Cardiac resynchronization therapy : determinants of patient outcome and emerging indications

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Chapter 25

Effects of cardiac resynchronization therapy in patients with heart failure having a narrow QRS complex enrolled in PROSPECT

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Heart 2010;96(14):1107-13

ABSTRACT

Introduction: Current guidelines recommend cardiac resynchronization therapy (CRT) in patients with severe symptomatic heart failure, depressed left ventricular (LV) systolic function and a wide QRS complex (≥120 ms). However, heart failure patients with a narrow QRS complex might also benefit from CRT.

Methods: During the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial, 41 patients were enrolled in a "narrow" QRS sub-study. These patients had a QRS complex <130 ms, but documented evidence of mechanical dyssynchrony by any of 7 pre-defined echocardiographic measures.

Results: After 6 months of CRT, 26 (63.4%) patients showed improvement according to the Clinical Composite Score (CCS), 4 (9.8%) remained unchanged and 11 (26.8%) worsened. In patients with paired data, the 6-minute walking distance increased from 334±118 m to 382±128 m, ($p = 0.003$) and quality-of-life score improved from 44.2±19.7 to 26.8±20.2 ($p<0.0001$). Furthermore, there was a significant decrease in LV end-systolic diameter (from 59±9 mm to 55±12 mm, $p = 0.002$) and in LV end-diastolic diameter (from 67±9 mm to 63±11 mm, $p = 0.007$).

Conclusions: The results suggest that CRT may have a beneficial effect in heart failure patients with a narrow QRS complex and mechanical dyssynchrony as assessed by echocardiography. The majority of patients improved on clinical symptoms and there was an evident reduction in LV diameters. Larger studies are needed to clearly define selection criteria for CRT in patients with a narrow QRS complex.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment option for patients with severe symptomatic heart failure, depressed left ventricular (LV) systolic function and presence of cardiac dyssynchrony, defined as a wide QRS complex (≥120 ms).[1] The beneficial effects of CRT on heart failure symptoms, LV systolic function and prognosis in these selected patients have been widely demonstrated.[2-4] However, only 30% of heart failure patients demonstrate QRS prolongation and many are therefore not considered candidates to CRT.[5, 6] Furthermore, it has been shown that patients with depressed LV systolic function but a narrow QRS complex can also exhibit LV mechanical dyssynchrony, as assessed by echocardiography.[7-9]

In addition, previous single and multi centre studies in patients with narrow QRS complexes and mechanical dyssynchrony have suggested beneficial effects of CRT in these patients.[9-12] However, the results of the first randomized trial of CRT in these patients were ambiguous, and thus the full potential of CRT in patients with a narrow QRS complex remains currently unresolved.[13]

PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) was the first large-scale, multicenter clinical trial that evaluated the performance of several echocardiographic measures of mechanical ventricular dyssynchrony to predict response to CRT.[14] Response to CRT was defined as either improvement in clinical composite score, or a reduction in LV end-systolic volume (LVESV) at 6 months follow-up. Outside the United States, the protocol allowed inclusion of patients with a QRS complex <130 ms in a prospectively defined sub-study. In total, 41 patients were included, which have not been included in the main study cohort (a protocol-defined exclusion).[14]

This study reports the results of CRT on clinical symptoms as well as LV dimensions and LV function in these "narrow QRS" patients.

METHODS

Patient population and study protocol

In this sub-study of the PROSPECT trial,[14] heart failure patients with a narrow QRS complex (<130 ms) were evaluated. Patients were included according to the following criteria: left ventricular ejection fraction (LVEF) ≤35%, NYHA class III or IV, and QRS duration <130 ms with documented evidence of mechanical dyssynchrony by any of seven pre-defined echocardiographic measures (Table 1). All patients were treated, unless contraindicated, with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (for at least 1

month before enrolment) and a β-blocker (started at least 3 months before and unchanged for at least 1 month).

Patients were enrolled in 15 centers in Europe and 1 centre in Hong Kong between March 2004 and November 2005. Patients underwent extensive evaluation before CRT implantation (baseline), at the time of implantation, immediately after implantation, and at 1, 3 and 6 months follow-up. This study complied with the Declaration of Helsinki and was approved by the Ethical Committee of each participating centre. All patients gave their consent to participate.

