Cardiac resynchronization therapy modulation of exercise left ventricular function and pulmonary O₂ uptake in heart failure

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PULMONARY O₂ UPTAKE (V˙O₂) kinetics at exercise onset are slower in patients with systolic heart failure (HF) compared with healthy individuals (27, 29, 47), and progressively worsening HF is associated with a concomitant slowing of V˙O₂ kinetics (8). Additionally, peak V˙O₂ may be reduced by 30–50% (13, 22, 55). The slowing of V˙O₂ kinetics and the reduction in peak V˙O₂ in patients with HF may be secondary to impaired metabolic processes within the exercising muscle (54) or by a reduction in the availability of O₂ for the exercising muscle (16, 23) or a combination of both. Given that HF is characterized in part by a reduced left ventricular (LV) end-systolic volume (ESV) and end-diastolic volume (EDV) reserve, impaired exercise cardiac function may explain an important mediating factor accounting for the delayed V˙O₂ kinetic response to exercise (27, 29, 35) and reduction in peak V˙O₂ (16, 22, 27, 55, 56), and this is supported by major trials having demonstrated that cardiac resynchronization therapy (CRT) increases peak V˙O₂ (1, 6, 15, 33, 62). However, whether improving exercise cardiac function with CRT can reverse the impaired V˙O₂ kinetics in patients with HF has not been studied, and the CRT-mediated changes in LV function at peak exercise are not known. Therefore, the degree to which a centrally mediated limitation (i.e., poor LV function) impacts exercise in advanced HF, and its potential “reversibility,” has thus far been unanswered.

CRT with a biventricular pacemaker improves resting cardiac function in patients with HF and interventricular conduction delay. These changes include a reduction in both LV EDV and ESV with a net benefit of increasing LV ejection fraction (EF) and stroke volume (SV) (1, 19, 33, 51, 53). The CRT-mediated increase in V˙O₂ at peak exercise may be due to an improvement in exercise systolic performance (52). The potential for CRT to improve exercise systolic function during the transition to moderate-intensity exercise (i.e., exercise below the ventilatory threshold) may further confer a speeding in the rate of muscle O₂ uptake adaptation in patients with HF by increasing O₂ transport throughout the transition from rest to steady-state exercise.

The purpose of this study was to investigate the effects of 6 mo of CRT on V˙O₂ kinetics, exercise LV function, and peak V˙O₂ in patients with HF. We tested the hypothesis that 6 mo of biventricular pacing with a CRT device would speed phase II V˙O₂ kinetics in patients with HF and that this would be due to an increase in exercise SV. A secondary hypothesis was that the increase in exercise SV would be attributable to a further reduction in LV ESV from rest to exercise and that resting and exercise heart rates (HRs) would be lower after CRT secondary to an increase in SV. For peak exercise, we hypothesized that CRT would increase reserve and peak cardiac output and that the increase in V˙O₂ at peak exercise would be related to an increase in cardiac output reserve.

METHODS

Subjects. Twenty-one subjects provided written and informed consent to participate in this investigation, which was approved by the University of Alberta Hospital Research Ethics Board. Subjects met our hospital criteria for a CRT biventricular pacemaker, which included a diagnosis of New York Heart Association functional class III or IV HF with persistent symptoms despite stable and optimal medical treatment for >3 mo. All patients were on maximally tolerated pharmacological therapy for HF and had been referred for CRT at the discretion of their cardiologist. The average time from diagnosis to first CRT implantation was 8.9 ± 3.9 yr. The average age was 72 ± 11 yr, and the average ejection fraction was 31 ± 5%.

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therapy, a LV EF ≤ 35%, and a QRS duration > 120 ms, consistent with interventricular conduction delay. Subjects further met our study criteria if they had a normal sinus rhythm and did not require atrial pacing, if their medications and HF symptoms had not changed in the previous 3 mo, if they reported being able to perform stationary cycle ergometry exercise, and had no change in medications while enrolled in our study. Subjects were excluded if they did not have a normal intrinsic sinus rhythm, the CRT device/lead wire implantation was not successful, or if HF symptoms/condition or comorbidities precluded exercise testing. HF-related medications, including β-blocker therapy, were not discontinued for the exercise tests.

