaluation of TAPSE for the prediction of death over and above recognised prognostic indices is displayed in figure 2. The unadjusted relative risk of the primary endpoint as a function of baseline TAPSE is presented in figure 3. This demonstrates progressive increase in the risk of death with poorer baseline TAPSE, in spite of CRT.

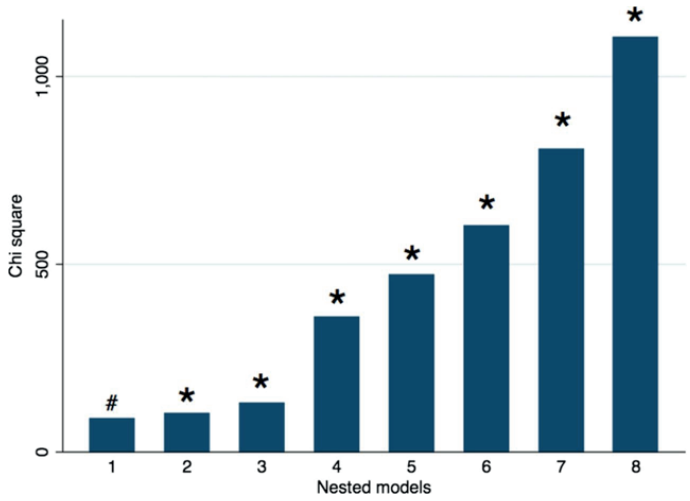

Figure 2. Incremental prognostic value of right ventricular (RV) function over routine clinical and echocardiographic characteristics. Comparison of nested models for the prediction of the mortality using the likelihood ratio test #p < 0.001 compared with intercept-only model and *p < 0.001 compared with adjacent nested model by likelihood ratio test. 1 = New York Heart Association class; 2 = 1 + heart failure aetiology; 3 = 2 + diabetes mellitus; 4 = 3 + atrial fibrillation; 5 = 4 + renal function; 6 = 5 + left ventricular (LV) end-systolic volume; 7 = 6 + LV dyssynchrony; 8 = 7 + RV function. This figure is only reproduced in colour in the online version.

RV functional changes following CRT

During the first 6 months following CRT, 54 (6.4%) individuals died. The following analysis was based on the remaining 794 patients, of whom 738 (93%) had echocardiography at 6 months. Across the cohort as a whole, a significant improvement of TAPSE and RV systolic pressure was demonstrated. In particular, TAPSE increased from 17±5 mm at baseline to 19±6 mm (p<0.001), while estimated RV systolic pressure declined from 38±14 mmHg to 35±12 mmHg (p<0.001). In addition, the mean left ventricular end-systolic volume (LVESV) decreased from 165±70 ml at baseline to 136±64 ml (p<0.001), LVEF increased from 26±8% at baseline to 32±10% (p<0.001) and E/E′ ratio improved from 21±14 at baseline to 18±11 (p<0.001) at 6 months.

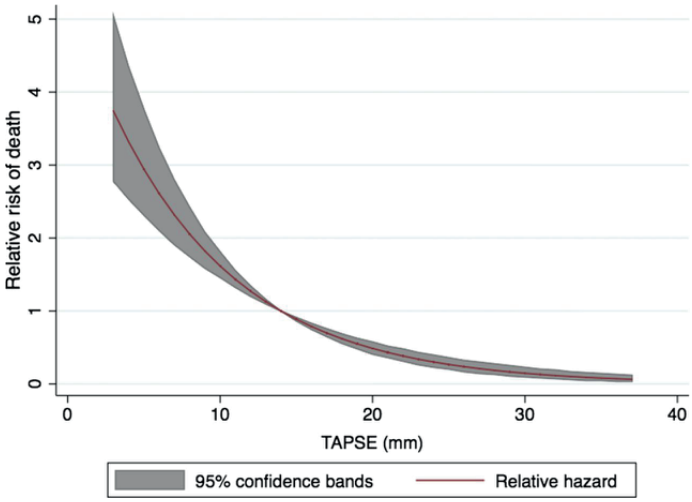

Figure 3. Risk of death following cardiac resynchronisation therapy (CRT) and baseline right ventricular (RV) function. Unadjusted relative risk (red curve) with 95% confidence bands (grey shaded zones) of the death following CRT, as a function of baseline RV function: the poorer the baseline RV function the greater the risk of death despite CRT. This figure is only reproduced in colour in the online version.