Table 1. Mechanical dyssynchrony parameters

Parameter	Description	Cut-off value
LVFT/RR[18]	Percentage left ventricular filling time (LVFT) in relation to cardiac cycle length (RR) as measured by transmitral pulsed wave Doppler	LVFT/RR ≤40%
LPEI[18]	Left ventricular pre-ejection interval (LPEI), defined as the time interval between the beginning of QRS and the beginning of left ventricular ejection (onset of aortic flow by Doppler)	LPEI ≥140 ms
LLWC[18]	Intraventricular dyssynchrony left lateral wall contraction (LLWC), defined as the presence of overlap between the end of lateral wall contraction (M-Mode) and onset of LV filling (transmitral pulsed wave Doppler)	any overlap
SPWMD[19]	Septal to posterior wall motion delay (SPWMD) in parasternal M-mode	SPWMD ≥130 ms
T_S-SD[20, 21]	Standard deviation of time from QRS to peak systolic velocity for 12 segments (6 basal + 6 middle), as measured by tissue Doppler imaging	T_S-SD ≥32 ms
T_S-(lateral – septal)[22]	Delay between time to peak systolic velocity of basal septal and basal lateral segments, as measured by tissue Doppler imaging	T_S-(lateral – septal) ≥60 ms
DLC[23, 24]	Delayed longitudinal contraction (DLC) measured in the 6 basal left ventricular segments with a systolic contraction component in early diastole by tissue Doppler imaging	≥2 basal segments

Clinical evaluation

The intrinsic QRS duration was determined within 30 days prior to implantation. Before CRT implantation, the clinical status was assessed including NYHA functional class, quality of life score (using the Minnesota Living With Heart Failure questionnaire), and the 6-minute walk test. These evaluations were also performed at each scheduled follow-up visit.

Echocardiographic evaluation

Echocardiography was performed within 30 days prior to implantation, after device implantation and at 6 months follow-up. Left ventricular (LV) dimensions (LV end-diastolic diameter [LVEDD] and LV end-systolic diameter [LVESD]) were measured from M-mode recordings obtained at the parasternal long-axis views. Left ventricular end-diastolic volume (LVEDV) and LVESV were measured at the apical 2- and 4-chamber views, and LVEF was calculated using the biplane Simpson's method.[15] Severity of mitral regurgitation was graded semi-

quantitatively from color-flow Doppler images at the parasternal long-axis and the apical 4-chamber view and expressed as the ratio of regurgitant jet area to left atrial area.[16] For evaluation of global LV systolic and diastolic function, the myocardial performance index (MPI) was calculated as described previously.[17] Time between cessation and onset of the mitral inflow and the LV ejection time were measured at the pulsed-wave Doppler recordings of the mitral inflow and the LV outflow.[17]

Mechanical dyssynchrony was assessed with the following measures (Table 1): left ventricular filling ratio (LVFT/RR),[18] left ventricular pre-ejection interval (LPEI),[18] intraventricular dyssynchrony left lateral wall contraction (LLWC),[18] septal-to-posterior wall motion delay (SPWMD),[19] standard deviation of time from QRS to peak systolic velocity for 12 segments (TS-SD),[20, 21] septal to lateral delay (TS-[lateral – septal]),[22] and finally, delayed longitudinal contraction (DLC).[23, 24]

Finally, atrioventricular (A-V) optimization was performed using the Ritter's method.[25] The sonographer collecting echo data at follow-up was blinded to patient clinical response to CRT.

All echocardiographic recordings were analyzed in the core laboratories: the Emory University-Crawford Long Hospital (Atlanta, USA) processed all studies from Hong Kong; the Policlinico San Matteo (Pavia, Italy) analyzed all European standard 2-dimensional measurements. Analysis of European tissue Doppler imaging (TDI) measurements was divided between Pavia and Hammersmith (London, UK) depending on availability of equipment. The echocardiographic core labs were blinded to patient clinical response to CRT.

CRT device implantation

Any Medtronic market-released CRT device, with or without implantable cardioverter defibrillator (ICD) functionality could be used. Implantation of the CRT system followed standard procedures.[2]

All patients with a successful CRT implantation underwent A-V optimization within 7 days using the Ritter's method to maximize diastolic filling.[25] Devices with programmable V-V timing remained programmed to nominal biventricular pacing.