**Peak exercise protocol.** Subjects underwent 2 days of testing. On the first day, a peak exercise test to volitional fatigue was completed on a customized semirecumbent (112° seat angle) electronically braked cycle ergometer (Corival, Lode, Groningen, The Netherlands). The test began at 15 W for 1 min followed by 10-W/min increments. Subjects were provided standardized encouragement and assessment at regular intervals by an investigator. Exercise was terminated when subjects indicated they could no longer continue or if subjects could no longer sustain a pedal rate of 50 revolutions/min. A 12-lead electrocardiogram (CASE 8000, GE Healthcare, Freiburg, Germany), manual brachial cuff blood pressure (BP), and pulse oximetry were monitored every 2 min. Breath-by-breath gas exchange and ventilation variables [tidal volume, breathing frequency, and minute ventilation (Ve)] were measured. Peak VO2 and corresponding gas exchange and ventilation parameters were measured as the highest 30-s values within the last 1 min of exercise.

Data from this test were also used to develop individualized work rates approximating 90% of the ventilatory threshold for subsequent square-wave moderate-intensity exercise testing. The ventilatory threshold was identified by one investigator as the point of change in the CO2 production (VCO2) and VO2 slope as described by Beaver et al. (7). A discrepancy in ventilatory threshold, if present, was examined by a second experienced physiologist not involved in the study, corroborated with a rise in Ve/VO2 and the end-tidal PO2 without an increase in Ve/VCO2 or a decrease in the end-tidal Pco2, and consensus was reached.

After a resting period after the peak exercise test, subjects were familiarized with the square-wave exercise protocol and specifically trained on obtaining and strictly maintaining a constant target pedal rate from quiet rest within one to two revolutions upon verbal command; this was easily achieved in all subjects.

**Square-wave exercise protocol.** Subjects completed four square-wave exercise tests 1 wk after the peak exercise test. The square-wave protocol was completed at the same time of day as the peak test. We separated each square-wave test by a 30-min rest period to ensure that subjects were fully rested and able to perform the four square-wave repetitions. The protocol entailed a 5-min resting baseline followed by an abrupt commencement of exercise to a predetermined work rate approximating the VO2 at 90% of the gas exchange ventilatory threshold. The duration of exercise was 5 min. A target pedal rate of 50 revolutions/min was obtained within 1–2 revolutions from rest. Subjects had visual feedback of their pedal rate on a display for the test duration. Because a low VO2 amplitude response negatively impacts the confidence estimate of the VO2 time constant (32), and because we expected relatively low moderate-intensity work rates from our study group, we elected to have subjects begin exercise from a resting baseline to further enhance our estimation of time-course changes in VO2 by increasing the amplitude response of the nonlinear adjustment in VO2 and subsequently increasing the number of data points for curve fitting.

**Pulmonary gas exchange: square-wave and peak exercise.** Breath-by-breath pulmonary gas exchange was measured using a commercial system (SensorMedics Vmax 229, VIASYS Healthcare Respiratory Technologies, Yorba Linda, CA). Before both the peak exercise and square-wave exercise protocols, the low-resistance, low-deadspace (90 ml), bidirectional mass flow sensor was calibrated with a 3.0-liter syringe across expected breathing frequencies. The paramagnetic O2 analyzer and nondispersive infrared CO2 analyzer were calibrated using a two-point calibration with known gas concentrations. The gas analyzers were also calibrated between each square-wave test, and a second mass flow sensor calibration was completed after two square-wave bouts.

**Contrast-enhanced echocardiography: square-wave and peak exercise.** Resting and exercise contrast-enhanced two-dimensional echocardiograms (Vivid-i or Vivid 7, GE Medical Systems, Milwaukee, WI) were performed during the square-wave tests when we assessed VO2. Two-dimensional echocardiograms were also obtained at peak exercise. All images were obtained with subjects sitting on the semirecumbent cycle ergometer at a 112° seat angle. Before subjects were tested, an intravenous line was established on the dorsum of the hand or antebrachium. Once an apical four-chamber viewing window was established, the sonographer’s arm was stabilized on an adjustable stand and the transducer was kept in place at rest and for the duration of exercise. Image acquisition was preceded by a slow bolus 0.2-ml intravenous injection of commercial contrast agent (Definity, Bristol-Myers Squibb, New York, NY), which was followed by a normal saline flush at a manual rate that optimized LV cavity opacification. Single-plane apical four-chamber cine images of five loops were then recorded to determine LV volumes (24). A single-plane view for determining LV volumes was used to ensure consistency in the viewing window between resting and exercise images. Exercise echocardiograms were obtained within the last 90 s of exercise for square-wave testing. Peak exercise echocardiograms were obtained within the approximate last 30 s of peak exercise. An investigator determined that a subject was nearing peak exercise termination based on their VCO2/VO2, self-rated perceived exertion on a 10-point scale, and querying fatigue level by having the subject answer standardized questions using predetermined hand signals. A cardiologist or sonographer with experience in exercise cardiac imaging performed the imaging protocol. HR was measured continuously by electrocardiogram.