Potential determinants of the improvement in RV function following 6 months' CRT, and in particular the association with improvement in LV function, were explored using mixed effects modelling. While at baseline and follow-up there was a significant positive association between LVEF and TAPSE (coefficient 0.11, 95% CI 0.075 to 0.15, p<0.001), the change in TAPSE from baseline to follow-up was independent of the change in LVEF (p value of the LVEF-visit time interaction term=0.4). A trend towards a time-dependent relationship between TAPSE and LVESV was observed (p value of the LV end systolic volume-visit time interaction term=0.06) but did not reach statistical significance. However, the change in TAPSE was significantly and inversely related to the change in E/E' (p value of the E/E'-visit interaction term <0.001), such that reduction in E/E' following 6 months' CRT was associated with improvement in TAPSE. Change in TAPSE was not directly related to the improvement in MR (MR-visit interaction term p value 1.0), although there was a significant negative relationship between MR grade and TAPSE at baseline and follow-up (coefficient –0.50, 95% CI –0.79 to –0.21, p=0.001). Finally, at baseline there was no significant relationship between TAPSE and estimated RV systolic pressure; however, improvement in TAPSE over 6 months was associated with the reduction in RV systolic pressure (RV systolic pressure-visit interaction term p=0.003).

Of 236 individuals with impaired baseline RV function (TAPSE≤14 mm) who were evaluated at 6 months, 126 (53%) exhibited improvement in RV function with a follow-up TAPSE>14 mm. Among the 502 patients with preserved baseline RV func-

tion, only 36 (7%) showed a worsening of TAPSE to 14 mm or below, despite CRT. The relationship between change in TAPSE over the 6 months and subsequent long-term mortality was examined. CRT recipients whose TAPSE was >14 mm at 6 months follow-up displayed significantly superior survival to those whose 6-month TAPSE was ≤14 mm, irrespective of the degree of baseline RV function (figure 4).

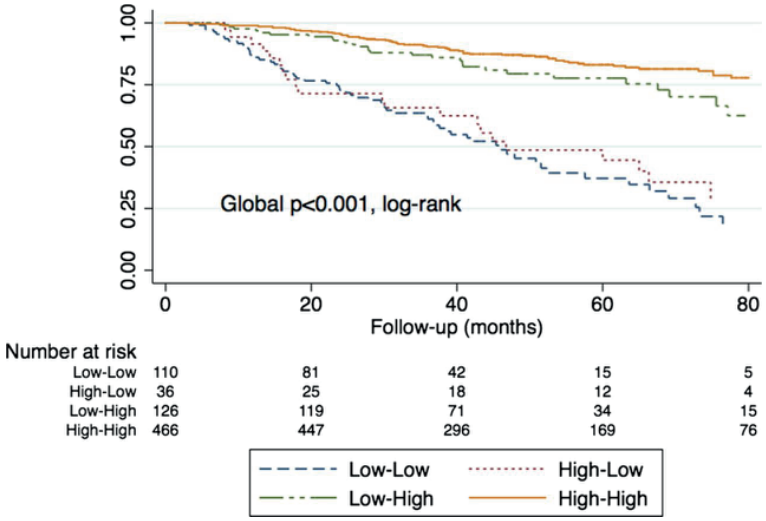

Figure 4. Survival is associated with functional right ventricular (RV) response following cardiac resynchronisation therapy (CRT). Kaplan-Meier survival estimates from CRT implant according to RV functional response to CRT. Low-Low indicates individuals with pre-CRT tricuspid annular plane systolic excursion (TAPSE)≤14 mm and 6-month TAPSE≤14 mm; Low-High indicates a pre-CRT TAPSE≤14 mm and 6-month TAPSE>14 mm; High-Low indicates a pre-CRT TAPSE>14 mm and 6-month TAPSE≤14 mm; High-High indicates a pre-CRT TAPSE>14 mm and 6-month TAPSE>14 mm. *p>0.0085=1–0.95$^{1/6}$ according to the Bonferroni adjustment for the six possible pair-wise comparisons between groups.[14]

DISCUSSION

The key findings of this study are: (1) baseline RV function, as quantified by TAPSE as a highly feasible echocardiographic measure, is an independent predictor of all-cause mortality following CRT and confers incremental prognostic value over a broad range of clinical and echocardiographic parameters; (2) CRT exerts a beneficial effect over RV function which is independent of the improvement in LV systolic function or of the reduction in MR, but is associated with improvement in LV diastolic function.

