Short-Term Hemodynamic Effects of Cardiac Resynchronization Therapy in Patients With Heart Failure, a Narrow QRS Duration, and No Dyssynchrony

Lynne K. Williams, MRCP; Susan Ellery, MRCP; Kiran Patel, MRCP; Francisco Leyva, FRCP; Robert A. Bleasdale, MRCP; Thanh T. Phan, MRCP; Berthold Stegemann, PhD; Vince Paul, MB, BCh; Paul Steendijk, PhD; Michael Frenneaux, FRCP

Background — Cardiac resynchronization therapy produces both short-term hemodynamic and long-term symptomatic/mortality benefits in symptomatic heart failure patients with a QRS duration >120 ms. This is conventionally believed to be due principally to relief of dyssynchrony, although we recently showed that relief of external constraint to left ventricular filling may also play a role. In this study, we evaluated the short-term hemodynamic effects in symptomatic patients with a QRS duration <120 ms and no evidence of dyssynchrony on conventional criteria and assessed the effects on contractility and external constraint.

Methods and Results — Thirty heart failure patients (New York Heart Association class III/IV) with a left ventricular ejection fraction ≤35% who were in sinus rhythm underwent pressure-volume studies at the time of pacemaker implantation. External constraint, left ventricular stroke work, dP/dtmax, and the slope of the preload recruitable stroke work relation were measured from the end-diastolic pressure-volume relation before and during delivery of biventricular and left ventricular pacing. The following changes were observed during delivery of cardiac resynchronization therapy: Cardiac output increased by 25±5% (P<0.05), absolute left ventricular stroke work increased by 26±5% (P<0.05), the slope of the preload recruitable stroke work relation increased by 51±15% (P<0.05), and dP/dtmax increased by 9±2% (P<0.05). External constraint was present in 15 patients and was completely abolished by both biventricular and left ventricular pacing (P<0.05).

Conclusion — Cardiac resynchronization therapy results in an improvement in short-term hemodynamic variables in patients with a QRS <120 ms related to both contractile improvement and relief of external constraint. These findings provide a potential physiological basis for cardiac resynchronization therapy in this patient population. (Circulation. 2009;120:1687-1694.)

Key Words: cardiac output • heart failure • hemodynamics • pacing

The effects of cardiac resynchronization therapy (CRT) in patients with heart failure and a QRS duration ≥120 ms are well established.1,2 In the Cardiac Resynchronization Therapy Heart Failure (CARE-HF) study, CRT was associated with a 40% reduction in all-cause mortality.2 This and other studies have also shown that CRT leads to an improvement in symptoms and a reduction in hospitalization. The predominant mechanism of benefit has been considered to be improvement in both interventricular and intraventricular (left ventricular [LV]) dyssynchrony. However, additional mechanisms independent of resynchronization contribute to the benefit derived from CRT. We previously showed that LV pacing (LVP) produces a short-term hemodynamic benefit (reduced pulmonary capillary wedge pressure, increased stroke volume) in patients with heart failure and a QRS <120 ms,3 although these patients had not undergone any prior assessment for the presence or absence of dyssynchrony. In a previous study, we also demonstrated4 that LVP resulted in relief of external constraint to LV filling by the right ventricle (RV) and pericardium (external constraint), providing an additional potential mechanism of benefit of LVP, although the impact of biventricular pacing (BIVP) on external constraint was not assessed. Even patients with narrow QRS complexes who do not have dyssynchrony might be expected to benefit from LVP and potentially BIVP by relief of external constraint if present.

Editorial see p 1651
Clinical Perspective on p 1694

In this study, we assessed the short-term hemodynamic effects of both BIVP and LVP in symptomatic heart failure patients with a QRS duration <120 ms who did not meet the
conventional criteria for dyssynchrony. Recent data suggest that these conventional criteria may underestimate dyssynchrony. Accordingly, we evaluated the effects of pacing on both contractility and external constraint.