**Pacemaker programming.** Pacemaker device programming was standardized and implemented at the time of device implant. All subjects received a combined CRT-implantable cardiodefibrillator device (ICD), and one subject received a CRT device without an ICD based on their clinical status. Device programming was designed to ensure atrial sensed ventricular pacing while maintaining ventricular capture and LV before right ventricular (RV) stimulation. The base rate, which is the lowest intrinsic sinus rate detected before the CRT device setting the pacing rate, was programmed at 50 beats/min. The atrioventricular delay was set at 100–120 ms and was fixed to not rate adapt with changes in sinus rate. The interventricular delay was set to stimulate the LV 20 ms before RV stimulation. To avoid unwanted ICD shocks on testing days, the defibrillation threshold was programmed 20 beats/min above the estimated exercise HR and the ventricular tachycardia detection mode was turned off for exercise testing. Settings were restored upon the completion of exercise testing.

**Curve fitting: VO2 and HR kinetics.** For each exercise repetition, breath-by-breath VO2 was filtered for aberrant breaths (32) and linearly interpolated to 1-s intervals, time aligned, and averaged to 10-s intervals. Data were then superimposed and ensemble averaged to yield a single response profile for each subject. Curve fit parameter estimates for VO2 responses during the on- transient were determined using a first-order mathematical model of the following form: 

\[Y(t) = Y_{in} + A \times [1 - e^{-\frac{t}{T_{DTRY}}}] \]

where \(Y_{in}\) is the VO2 at a given time \(t\), \(Y_{in}\) is the baseline (resting) value of VO2 over the last 60 s before exercise onset, \(A\) is the amplitude change in the VO2 response, \(\tau\) is the time constant or time for VO2 to reach 63% of \(A\), and TD is the time delay before the exponential onset of VO2. Steady-state VO2 was measured as the value over the last 60 s of exercise. HR data were also filtered for aberrant beats (32), linearly interpolated to 1-s intervals, time aligned, averaged to 10-s intervals, superimposed, and ensemble averaged to yield a single response profile for each subject. HR curve-fitting parameter estimates were determined in the same fashion as VO2.
Kinetic parameters for $\bar{V}O_2$ and HR were determined using nonlinear regression, and the iterative procedure of the computer program (Origin 7.5, OriginLab, Northampton, MA) used a Levenberg-Marquardt algorithm where the best fit was defined by minimization of the residual sum of squares. For $\bar{V}O_2$, the data-fitting window was extended from the phase II exponential onset to the end of exercise (300 s) to exclude the cardiodynamic phase increase in $\bar{V}O_2$ that is associated with preexercise venous blood return to the lungs and to characterize only the muscle metabolic changes associated with exercise onset. The phase II $\bar{V}O_2$ onset was determined by visual inspection of the model curve for fit, the residuals for clustering and systematic deviation from the x-axis, sudden changes in $\tau$, and demonstration of a local threshold in the reduced $\chi^2$-statistic (44). HR kinetics were determined from exercise onset to the end of exercise to characterize the overall exercise response. To highlight the accuracy of our parameter estimation, 95% confidence intervals for the estimation of phase II $\bar{V}O_2$ $\tau$ and the effective HR $\tau$ were calculated using the method described by Lamarra et al. (32).

Cardiovascular analyses: square-wave and peak exercise. For determining ventricular volumes, endocardial borders were manually traced with papillary muscles and trabeculations included in the ventricular cavity using commercial software (Xcelera, Philips Healthcare, Andover, MA). LV EDV was measured as the largest cavity area before the onset of the QRS complex, and LV ESV was measured as the smallest cavity area before mitral valve opening. Single-plane volumes were calculated using the disk summation method. LV EF was calculated as $[(\text{LV EDV} - \text{LV ESV})/\text{LV EDV}] \times 100$, SV was calculated as $(\text{LV EDV} - \text{LV ESV})$, and cardiac output as $\text{SV} \times \text{HR}$. Reserve values were calculated as steady-state exercise or peak exercise – rest. Reported values were the average over three to five cardiac cycles. Manual brachial cuff BP was obtained with the subject’s arm unencumbered during testing and the average over three to five cardiac cycles. Manual brachial cuff BP required no additional stabilization on the investigator’s or subject’s part beyond what is normally used during a resting assessment. BP was obtained with the subject’s arm unencumbered during testing and the average over three to five cardiac cycles.