RV dysfunction in heart failure and outcome following CRT

In the present study of a large cohort of heart failure patients undergoing CRT, significant RV dysfunction (using a 14 mm TAPSE threshold) was observed in 34% of

individuals. In these patients, several causes for the development of RV dysfunction have been proposed, including the same cause (ischaemic or idiopathic) as the LV dysfunction (direct myocardial involvement), pulmonary venous hypertension secondary to LV impairment, ventricular interdependence and neurohormonal interactions.[18] Accordingly in the current study, patients with impaired RV function shared features of lower LVEF, less LV dyssynchrony and higher pulmonary pressures compared with patients with preserved RV function. They also exhibited a greater prevalence of ischaemic heart disease and AF, a poorer functional status and target organ compromise, such as renal dysfunction. These findings therefore represent one of the most comprehensive characterisations of patients with RV impairment in the context of LV failure, and suggest RV dysfunction as an important marker for more advanced heart failure.

In line with this hypothesis, the presence of RV dysfunction is also a well-known independent prognostic factor in heart failure patients.[3] However, the role of RV dysfunction in predicting outcome following CRT is only of emerging interest. Scuteri *et al*[19] have shown in a small group of patients that TAPSE is predictive of reverse LV remodelling following CRT. Among 130 CRT recipients, Tabereaux *et al*[20] recently demonstrated RV dysfunction to be an independent predictor of a heterogeneous composite adverse outcome including death, transplantation, need for LV assist device, lack of improvement in NYHA class and hospital care. Field *et al*[21] reported similar findings using RV myocardial performance as measurement of RV function. Finally, Kjaergaard *et al*[22] showed in 450 minimally symptomatic patients (NYHA class I or II) receiving CRT, that baseline RV dysfunction is an independent predictor of symptomatic deterioration and reduced reverse LV remodelling. The same authors acknowledged the need to study the relationship between CRT and RV function in CRT recipients with more advanced symptoms, and call for research on the role of RV function in survival following CRT.[22]

Thus, existing research has yet to demonstrate prognostic value for evaluation of RV function for all-cause mortality, and importantly has examined only to a limited extent whether the prognostic capacity of RV function assessment is confounded by other important determinants of outcome, such as LV function. The present study has applied TAPSE as a sensitive and easily acquired echocardiographic index of RV function[9] to address these remaining uncertainties. It has shown in a large series of CRT patients that RV dysfunction is associated with overall mortality independent of a broad range of potential confounding factors, conferring additive prognostic value to routinely evaluated clinical and echocardiographic parameters. Therefore, the evaluation of RV function among other recognised prognostic factors may help clinical decision-making prior to CRT prescription. Such a priori risk stratification

may be particularly relevant for individuals in whom the risk-benefit relationship for CRT is marginal.

RV function after CRT

To date, most evidence on the effects of CRT has focussed on its ability to promote LV reverse remodelling. There is a relative paucity of literature on its influence on the RV. Bleeker *et al*[23] have demonstrated that CRT results overall in significant RV reverse remodelling and that this beneficial effect was most marked in patients with more severe RV dilation at baseline. Beyond RV remodelling, Rajagopalan *et al*[24] and Donal *et al*[25] showed using tissue Doppler imaging that CRT might improve RV contractile function. Similarly, the present study showed in a large series of patients a significant improvement in RV function after CRT, using TAPSE as a simple and widely available echocardiographic measure.

A mechanistically important aim of this study was to identify potential determinants of improvement in RV function following CRT. Previous cross-sectional evidence in heart failure patients suggested that LV and RV function are closely associated.[26] Less clear is the temporal and causal relationship between the two, particularly in response to heart failure therapy. The present study has shown that improvement in RV function following CRT is independent of rather than secondary to the increase in LV systolic function, despite the association between LVEF and RV function observed before CRT implantation. However, a trend towards a significant association between change in RV function and change in LVESV was noted, and importantly the improvement in RV function was significantly associated with the reduction in LV filling pressures as estimated by the E/E′ ratio. However, the current study could not demonstrate a significant association between improvement in RV function and reduction in MR severity, despite a significant negative relationship between MR grade and TAPSE at baseline and follow-up. Taken together, these findings prompt speculation that CRT, in addition to its effect on LV systolic function, exerts a beneficial effect on RV function that is probably partially direct to the RV myocardium and partially secondary to the improvement in LV diastolic function and therefore related to ventricular interdependency.