Methods

Patients
Thirty patients (age, 58±17 years; range, 21 to 79 years) with heart failure resulting from ischemic (n=17) or nonischemic (n=13) cardiomyopathy were recruited into the study. All patients had an LV ejection fraction ≥55% as determined by echocardiography. Patients were in New York Heart Association class III (93%) or IV (7%) despite optimal tolerated medical therapy that included diuretics and angiotensin-converting enzyme inhibitors. In addition, all patients had a QRS ≤120 ms and no interventricular or intraventricular dyssynchrony. The former was defined as a Qp-Qa time delay >40 ms; the latter was defined as a septal-posterior wall motion delay >130 ms or an intraventricular septal-lateral wall delay >40 ms. Patients who met ≥2 of the above criteria were excluded. Baseline patient characteristics are shown in the Table.

Study Protocol
The investigations were performed with the approval of the local Research Ethics Committee. Written informed consent was obtained from all patients.

Short-Term Hemodynamic Studies
Short-term hemodynamic studies were performed in the cardiac catheterization laboratory at the time of CRT device implantation with patients in the nonsedated and supine state. LV catheterization was performed by a standard over-the-wire technique. The dual-field conductance catheter (CA-71103-PL catheter, CD Leycom, Zoetermeer, the Netherlands) was then positioned in the apex of the ventricle. The conductance catheter method provides a continuous online beat-by-beat measurement of LV pressure and volume. The conductance catheter calibration has been described elsewhere. Applied in a random order, each with a run-in (stabilization) period of 5 minutes.

The following parameters were derived from the pressure-volume loops at baseline (off), during inferior vena cava occlusion, and in both BIVP and LVP pacing modes: dP/dtmax and dP/dtmin, absolute LV stroke work, and end-diastolic volume (LVEDV). A plot was constructed of beat-by-beat LVEDV versus LV stroke work before and during inferior vena cava occlusion in all pacing modes. The slope of this relation, known as the preload recruitable stroke work relation, is a load-independent measure of LV contractile function (a much more linear relation than the commonly used end-systolic elastance measures, which appear to be much more load dependent). The end-systolic pressure-volume relation was determined through the use of the single-beat method (Ees) adopted from Takeuchi et al. The end-diastolic pressure-volume relation was determined through the use of the single-beat method to calculate the Ees (derived from a linear fit of the filling-phase trajectory of the pressure-volume loop) and the end-diastolic stiffness constant (Kves; derived by fitting an exponential curve to the diastolic trajectory of the pressure-volume loop) as previously described. We quantified external constraint to LV filling using a modification of the static equilibrium technique that we described previously. LV pressure and volume were recorded simultaneously, and the 40-mm balloon was then inflated in the low right atrium and withdrawn to the inferior vena cava. The normal response to progressive reduction in LV end-diastolic pressure (LVEDP) is a progressive reduction in LVEDV, stroke volume, and stroke work. In heart failure patients with higher LVEDPs, a very different pattern is observed. Initially, as LVEDP falls, LVEDV increases, and then further reductions in LVEDP are associated with a progressive reduction in LVEDV (see Figure 1). The magnitude of external constraint can be calculated as shown in Figure 1.

Statistical Analysis
All data are expressed as mean±SD. A 1-way ANOVA was used if the data were normally distributed on the basis of a Kolmogorov-Smirnov test. For data that were not normally distributed, a Kruskal-Wallis test was used. Statistical significance was assumed at P<0.05.