Statistics. We performed normality testing with the Shapiro-Wilk test. Only the TD for HR was significant (failed normality testing), and therefore a Mann-Whitney rank sum test was used for analysis for this variable. Paired t-tests were used to determine statistical differences between all other pre-CRT and post-CRT variables. Pearson’s product-moment correlation analysis was used to compare the relationship between cardiac output reserve and peak $\bar{V}O_2$ (SPSS 11.0.1, Chicago, IL). All data are presented as means ± SD unless otherwise specified, and $P < 0.05$ was considered statistically significant.

RESULTS

Adverse events. Nine subjects did not complete the study. One subject completed baseline testing and declined followup testing because of their HF symptoms. One subject completed baseline testing, but LV transvenous lead placement was unsuccessful and an epicardial lead was not considered based on the subject’s clinical status. One subject had symptomatic hypotension upon arrival for the first testing day and the protocol was not conducted for safety; this subject declined to undergo further testing at a later date. One subject consented to study participation but died before baseline testing and pacemaker implantation. Baseline testing was completed on three subjects who later had signs and/or symptoms of decompen- sated HF upon arrival at our center for their followup testing day. Another subject had signs and/or symptoms of decompen- sated HF upon arrival at our center on the baseline testing day. These four subjects were immediately seen by a cardiologist in the testing laboratory, admitted to the hospital without performing the exercise protocol, and died in the hospital at a later date. One subject completed baseline testing and returned for followup testing, although they were unable to perform their prescribed 10-W square-wave exercise protocol because of their HF symptoms. One subject completed peak exercise testing, was implanted with a CRT-ICD device before baseline square-wave exercise testing based on clinical status and phys- ician recommendation, and was subsequently hospitalized after suffering cardiac arrest during pacemaker implant; this subject was successfully resuscitated and continued with the study without further pacemaker related or neurological complications. Therefore, 11 subjects completed $\bar{V}O_2$ kinetics testing and 12 subjects completed peak $\bar{V}O_2$ testing.

Subject characteristics. HF etiology was ischemic in seven subjects and nonischemic in five subjects. Subject medications are shown in Table 1, and medications (and their respective dosages) did not change over the intervention period. All tests began at the same time of day (within −0.5 h) for pre-CRT and post-CRT time points to account for potential effects of plasma concentration changes in medication. All subjects confirmed medication self-administration at their regular time on testing days and the day before testing. The CRT device in all subjects had a passive fixed right atrial lead placed in the atrial appendage, an RV active fixed lead placed in the apex, and a transvenous LV lead placed about the posterolateral wall ($n = 4$) or lateral wall ($n = 7$). One subject received a LV lateral wall epicardial lead via thoracotomy the same day after unsuccess- ful transvenous lead placement.

Square-wave exercise. The exercise intensity for square- wave testing was $21 \pm 8$ W (range: 10–30 W, power output at ventilatory threshold: $38 \pm 13$ W). Individualized pre-CRT exercise intensities were used for post-CRT testing. The pre- CRT steady-state $\bar{V}O_2$ was $91 \pm 7\%$ of the ventilatory thresh- old. No subjects exercised above the ventilatory threshold, and visual inspection of the gas exchange data confirmed the

<table>
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<td>Height, cm</td>
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<td>Mass, kg</td>
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<tr>
<td>Diuretic, n (%)</td>
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<tr>
<td>Digitalis, n (%)</td>
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<td>Antiarrhythmic, n (%)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Anticoagulant, n (%)</td>
<td>7 (58)</td>
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| Data are means ± SD unless otherwise specified; n, number of subjects ($n = 12$ subjects total). NYHA, New York Heart Association; LV, left ventricular; EF, ejection fraction; ACE, angiotensin-converting enzyme; ARB, ANG II receptor blocker. |
absence of a further slow component rise in \( \dot{V}_O_2 \) in all subjects. One subject completed only three post-CRT square-wave bouts because of fatigue.

\( \dot{V}_O_2 \) kinetics. CRT did not affect resting \( \dot{V}_O_2 \) \( [Y_{b0}] \), the phase II \( \dot{V}_O_2 \) TD, or \( A \) (all \( P > 0.05 \); Table 2). The steady-state \( \dot{V}_O_2 \) during square-wave moderate-intensity exercise did not change (pre-CRT: 0.72 ± 0.23 l/min and post-CRT: 0.71 ± 0.20, \( P > 0.05 \)). CRT decreased the phase II \( \dot{V}_O_2 \) \( \tau \) by 22% (\( P < 0.05 \); Table 2 and Fig. 1) and the overall \( \dot{V}_O_2 \) mean response time (TD + \( \tau \)) from 110 ± 23 s to 95 ± 18 s (\( P < 0.05 \)). Based on the \( \dot{V}_O_2 \) amplitude response, and a SD of breath-to-breath fluctuation in \( \dot{V}_O_2 \) of 0.021 l/min pre-CRT and 0.018 l/min post-CRT, the 95% confidence interval for the estimation of phase II \( \dot{V}_O_2 \) \( \tau \) was ±3.0 s pre-CRT and ±2.4 s post-CRT.