Follow-up after 6 months CRT

Clinical changes after CRT were evaluated using the heart failure clinical composite score (CCS).[26] The CCS describes the clinical status of the patient at 6 months, regardless of vital status, and includes both objective and subjective clinical measures.

A patient's CCS was classified as one of the following:

•*Worsened*: the patient died or was hospitalized for or associated with worsening heart failure, demonstrated worsening in NYHA class at last observation carried forward, had moderate or marked worsening of patient global assessment score at last observation carried forward, or permanently discontinued CRT because of or associated with worsening heart failure.

•*Improved*: the patient had not worsened as defined above and demonstrated improvement in NYHA class at last observation carried forward or had moderate or marked improvement in patient global assessment score at last observation carried forward.

•*Unchanged*: the patient had neither improved nor worsened.

An independent end-point committee adjudicated all hospitalizations and CRT discontinuations for heart failure relatedness. A positive clinical change after CRT was defined as a designation of "*improved*". Other clinical measures included: change in NYHA functional class, change in distance covered in the 6-minute hall walk test and change in quality-of-life score.

Echocardiographic changes after CRT were assessed using changes in LV diameters and volumes (LVESD, LVEDD, LVESV and LVEDV), LVEF and MPI at 6 months follow-up, as compared to baseline (paired measurements).

Statistical analysis

End-point parameters are compared between baseline and 6 months using a paired Wilcoxon signed rank test including all patients with paired data. Baseline characteristics are compared between the PROSPECT narrow QRS and wide QRS cohorts using a two-sample t-test for continuous variables and a Fisher exact test for categorical variables. Data are presented as mean±SD for continuous variables and as counts and percentages for categorical variables. Reported baseline statistics include all patients with available data, comparative end-point statistics are based on patients with paired data. All analyses were done with the use of SAS software (version 9.1, SAS Institute Inc., Cary, NC). A p-value <0.05 was considered significant.

RESULTS

Study population

Forty one patients (29 male, mean age 64±13 years) with a narrow QRS complex (<130 ms) and mechanical dyssynchrony were successfully implanted with a CRT device. The LV lead location was lateral in 11 (27%) patients, postero-lateral in 18 (44%) patients, antero-lateral in 6 (15%) patients and posterior in 3 (7%) patients. In the remaining 3 (7%) patients, the LV lead

was inserted in the mid cardiac vein or the anterior vein. A total of 34 patients were enrolled in Europe and 7 in Hong Kong. A flow-chart of patient enrolment is presented in Figure 1.

Compared to the prolonged QRS patients enrolled in the PROSPECT trial, baseline clinical and echocardiographic characteristics of the narrow QRS population were generally similar, although patients in the current study were younger (Table 2). Also MPI was slightly better in the patients with a narrow QRS complex. By protocol design, patients in the present study had a shorter QRS duration and less frequently left bundle branch block configuration.

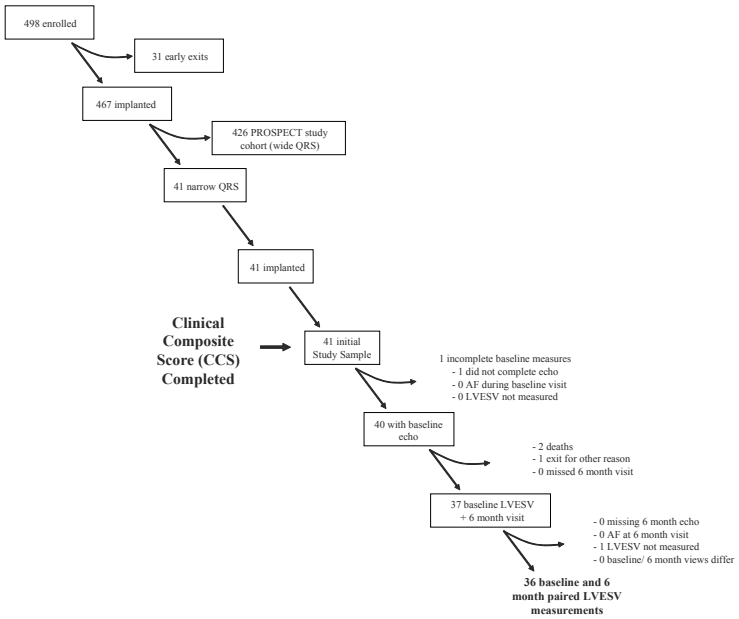

Figure 1. Enrolment and follow-up of patients.
AF = atrial fibrillation; LVESV = left ventricular end-systolic volume.