Results

Indices of LV Contractility and Systolic Function
Cardiac output increased from 2.6±1.2 to 3.2±1.4 L/min in response to both BIVP and LVP (P=0.04) (Figure 2). Absolute LV stroke work increased from 2504 mL·mm Hg (median, 1973 mL·mm Hg) to 3054 mL·mm Hg (median, 2967 mL·mm Hg) in response to BIVP and to 3145 mL·mm Hg (median, 2696 mL·mm Hg) in response to LVP (P=0.03) (Figure 3A). The slope of the recruitable stroke work relation increased from 45.8 (median, 36.4) to 61.2 (median, 48.2) in response to BIVP and to 59.6 (median, 47.0) in response to LVP (P=0.04) (Figure 3B). Data from a representative patient are demonstrated in Figure 3D. dP/dtmax increased from 956 mm Hg/s (median, 969 mm Hg/s) to 1035 mm Hg/s (median, 1031 mm Hg/s) with BIVP and to 1039 mm Hg/s (median, 1058 mm Hg/s) with LVP (P=0.03) (Figure 3C). The slope of the end-diastolic pressure-volume relation (Ees) increased from 1.46 (median, 0.99) to 1.71 (median, 1.34) in

<table>
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<td>Yu dyssynchrony index</td>
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NYHA indicates New York Heart Association; LVEF, LV ejection fraction; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blocker. Values are mean±SD when appropriate.
Figure 1. A. Plot from a patient with no evidence of external constraint. The normal response to RV volume unloading and a progressive reduction in LVEDP is a progressive reduction in LVEDV. B. Plot from a patient with evidence of external constraint with a high LVEDP. Initially, as LVEDP falls, LVEDV increases, and further reductions in LVEDP are associated with a progressive reduction in LVEDV. The magnitude of external constraint can be calculated as the difference in LVEDP for a given LVEDV. C, Diagrammatic representation of A and B. In healthy control subjects, both RV volume and LV volume decrease with RV volume unloading (top). In heart failure patients with evidence of external constraint/diastolic ventricular interaction, LV volume increases as RV volume falls and external constraint is diminished. CHF indicates congestive heart failure; IVCO, inferior vena caval occlusion.
response to BIVP and LVP (median, 1.54) (P/H11005 0.04) with LVP (Figure 4.). There were no significant differences between BIVP and LVP in any of these variables for the patient group as a whole.

Indices of LV Relaxation and Diastolic Function
Both dP/dtmin (P/H11005 0.92) and dP/dtmax (P/H11005 0.73) remained unchanged in response to BIVP and LVP (see Figure 5A and 5B, respectively). There was no significant change in either EED or KVED in response to either BIVP or LVP (see Figure 6A and 6B).

Indices of External Constraint (Diastolic Ventricular Interaction)
External constraint was present in 15 of the 30 patients and was reduced from 7.5±3.1 to 1.8±3.3 mm Hg with BIVP and to 1.4±2.3 mm Hg with LVP (P<0.05) (Figure 7A). Data from a representative patient are shown in Figure 7B.

Discussion
The important findings of this study were significant short-term increases in LV stroke work, dP/dtmax, and cardiac output in these symptomatic patients with a narrow QRS duration and no conventional measures of mechanical dysynchrony in response to both BIVP and LVP. Hemodynamic studies have previously demonstrated the short-term effects of CRT in patients with heart failure and a broad QRS duration. In this study, we have shown that CRT results in comparable hemodynamic improvement in patients with heart failure and a QRS ≤120 ms, amounting to as much as a 25% improvement in cardiac output and a 25% to 30% increase in LV stroke work. Data from studies by Kass et al\textsuperscript{15} and Auricchio et al\textsuperscript{13} demonstrated a short-term 15% increase in LV dp/dtmax in response to BIVP compared with the 9% increase we have demonstrated in the present study. Steendijk et al\textsuperscript{17} performed pressure-volume loop studies at 6 months in patients who had undergone BIVP and demonstrated a 34% increase in LV stroke work and an 18% increase in LV dp/dtmax in response to pacing. Prior studies have concentrated on measuring the effect of pacing on LV dp/dtmax, but in the present study, we have assessed the effect of pacing on several hemodynamic measures, including the effect on the slope of the preload recruitable stroke work relation, a far more reliable measure of LV contractile function because it is measured over a range of volumes during inferior vena caval occlusion and is hence less load dependent than LV dp/dtmax.