\( HR \) kinetics. CRT decreased resting HR \( [Y_{b1}] \) by 5 beats/min \( (P < 0.05; \) Table 2), CRT did not significantly alter the HR TD \( (P > 0.05; \) Table 2). CRT did decrease the amplitude change in HR (4 beats/min; Table 2) and the steady-state HR from 89 ± 20 to 80 ± 17 beats/min (both \( P < 0.05 \)). CRT significantly decreased HR \( \tau \) by 22% (\( P < 0.05; \) Table 2 and Fig. 2). Based on the HR amplitude responses shown in Table 2, and a SD of beat-to-beat fluctuation in HR of 1.1 beats/min pre-CRT and 1.1 beats/min post-CRT, the 95% confidence interval for the estimation of HR \( \tau \) was ±2.1 s pre-CRT and ±4.6 s post-CRT.

LV function at rest and during square-wave exercise. LV volumes during both rest and exercise for both pre-CRT and post-CRT time points were measured in 7 of 11 subjects. In these subjects, CRT decreased resting LV EDV by 8% and LV ESV by 14% and increased LV EF an absolute 5 percentage points (all \( P < 0.05 \); Fig. 3). Resting SV also increased 9 ml \( (P < 0.05; \) Fig. 3). The post-CRT steady-state exercise LV EDV and LV ESV were 9% and 20% lower, respectively, compared with pre-CRT steady-state exercise values \( (P < 0.05 \). CRT increased the exercise steady-state SV by 31% and the steady-state cardiac output 27% (all \( P < 0.05 \); Fig. 3). The change in moderate-intensity reserve (steady state − rest) for LV volumes and SV pre-CRT to post-CRT for individual subjects are shown in Fig. 4. LV ESV and SV reserve increased from pre-CRT to post-CRT \( (P < 0.05) \), whereas LV EDV did not change \( (P > 0.05) \).
Peak exercise \( \dot{V}_\text{O}_2 \) and LV function. All subjects tolerated peak exercise testing without any adverse events. Peak \( \dot{V}_\text{O}_2 \) increased 2.0 ± 2.4 ml·kg\(^{-1}\)·min\(^{-1} \) (range: −2.9 to 5.9 ml·kg\(^{-1}\)·min\(^{-1} \)) post-CRT (\( P < 0.05 \); Table 3). There was no effect of CRT on peak exercise ventilation (Table 3). Peak exercise power output increased 9 ± 15 W (range: −20 to 30 W) post-CRT (\( P = 0.059 \); Table 3).

Peak exercise LV EDV and LV ESV were lower post-CRT (\( P < 0.05 \); Table 3). LV EDV and LV ESV reserve were not statistically different from pre-CRT to post-CRT (Fig. 5). SV reserve (Fig. 5) and SV at peak exercise (Table 3) were significantly greater post-CRT. There was a 1.9-fold increase in cardiac output from rest to peak exercise pre-CRT (range of cardiac output reserve: 1.2 to 5.2 l/min) compared with a 2.3-fold increase post-CRT (range of cardiac output reserve: 2.3 to 6.4 l/min). Peak exercise cardiac output was higher post-CRT (\( P < 0.05 \), Table 3 and Fig. 5). SVR was significantly lower at peak exercise post-CRT. Cardiac output reserve was related to \( \dot{V}_\text{O}_2 \) at peak exercise (\( r = 0.48, P < 0.05 \)).