Table 2. Comparison of baseline clinical and echocardiographic characteristics between the narrow QRS sub-group and the original PROSPECT study population[14]

Variable	Narrow QRS (n = 41)	PROSPECT (n = 426)	p-value
Age (years)	64 ± 13	68 ± 11	**0.031**
Gender (male)	29 (71%)	302 (71%)	1.00
NYHA functional class III	39 (95%)	410 (96%)	0.67
Ischemic etiology	20 (49%)	231 (54%)	0.52
Diabetes	10 (24%)	140 (33%)	0.30
History of atrial fibrillation	4 (10%)	84 (20%)	0.14
History of ventricular tachycardia	11 (27%)	115 (27%)	1.00
QRS duration (ms)	108 ± 14	163 ± 22	**<0.0001**
Left bundle branch block	10 (24%)	327 (77%)	**<0.0001**
Medication:			
Diuretics	38 (93%)	355 (83%)	0.18
ACE-inhibitors	35 (85%)	390 (92%)	0.25
B-blockers	30 (73%)	361 (85%)	0.07
Spironolactone	17 (41%)	169 (40%)	0.87
LV end-diastolic diameter (mm)	67 ± 10	64 ± 11	0.24
LV end-systolic diameter (mm)	58 ± 9	56 ± 12	0.26
LV end-diastolic volume (ml)	241 ± 92	230 ± 99	0.51
LV end-systolic volume (ml)	174 ± 77	168 ± 89	0.68
LV ejection fraction (%)	25 ± 6	24 ± 7	0.27
Myocardial performance index	0.79 ± 0.24	0.89 ± 0.33	**0.030**
Mitral regurgitation (%)	21 ± 20	19 ± 17	0.64

ACE = angiotensin converting enzyme; LV = left ventricular; NYHA = New York Heart Association

Clinical changes at 6 months follow-up

After 6 months of CRT, 26 (63.4%) patients *Improved*, 4 (9.8%) remained *Unchanged*, and 11 (26.8%) *Worsened* (Figure 2), according to the CCS. Two patients (4.9%) died before the 6 months follow-up.

In the remaining patients, all other clinical measures improved significantly (Figure 3, Panels A-C). Mean NYHA functional class improved from 3.0±0.2 to 2.2±0.7 ($p<0.0001$, Figure 3, Panel A). Of note, 31 patients out of the initial 41 (76%) demonstrated an improvement ≥1 NYHA class. Furthermore, paired analysis demonstrated that the 6-minute walking distance increased from 334±118 m to 382±128 m ($p = 0.003$, Figure 3, Panel B) and finally, the Minnesota living with heart failure quality of life score improved from 44.2±19.7 to 26.8±20.2 ($p<0.0001$, Figure 3, Panel C).

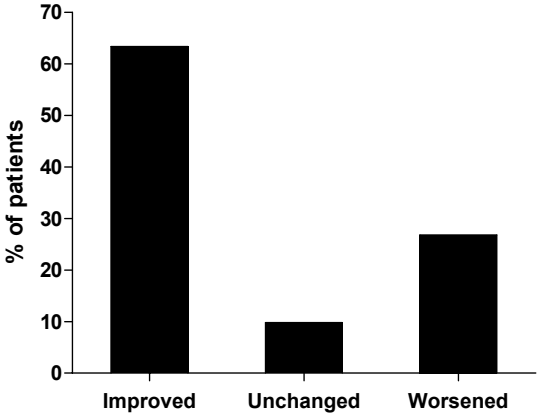

Figure 2. Clinical changes at 6 months follow-up according to the Clinical Composite Score results.