Given the normal QRS duration and absence of conventional measures of dyssynchrony, these findings may at first glance be surprising. Recent evidence suggests that conventional measures of dyssynchrony have high interobserver variability\textsuperscript{5} and may underestimate the magnitude of dyssynchrony because they ignore radial dyssynchrony. Current dyssynchrony analysis is based on echocardiographic Doppler methods that are derived largely from longitudinal motion data.\textsuperscript{18} This choice of orientation is based mainly on practical grounds given the available echocardiographic windows for transducer positioning. However, because of epicardial and subendocardial fiber orientation, cardiac contraction is principally radial. Helm and colleagues\textsuperscript{19} have demonstrated in a failing heart that dyssynchrony assessed by longitudinal motion is much less sensitive, suggesting that longitudinal motion data may not provide the most accurate and comprehensive means of assessing LV dyssynchrony. Therefore, a possible explanation for the benefit observed is an improvement in “occult” dyssynchrony. Consistent with this, there was a substantial improvement in LV preload recruitable stroke work, a load-independent, robust measure of contractile function.

Furthermore, we recently demonstrated that LVP ameliorated external constraint to LV filling by the RV through the interventricular septum (diastolic ventricular interaction) and by the pericardium (pericardial constraint) (the combined impact of which we call external constraint).\textsuperscript{4} Our present data show that in this population both BIVP and LVP significantly reduce external constraint. In a previous study in a more conventional patient group, we studied LVP exclusively and reported a reduction in external constraint. Relief of external constraint causes a short-term increase in LV diastolic volume despite a similar LVEDP, thereby increasing stroke work by the Starling mechanism. Static equilibrium analysis has been used to quantify the external constraint to LV filling in animal models.\textsuperscript{20,21} With this technique, external constraint is quantified as the difference in LVEDP before and after removal of the pericardium while a constant
LVEDV is maintained. This technique can be used only when the chest is open. However, in the present study, we applied a modified approach by continuously measuring LV pressure and volume during occlusion of the inferior vena cava to reduce RV volume and pressure for the short term. This short-term reduction in RV volume removes external constraint to LV filling from the RV and pericardium. In the present study, we confirm that at least part of the short-term hemodynamic benefit of CRT in this population is due to a reduction in external constraint to LV filling. The mechanism for the reduction in external constraint is probably related to the induction of a phase shift in the timing of LV filling relative to RV filling (more pronounced with LVP compared with BIVP), resulting in the timing of events being moved forward in the LV. This effectively results in LV filling occurring at a time when RV pressure and volume are lower; hence, RV diastolic pressure and pericardial pressure are likely to be lower at any given LV diastolic volume.

We also demonstrate an increase in the slope of the preload recruitable stroke work relation in these patients with both BIVP and LVP. This indicates an increase in LV contractility even though these patients did not meet current criteria for dyssynchrony. Although increases in LV compliance result in a move upward along the same recruitable stroke work relation, thereby increasing stroke work, they do not alter the slope of this relation; therefore, an increase in the slope reflects an increase in contractility.

Whether these short-term hemodynamic effects will translate into long-term symptomatic benefit and evidence of reverse remodeling has yet to be determined. Previous small studies in patients with a narrow QRS duration have focused on clinical and echocardiographic end points. Although they have shown a benefit from CRT based on clinical and echocardiographic parameters, these studies included QRS durations of <150 ms as narrow and were limited to patients with evidence of dyssynchrony on echocardiography. Achilli et al reported on the efficacy

Figure 3. Effect of BIVP and LVP on absolute LV stroke work (A; LVSW in mL · mm Hg; *P* = 0.03), the slope of the preload recruitable stroke work relation (B; PRSW; *P* = 0.04), and dP/dt max (C; in mm Hg/s; *P* = 0.03) vs values (off). D, Effect of BIVP and LVP on the PRSW in a representative patient. Error bars indicate ±1 SD.