DISCUSSION

The main new finding of this study was that CRT led to a significant speeding in phase II \( \dot{V}_\text{O}_2 \) kinetics during the transition to moderate-intensity exercise (i.e., exercise below the ventilatory threshold) from rest, thus suggesting that a faster rate of oxidative phosphorylation to meet ATP demands during the transition to moderate-intensity exercise may have occurred. Second, SV during steady-state exercise was significantly increased, and this was due to a decrease in submaximal exercise LV ESV that was independent of cardiac preload, as the reserve in LV EDV did not increase from rest to exercise after CRT. CRT also improved HR, measured as a lower resting and steady-state exercise HR. An unexpected finding was that CRT also resulted in faster HR kinetics, suggesting that autonomic control of HR during the transition to moderate-intensity exercise also changes with CRT. Finally, CRT increased reserve and peak cardiac output, and the increase in \( \dot{V}_\text{O}_2 \) at peak exercise was related to an increase in cardiac output reserve. Cumulatively, the novel findings of this study indicate that the faster \( \dot{V}_\text{O}_2 \) adaptation to moderate-intensity exercise after chronic CRT in subjects with HF may be the combined result of an enhanced exercise SV response and faster HR kinetics and that the increase in peak \( \dot{V}_\text{O}_2 \) is associated with beneficial exercise cardiac adaptation.

\( \dot{V}_\text{O}_2 \) kinetics in HF and the effects of CRT. Phase II \( \dot{V}_\text{O}_2 \) kinetics have previously been shown to be prolonged in patients with HF (29, 35, 49, 57), in part because of impaired exercise cardiac function (58). At the onset of square-wave exercise, cardiac output increases rapidly and in an exponential manner at a rate that is often faster (31) or approximate (26) to \( \dot{V}_\text{O}_2 \) kinetics in healthy subjects. Given that exercise cardiac output and muscle blood flow are tightly coupled (37), in addition to cardiac output kinetics having been shown to be slower than \( \dot{V}_\text{O}_2 \) kinetics in patients with HF (27), supports the hypothesis that slower \( \text{O}_2 \) delivery to exercising muscles may significantly contribute to the slowing in \( \dot{V}_\text{O}_2 \) kinetics. However, little is known about the underlying cardiac mechanisms accounting for a delay in \( \dot{V}_\text{O}_2 \) kinetics in patients with HF.
patients with HF and whether improving exercise cardiac function can reverse the impaired VO2 kinetics.

Matsumoto and colleagues (35) demonstrated in relatively less fit HF patients that cardiac output and VO2 kinetics were 54% and 38% slower, respectively, compared with relatively more fit HF patients. Notably, the slower cardiac output kinetics were well correlated with prolonged VO2 kinetics. In that same study (35), O2 delivery, and not O2 extraction ability, was a rate-limiting step for VO2 kinetics. Consistent with an important cardiac role for affecting VO2 kinetics, Taniguchi et al. (57) showed that increasing LV EF (a 14% absolute change) with 6 mo of β-blocker was associated with a 31% speeding in VO2 kinetics, suggesting that β-blockade may have conferred an improvement in exercise SV (3). In addition, Koike et al. (29) demonstrated that both cardiac output and VO2 kinetics were 21% slower in patients with a lower LV EF compared with those with a higher LV EF, indicating a tight coupling between O2 delivery and O2 utilization that may be mediated by LV function. More recently, Sperandio et al. (49) demonstrated that the significantly slower VO2 and cardiac output kinetics in patients with HF also causes a “downstream” slowing in muscle microvascular O2 delivery. A functional consequence of the central-mediated slowing in O2 delivery shown in previous reports of patients with HF is a perturbation in oxidative phosphorylation rate secondary to a reduction red blood cell flux (28, 42), thus causing a slowing in VO2 kinetics (for a review, see Ref. 40). Here, we extend these previous reports (29, 35, 49, 57) by demonstrating that improving exercise cardiac function by increasing LV ESV reserve and speeding HR kinetics, and presumably the rate of O2 delivery, can speed VO2 kinetics.

Effect of CRT on HR kinetics during moderate-intensity exercise. Previous studies have shown that patients with HF exhibit autonomic dysfunction, as indicated by sympathoexcit...
In healthy individuals, the rapid increase in HR from rest to exercise onset is primarily due to a rapid reduction in parasympathetic activity that allows HR to accelerate quickly, and this effect predominates up to ~60% of the ventilatory threshold (61). During exercise above the ventilatory threshold, sympathetic nervous system activation accounts for further (and slower) increases in HR (61). Therefore, the shift from parasympathetic to sympathetic nervous control of HR during incrementally increasing exercise intensities likely accounts for the respective fast and slow HR kinetics reported in a previous study (25) in young healthy individuals. Thus, it is possible that sympathoexcitation typically exhibited in patients with HF (38, 39, 43) may account, in part, for the slow HR kinetics that we found pre-CRT. We hypothesize that CRT shifted the autonomic “profile” of cardiac control toward a more normalized parasympathetic control of HR at rest (2, 17, 21) and during moderate-intensity exercise. Subsequently, this effect would result in a speeding in HR adaptation as parasympathetic withdrawal would be the primary “controller” of HR, and sympathetic drive to a lesser degree. Consistent with this reasoning and indicative of enhanced resting vagal tone, Hamdan et al. (21) reported a significant reduction in muscle sympathetic nerve activity with CRT. Adamson et al. (2) found that CRT increased HR variability, and Fantoni et al. (17) showed that CRT decreased resting HR 4 beats/min and increased HR variability. Similarly, we also found that CRT decreased resting HR 5 beats/min. However, our study extends the findings of these previous reports (2, 17, 21) by demonstrating that the shift toward greater parasympathetic HR control at rest may also contribute to a functional speeding in HR adaptation from rest to moderate-intensity exercise, measured as a faster effective HR \( \tau \).