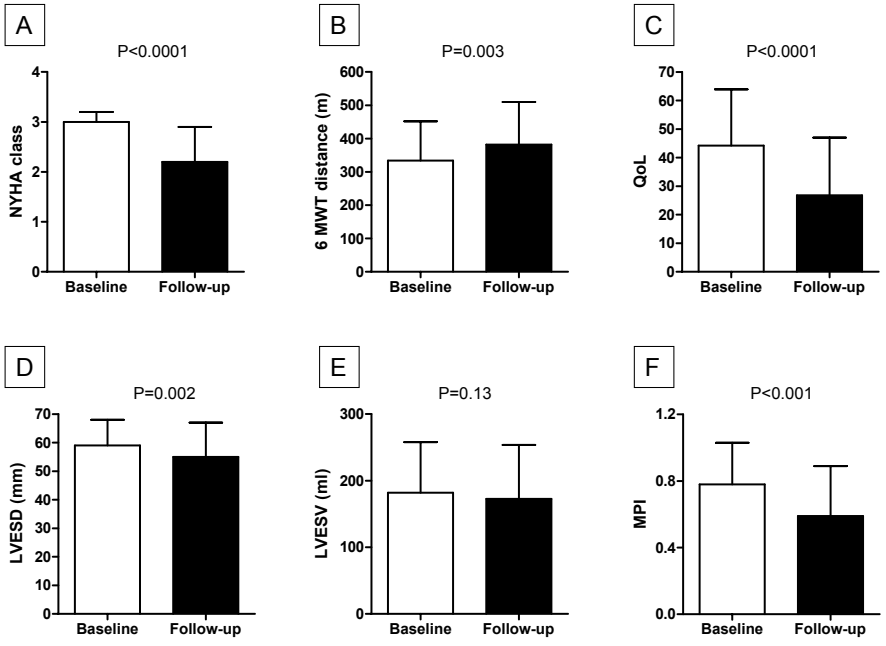

Figure 3. Clinical and echocardiographic changes at 6 months follow-up in patients with paired measurements.
There were significant improvements in NYHA functional class (Panel A), 6-minute walking distance (Panel B) and quality-of-life score (Panel C) at 6 months follow-up. Additionally, a significant reduction in LVESD was observed (Panel D), but no significant reduction in LVESV (Panel E). Nonetheless, a significant reduction in MPI was observed (Panel F), indicating an improvement in global LV systolic and diastolic function.
6 MWT = 6-minute walk test; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MPI = myocardial performance index; NYHA = New York Heart Association; QoL = quality of life.

Echocardiographic changes at 6 months follow-up

In the patients with paired echocardiographic measurements, there was a significant decrease in LVESD (from 59±9 mm to 55±12 mm, p = 0.002, Figure 3, Panel D) and in LVEDD (from 67±9 mm to 63±11 mm, p = 0.007) at 6 months follow-up. No significant changes in LVESV (from 182±76 ml to 173±81 ml, p = 0.13, Figure 3, Panel E) or LVEDV (from 252±90 ml to 244±92 ml, p = 0.42) were observed at 6 months follow-up. There was a slight, but non-significant increase in LVEF (from 29±7% to 31±11%, p = 0.14). Finally, the MPI improved significantly at 6 months follow-up (from 0.78±0.25 to 0.59±0.30, p<0.001, Figure 3, Panel F).

DISCUSSION

The main findings in the current study are that in heart failure patients with narrow QRS complexes and echocardiographic evidence of mechanical dyssynchrony, 6 months of CRT leads to clinical improvement and significant reduction in LV diameter (LVEDD, LVESD), as well as an improvement in MPI.

Cardiac resynchronization and the use of mechanical dyssynchrony

Presently, cardiac resynchronization therapy is considered a class I indication in heart failure patients in NYHA functional class III or IV, with a depressed LVEF (≤35%) and a QRS duration >120 ms.[1] Nonetheless, approximately 30% of patients do not demonstrate clinical improvement after CRT. In an effort to optimize patient selection and outcome after CRT, many studies have used echocardiographic measures of mechanical dyssynchrony to better identify potential responders to CRT.[18, 19, 21, 23, 27] These studies were performed under the assumption that correction of mechanical dyssynchrony is the key mechanism in improving cardiac function and clinical outcome in heart failure patients treated with CRT. Accordingly, numerous echocardiographic markers of baseline mechanical dyssynchrony have been reported to identify patients with a favorable response to CRT.[18, 19, 21, 23, 27] PROSPECT was the first large multicenter clinical trial to evaluate these echocardiographic measures to predict response to CRT.[14]

More recently, improvements in the success of CRT have been related to positioning the LV pacing lead at the site of latest mechanical activation, as assessed with echocardiography.[28, 29] Ansalone et al investigated 31 patients with nonischemic cardiomyopathy and indicated that patients with the LV lead positioned in the region of latest mechanical activation (identified with TDI) had the most benefit from CRT.[28]