Figure 4. The effect of BIVP and LVP on Ees vs baseline values (off) (*P* = 0.04). Error bars indicate ±1 SD.
of CRT in such a group of patients, with 14 of the 56 patients with a QRS duration of <120 ms. These findings were supported by Gasparini and colleagues, who reported an improvement in clinical and echocardiographic parameters in patients with a narrow QRS (13 of whom had a QRS <120 ms). The studies by Bleeker et al and Yu et al included 33 and 51 patients, respectively, with a QRS <120 ms. These studies showed an improvement in clinical parameters and evidence of LV reverse remodeling, but the study by Yu et al also showed an improvement in exercise capacity, as evidenced by an improvement in maximal metabolic equivalent achieved in treadmill testing.

However, a recent, much larger study (Resynchronization Therapy in Patients with Narrow QRS [RETHINQ]) in an implantable cardioverter-defibrillator population that met conventional dyssynchrony criteria for CRT but had QRS duration <130 milliseconds did not report a significant improvement in exercise capacity or evidence of reverse remodeling. The patients recruited into the present study were entered in a randomized controlled trial of CRT with VO₂max as the primary end point and echocardiographic measures as secondary end points. This study will be completed and reported shortly. The patient population in RETHINQ is indistinguishable from our patient group with regard to demographics, origin of heart failure, baseline LV function, and exercise capacity, and it will be interesting to see whether the short-term hemodynamic benefits that we have demonstrated in this study will translate into a long-term improvement in symptoms, quality of life, and LV function.
Study Limitations
Patients were assessed for the presence of intraventricular and intraventricular dyssynchrony with tissue Doppler imaging. Recent evidence suggests that conventional measures of dyssynchrony have high interobserver variability and may underestimate the magnitude of dyssynchrony because they ignore radial dyssynchrony. However, the limitation of this form of dyssynchrony analysis is that it is based on echocardiographic Doppler methods that are derived largely from longitudinal motion data; hence, the presence of radial dyssynchrony was not specifically excluded in this group of patients.

The calibration method of the conductance catheter was not based on assessment of absolute volume. However, this would not affect our results, which depend entirely on relative changes within each patient in response to the pacing mode.

The catheter was calibrated during steady state at the beginning of the study. Vena caval occlusion, which results in a fall in RV volume, could result in a decrease in parallel conductance, which may result in a modest underestimation of LV volume. To estimate the effect of inferior vena caval occlusion, we assessed parallel conductance at baseline and repeated the measurement during caval occlusion in 3 patients. Results show that the decrease in parallel conductance was <5% in each patient, which would translate into an apparent (ie, artificial) decrease of 10 mL in absolute volume at most. Because of the invasive nature of the study, only a small sample of patients were studied in the short term; at most. Because of the invasive nature of the study, only a small sample of patients were studied in the short term; hence, results may not predict the medium- and long-term effects of CRT on cardiac function.

Conclusions
In the present study, we demonstrate that CRT results in an improvement in short-term hemodynamic variables in heart failure patients with a narrow QRS duration that is comparable to the effects seen in heart failure patients with a broad QRS duration. Detailed invasive hemodynamic studies (including analysis of pressure-volume loop data) have previously been published, reporting both the short-term14,16 and long-term effects17 of CRT in patients with heart failure and a broad QRS duration. Bleasdale et al18 have reported the effects of LVP in narrow QRS patients with a pulmonary capillary wedge pressure >15 mm Hg, but to the best of our knowledge, this is the first study to assess the short-term hemodynamic effects of both BIVP and LVP in a group of patients with both a narrow QRS duration and no evidence of significant interventricular or intraventricular dyssynchrony at rest.

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Disclosures
Professor Frenneaux is a consultant for Medtronic Inc. The other authors report no conflicts.

References
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