Impaired cardiac output adaptation to exercise because of slower HR kinetics in patients with HF has previously been attributed, in part, to β-blocker use (49). However, β-blocker use was not altered over the duration of the study in our

![Graphs showing individual subject and mean SD data.](http://ajpheart.physiology.org/)

Fig. 4. Effects of CRT on submaximal exercise cardiac reserve (steady-state exercise – rest). Graphs show individual subject and mean ± SD data. \( n = 7 \) subjects.

Table 3. Effects of CRT on peak exercise gas exchange and ventricular function

<table>
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<th>Pre-CRT</th>
<th>Post-CRT</th>
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<tr>
<td>( \text{V} \text{O}_2, \text{l/min} )</td>
<td>0.79 ± 0.26</td>
</tr>
<tr>
<td>( \text{V} \text{O}_2, \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>9.4 ± 2.2</td>
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<tr>
<td>Peak exercise</td>
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<tr>
<td>Power output, W</td>
<td>72 ± 24</td>
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<tr>
<td>( \text{V} \text{O}_2, \text{l/min} )</td>
<td>1.08 ± 0.37</td>
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<tr>
<td>( \text{V} \text{O}_2, \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
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<td>( \text{V} \text{O}_2 / \text{V} \text{CO}_2 )</td>
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<tr>
<td>( \text{V} \text{O}_2 / \text{V} \text{CO}_2 )</td>
<td>1.23 ± 0.16</td>
</tr>
<tr>
<td>Minute ventilation, l/min</td>
<td>55 ± 11</td>
</tr>
<tr>
<td>Tidal volume, liters</td>
<td>1.54 ± 0.47</td>
</tr>
<tr>
<td>Breathing frequency, breaths/min</td>
<td>37 ± 7</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>113 ± 19</td>
</tr>
<tr>
<td>LV end-diastolic volume, ml</td>
<td>248 ± 48</td>
</tr>
<tr>
<td>LV end-systolic volume, ml</td>
<td>196 ± 49</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>52 ± 13</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.8 ± 1.4</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>22 ± 6</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn-s^{-1}-cm^{-5}</td>
<td>1.041 ± 252</td>
</tr>
</tbody>
</table>

Data are means ± SD; \( n = 12 \) subjects for pulmonary gas exchange and ventilation data and 10 subjects for cardiovascular data. \( \text{V} \text{CO}_2 \) output. \*Significantly different (\( P < 0.05 \)) from pre-CRT values; \( \dagger P = 0.059 \); \( \ddagger P = 0.053 \).
subjects, and thus any effect of β-blockade on HR kinetics parameter estimates would have been controlled for with our study design. Therefore, it is unlikely that β-blockade use confounded our study findings and rather emphasizes the added exercise cardiovascular benefit of CRT to optimal pharmacological therapy in patients with systolic HF.

Effect of CRT on resting LV volumes. CRT was associated with reverse LV remodeling, as measured by a significant reduction in LV volumes and an increase in LV EF. Specifically, LV EDV decreased 8% and LV ESV decreased 14%. This approximates to the 9–10% reduction in LV EDV and 10–14% reduction in LV ESV previously reported (46, 51, 53) but is less than the 18% reduction in LV EDV and 25% reduction in LV ESV reported in a study by Yu et al. (63). We found that LV EF increased an absolute 5%, which is similar to reports of an approximate absolute 4–5% increase in LV EF (1, 19, 51, 53), although is less than the absolute 11% increase in a study by Steendijk et al. (52). Also owing in part to the greater reduction in LV ESV versus LV EDV (51, 53, 63), we found that CRT increased resting SV. Therefore, relative to larger studies, the magnitude of LV reverse remodeling that we report here is similar.