Another study by Ypenburg et al assessed LV dyssynchrony and the site of latest mechanical activation with novel speckle-tracking two-dimensional radial strain in a large cohort of 257 ischemic and nonischemic heart failure patients undergoing CRT.[29] The LV lead position was determined from the chest X-ray obtained after CRT implantation. At 6 months follow-up, LVESV decreased from 189±83 ml to 134±71 ml ($p<0.001$) in patients with the LV lead positioned at the site of latest mechanical activation, whereas in the group with the LV lead placed outside the area of latest mechanical activation, no significant changes in LVESV were observed (172±61 ml to 162±63 ml, p = NS). More importantly, the 2-year mortality rate in patients with a concordance between the LV lead position and the site of latest mechanical activation was 15% (23 patients) as compared with 21% (19 patients) in patients with a discordance between the LV lead position and the site of latest mechanical activation ($p<0.05$).

The abovementioned results suggest an important interplay between the LV lead position and the site of latest mechanical activation, resulting in both higher response rate (LV reverse remodeling) and superior long-term survival. However, no studies on the relation between the LV lead position and the site of latest mechanical activation in patients with a narrow QRS complex have been performed to date. Therefore it seems premature to extrapolate these favorable results to a "narrow" QRS population.

Mechanical dyssynchrony and CRT in "narrow" QRS patients

In the past decade, several studies have observed mechanical dyssynchrony in heart failure patients with a depressed LVEF and narrow QRS complex (<130 ms).[7-9] The hypothesis that CRT might result in clinical improvement in heart failure patients with narrow QRS has recently been explored by a number of investigators. Turner et al reported acute hemodynamic improvement in heart failure patients with a normal QRS duration (≤120 ms) when treated with LV pacing.[30] Temporary pacing leads were placed in the right atrium and at the LV free wall in 20 patients with a depressed LVEF (mean 31%, range 15% - 40%). Left ventricular pacing was applied with the longest atrioventricular delay that ensured ventricular capture. The authors reported an acute increase in cardiac output, predominantly in patients with pulmonary wedge pressure >15 mmHg at baseline.

Achilli and co-workers were the first to investigate the longer-term effects of CRT in heart failure patients with a narrow QRS complex and evidence of mechanical dyssynchrony.[11] The authors studied clinical and functional changes after CRT in 14 "narrow" QRS (≤120 ms) patients and compared these changes with 38 "wide" QRS patients. At 6 months follow-up, patients in the narrow QRS group did not only show improvement in NYHA functional class (from 3.3±0.5 to 1.7±0.6, $p<0.001$) and 6-minute walking distance (from 276±89 m to 370±70 m, $p<0.001$), but also demonstrated a marked reduction in LV diameters (LVEDD from 72±9 mm to 66±9 mm and LVESD from 61±8 mm to 56±8 mm, $p<0.05$ for both). More importantly,

there were no differences in changes from baseline to follow-up between the narrow and wide QRS groups, suggesting that patients with a narrow QRS complex had similar benefit from CRT as compared to patients with a wide QRS complex.

Bleeker et al evaluated the effects of CRT in 33 prospectively selected patients with a narrow QRS complex who demonstrated significant LV dyssynchrony (Ts-[lateral-septal] ≥65 ms).[10] At 6 months follow-up, patients improved in NYHA class (from 3.1±0.3 to 2.0±0.6, p<0.001) and showed a significant decrease in LV volumes (LVESV from 189±60 ml to 144±58 ml and LVEDV from 238±72 ml to 203±66 ml, p<0.001 for both). Other studies focusing on the potential favorable effects of CRT in patients with a narrow QRS complex and echocardiographic evidence of mechanical dyssynchrony have supported these findings.[9, 12]