Novel to the current study is also the observation that improvement in RV function is not uniform following CRT. While it was observed that baseline RV function is poorer among CRT recipients who experienced an adverse outcome during follow-up, this study importantly also demonstrated that amelioration or preservation of good RV function after CRT was associated with improved survival. In contrast, progressive decline in RV function or lack of significant RV function improvement after CRT were associated with a poor outcome.

Limitations

Owing to its observational nature, this study is unable to conclude whether patients with severe RV dysfunction should not receive otherwise indicated CRT. This postulate should be addressed in a prospective study of CRT on the basis of RV function. However, the current study emphasises the importance of assessing RV function before and after CRT for optimal patient management.

CONCLUSIONS

This study indicates that baseline evaluation of RV function confers additive predictive value over and above a wide range of recognised prognostic factors. Improvement in RV function after CRT was independent of improvement in LV systolic function and associated with improvement in LV diastolic function. Furthermore, favourable RV functional response to CRT was associated with superior survival.

REFERENCES

1. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA 2007;297:2502–14.
2. Cleland J, Freemantle N, Ghio S, et al. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. J Am Coll Cardiol 2008;52: 438–45.
3. de Groote P, Millaire A, Foucher-Hossein C, et al. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. J Am Coll Cardiol 1998;32:948–54.
4. Donal E, Roulaud M, Raud-Raynier P, et al. Echocardiographic right ventricular strain analysis in chronic heart failure. Eur J Echocardiogr 2007;8:449–56.
5. van Bommel RJ, Borleffs CJ, Ypenburg C, et al. Morbidity and mortality in heart failure patients treated with cardiac resynchronization therapy: influence of pre-implantation characteristics on long-term outcome. Eur Heart J 2010;31: 2783–90.
6. Dickstein K, Vardas PE, Auricchio A, et al. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: An update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Eur Heart J 2010;31:2677–87.
7. Haeck ML, Hoogslag GE, Rodrigo SF, et al. Treatment options in end-stage heart failure: where to go from here? Neth Heart J 2012;20: 167–75.
8. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
9. Leong DP, Grover S, Molaee P, et al. Non-volumetric echocardiographic indices of right ventricular systolic function: validation with cardiovascular magnetic resonance and relationship with functional capacity. Echocardiography 2012;9:45563.
10. Ghio S, Recusani F, Klersy C, et al. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol 2000; 85:837–42.
11. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23: 685–713; quiz 86–8.
12. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol 2006;48:e1–148.
13. Bax JJ, Marwick TH, Molhoek SG, et al. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. Am J Cardiol 2003;92:1238–40.
14. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. Stat Med 1990;9:811–8.
15. Schoenfeld D. Partial residuals for the proportional hazards regresssion model. Biometrika 1982;69:239–41.

16. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–26.
17. Harrell FE Jr.., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996; 15:361–87.
18. Haddad F, Doyle R, Murphy DJ, et al. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation 2008;117:1717–31. [
19. Scuteri L, Rordorf R, Marsan NA, et al. Relevance of echocardiographic evaluation of right ventricular function in patients undergoing cardiac resynchronization therapy. Pacing Clin Electrophysiol 2009;32:1040–9.
20. Tabereaux PB, Doppalapudi H, Kay GN, et al. Limited response to cardiac resynchronization therapy in patients with concomitant right ventricular dysfunction. J Cardiovasc Electrophysiol 2010;21:431–5.
21. Field ME, Solomon SD, Lewis EF, et al. Right ventricular dysfunction and adverse outcome in patients with advanced heart failure. J Card Fail 2006;12:616–20.
22. Kjaergaard J, Ghio S, St John Sutton M, et al. Tricuspid annular plane systolic excursion and response to cardiac resynchronization therapy: results from the REVERSE Trial. J Card Fail 2011; 17:100–7.
23. Bleeker GB, Schalij MJ, Nihoyannopoulos P, et al. Left ventricular dyssynchrony predicts right ventricular remodeling after cardiac resynchronization therapy. J Am Coll Cardiol 2005;46: 2264–9.
24. Rajagopalan N, Suffoletto MS, Tanabe M, et al. Right ventricular function following cardiac resynchronization therapy. Am J Cardiol 2007; 100:1434–6.
25. Donal E, Thibault H, Bergerot C, et al. Right ventricular pump function after cardiac resynchronization therapy: a strain imaging study. Arch Cardiovasc Dis 2008;101:475–84.
26. Desai RV, Meyer P, Ahmed MI, et al. Relationship between left and right ventricular ejection fractions in chronic advanced systolic heart failure: insights from the BEST trial. Eur J Heart Fail 2011;13:392–7.