Cardiac resynchronization therapy in narrow QRS – the RethinQ study

Based on the encouraging outcomes of these observational studies, a randomized, multicenter trial was conducted to determine the effect of CRT in heart failure patients with a narrow QRS complex. In the Resynchronization therapy in narrow QRS (RethinQ) study, 172 patients with a narrow QRS complex were randomized in a 1:1 fashion to a CRT ON group and a control group (CRT OFF).[13] All patients had documented echocardiographic evidence of mechanical dyssynchrony, defined as either SPWMD ≥130 ms or septal to LV free wall (lateral or posterior) delay ≥65 ms. The study failed to demonstrate a significant difference in the primary end-point (increase in peak oxygen consumption ≥1.0 ml per kilogram of body weight per minute during exercise testing at 6 months) between the CRT and the control groups. Nonetheless, there was a significant difference in change in NHYA class (54% improved in the CRT group, as compared to 29% in the control group, p = 0.006). This discrepancy between peak oxygen consumption and quality of life has been described previously. In an early study by Wilson et al, over 50% of potential heart transplant candidates with an LVEF <35% and a reduced peak oxygen consumption (mean 13.3±2.7 ml/min per kg) exhibited only mild or moderate hemodynamic dysfunction during exercise testing.[31] Another study by Mancini et al was able to identify peak oxygen consumption as a predictor of mortality in 114 ambulatory heart failure patients screened for cardiac transplantation.[32] However, patients were either granted or denied transplantation based on baseline peak oxygen consumption results. Since peak oxygen consumption influenced cardiac transplantation (and thereby survival), these results cannot be used to validate peak oxygen consumption as an independent predictor of mortality in heart failure. In addition, other studies have identified peak oxygen consumption as being unable to predict survival in heart failure patients.[33, 34] Consequently, (changes in) peak oxygen consumption may not be the preferred method to assess response to CRT. Conversely, 6-minute walking distance has been demonstrated to show a good relation with both heart failure symptoms and outcome after CRT.[35] Finally, Castel et al recently

demonstrated that 6-minute walking distance is an independent predictor of mortality in patients undergoing CRT.[36] In the current study, 6-minute walking distance improved significantly, indicating benefit from CRT.

At this point, relative merits of CRT with regard to long-term clinical outcomes (worsening heart failure, survival) in narrow QRS patients remain unclear. The currently ongoing trial, EchoCRT (ClinicalTrials.gov identifier: NCT00683696) will further address this issue since it will include over 1200 heart failure patients with a narrow QRS complex and randomize them to a CRT or control group.[37] Main end-points in this trial will be the reduction in all-cause mortality or first hospitalization for worsening heart failure during a follow-up of at least 24 months.

Changes in LV diameters vs. changes in LV volumes

In the current study, while end-diastolic and end-systolic LV diameters appear to decrease with CRT, there was no detectable change in LV volumes. If this discrepancy is the result of variability of measurement in a small sample size, then no firm conclusions can be drawn as to the real effect of CRT in this population. However, given that both end-diastolic and end-systolic diameters are smaller at 6 months, and that diameter measurements have higher reproducibility than volume measurements, it is less likely that the findings are purely due to chance. Conversely, the higher variability for measurements of LV volumes may explain the lack of significant reduction in LVESV at 6 months follow-up. Off note, there was a small decrease in LVESV, but this did not reach statistical significance. Possibly, with only 36 patients with paired LVESV measurements, the study was not powered to detect this small decrease as significant. Nonetheless, if this discrepancy is due to a true physiologic effect of CRT, then the differential effect on the basal diameters and volume *must be* due to a more spherical LV shape at 6 months, which would be contrary to previous reports.[20, 38] One possibility for this discrepancy is that in this population, changes in LV diameter may occur before changes in volume are detected. The much larger prospective study, EchoCRT, should shed more light on this issue.

Limitations

Main limitations of this study include its small sample size and uncontrolled design. As such, this study should be considered a pilot, hypothesis generating study, conducted in a multicenter setting. In addition, no long-term outcome data are available. More remodeling may take longer and can occur after the 6 month follow-up. Also, no data are available with regard to morbidity and mortality.

REFERENCES

1. Strickberger SA, Conti J, Daoud EG et al. Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. *Circulation* 2005;111:2146-2150.
2. Abraham WT, Fisher WG, Smith AL et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.
3. Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.
4. Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-1549.
5. Wang NC, Maggioni AP, Konstam MA et al. Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction. *JAMA* 2008; 299:2656-2666.
6. Shenkman HJ, Pampati V, Khandelwal AK et al. Congestive heart failure and QRS duration: establishing prognosis study. *Chest* 2002;122:528-534.
7. Bleeker GB, Schalij MJ, Molhoek SG et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. *J Cardiovasc Electrophysiol* 2004;15:544-549.
8. Bleeker GB, Schalij MJ, Molhoek SG et al. Frequency of left ventricular dyssynchrony in patients with heart failure and a narrow QRS complex. *Am J Cardiol* 2005;95:140-142.
9. Yu CM, Chan YS, Zhang Q et al. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. *J Am Coll Cardiol* 2006;48:2251-2257.
10. Bleeker GB, Holman ER, Steendijk P et al. Cardiac resynchronization therapy in patients with a narrow QRS complex. *J Am Coll Cardiol* 2006;48:2243-2250.
11. Achilli A, Sassara M, Ficili S et al. Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and "narrow" QRS. *J Am Coll Cardiol* 2003;42:2117-2124.
12. Cazeau SJ, Daubert JC, Tavazzi L, Frohlig G, Paul V. Responders to cardiac resynchronization therapy with narrow or intermediate QRS complexes identified by simple echocardiographic indices of dyssynchrony: the DESIRE study. *Eur J Heart Fail* 2008;10:273-280.
13. Beshai JF, Grimm RA, Nagueh SF et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;357:2461-2471.
14. Chung ES, Leon AR, Tavazzi L et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;117:2608-2616.
15. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-367.
16. Bonow RO, Carabello BA, Kanu C 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. *Circulation* 2006;114:e84-e231.

17. Tei C, Dujardin KS, Hodge DO, Kyle RA, Tajik AJ, Seward JB. Doppler index combining systolic and diastolic myocardial performance: clinical value in cardiac amyloidosis. *J Am Coll Cardiol* 1996;28: 658-664.
18. Cazeau S, Bordachar P, Jauvert G et al. Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: a prospective study. *Pacing Clin Electrophysiol* 2003;26: 137-143.
19. Pitzalis MV, Iacoviello M, Romito R et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol* 2002;40:1615-1622.
20. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. *Am J Cardiol* 2003;91:684-688.
21. Yu CM, Fung JW, Zhang Q et al. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. *Circulation* 2004;110:66-73.
22. 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;92:1238-1240.
23. Sogaard P, Egeblad H, Kim WY et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol* 2002;40:723-730.
24. Sogaard P, Egeblad H, Pedersen AK et al. Sequential vs. simultaneous biventricular resynchronization for severe heart failure: evaluation by tissue Doppler imaging. *Circulation* 2002;106:2078-2084.
25. Ritter P, Daubert C, Mabo P, Descaves C, Gouffault J. Haemodynamic benefit of a rate-adapted A-V delay in dual chamber pacing. *Eur Heart J* 1989;10:637-646.
26. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;7:176-182.
27. Bax JJ, Bleeker GB, Marwick TH et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;44:1834-1840.
28. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. *J Am Coll Cardiol* 2002;39:489-499.
29. Ypenburg C, van Bommel RJ, Delgado V et al. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. *J Am Coll Cardiol* 2008; 52:1402-1409.
30. Turner MS, Bleasdale RA, Mumford CE, Frenneaux MP, Morris-Thurgood JA. Left ventricular pacing improves haemodynamic variables in patients with heart failure with a normal QRS duration. *Heart* 2004;90:502-505.
31. Wilson JR, Rayos G, Yeoh TK, Gothard P. Dissociation between peak exercise oxygen consumption and hemodynamic dysfunction in potential heart transplant candidates. *J Am Coll Cardiol* 1995; 26:429-435.
32. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;83:778-786.
33. Shakar SF, Lowes BD, Lindenfeld J et al. Peak oxygen consumption and outcome in heart failure patients chronically treated with beta-blockers. *J Card Fail* 2004;10:15-20.

34. Rostagno C, Olivo G, Comeglio M et al. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *Eur J Heart Fail* 2003;5:247-252.
35. Olsson LG, Swedberg K, Clark AL, Witte KK, Cleland JG. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. *Eur Heart J* 2005;26:778-793.
36. Castel MA, Mendez F, Tamborero D et al. Six-minute walking test predicts long-term cardiac death in patients who received cardiac resynchronization therapy. *Europace* 2009;11:338-342.
37. Holzmeister J, Hurlimann D, Steffel J, Ruschitzka F. Cardiac resynchronization therapy in patients with a narrow QRS. *Curr Heart Fail Rep* 2009;6:49-56.
38. Zhang Q, Fung JW, Auricchio A et al. Differential change in left ventricular mass and regional wall thickness after cardiac resynchronization therapy for heart failure. *Eur Heart J* 2006;27:1423-1430.