Effect of CRT on moderate-intensity and peak exercise LV function. Steady-state SV increased after CRT, which is consistent with a previous study (10) showing that optimized sequential biventricular pacing (LV before RV stimulation) increased SV during submaximal cycle ergometry exercise compared with LV or simultaneous biventricular pacing. Our
finding of an increase in exercise SV was due primarily to enhanced systolic function, as measured by a decrease in exercise LV ESV and an increase in LV ESV reserve. The increase in LV ESV reserve was independent of an increase in cardiac preload as there was no change in LV EDV from rest to exercise. Compared with no pacing, acute LV pacing alone has been shown to increase LV EDV by 10 ml and SV by 11 ml without a further reduction in LV ESV in patients with HF (9). These findings were attributed to LV pacing reducing the external constraint to LV filling by modulating a relatively earlier LV diastolic filling period before the RV (9). Compared with biventricular pacing, however, 6 mo of LV pacing alone has been shown to confer significantly less change in LV end-diastolic dimension (59), and this has been confirmed in a randomized multicenter trial (41). Our findings suggest that an enhanced Frank-Starling effect may not be present with sequential biventricular stimulation (LV before RV) during upright whole body exercise compared with rest after chronic CRT.

The increase in cardiac output at peak exercise post-CRT compared with pre-CRT is attributable to the combined effects of a smaller reduction in LV EDV reserve and a greater increase in LV ESV reserve. The net effect of these changes in LV EDV and LV ESV reserve significantly increased SV reserve and SV at peak exercise. The increase in LV ESV reserve that we did find may be due, in part, to a reduction in LV afterload (18, 20), as SVR was lower at peak exercise post-CRT. It is also noteworthy that, although not significant, HR reserve increased subsequent to a reduction in resting HR, which is consistent with previous findings (4). It is likely that this small (6 beat/min) increase in HR reserve also facilitated an increase in cardiac output reserve.

Several factors may explain the lower LV ESV during moderate-intensity and peak exercise. First, an improvement in β-adrenergic receptor sensitivity after CRT may increase myocyte sarcomere shortening rate (12), thus conferring an increase in contractility at rest (48, 52, 60), during dobutamine stress (60), and during atrial pacing (52). The lower exercise LV ESV may also be due, in part, to a reduction in intraventricular dyssynchrony (63). Finally, the lower exercise LV ESV may also be secondary to a reduction in afterload that may be modulated by CRT (52), as we also found that SVR was lower post-CRT during moderate-intensity and peak exercise. Our study extends these previous reports by demonstrating that LV ESV is lower and LV ESV reserve is higher during moderate-intensity and peak exercise after CRT.

Factors affecting peak Vo2 in HF and the effects of CRT. Peak Vo2 is upwards of 50% lower in patients with HF compared with healthy controls (22, 55). The impairment in peak Vo2 can be attributed, in part, to a concomitant reduction in peak cardiac output (55) that is secondary to a decrease in HR and a reduction in both LV ESV reserve and use of the Frank-Starling mechanism (thus reducing SV) (30, 45, 55).

Several studies (1, 4, 5, 11, 15, 19, 33) have previously shown that CRT improves exercise capacity in patients with HF, measured as an average increase in peakVo2 ranging from 1.1 to 3.1 ml·kg⁻¹·min⁻¹. We also found that CRT increased exercise capacity, as measured by a 9% increase (2.0 ± 2.4 ml·kg⁻¹·min⁻¹) in peak Vo2, and this was attributable, in part, to an increase in cardiac output reserve.

In their study, Duncan et al. (15) reported that the change in resting LV end-systolic dimension accounted for 22% of the variance in the change in peak Vo2. We found that an increase in cardiac output reserve accounted for only 23% of the variance in peak Vo2. Together, these data suggest that the CRT-mediated changes in peak Vo2 are not restricted solely to improvements in resting and exercise LV function (i.e., reduction in LV ESV and an increase in SV and cardiac output), as a reduction in limb blood flow (16, 55) and an unfavorable shift in skeletal muscle fiber composition (14, 54) and reduction in cross-sectional area (22) also occur in HF. Thus, other factors not measured in the present study that could potentially contribute to the increase in peak Vo2 secondary to a CRT-modulated reduction in sympathoexcitation (2, 17, 21) include a reversal of chronic skeletal muscle underperfusion, reversal of skeletal muscle myopathy, and a subsequent shift toward greater oxidative metabolism (36). These proposed mechanisms require study, however.

Limitations. This study has limitations. We did not investigate the time course of SV throughout the transition from rest to exercise, and therefore we are not able to exclude a potential speeding in SV adaptation as an additional mechanism attributing to our observation of faster Vo2 kinetics in patients after CRT. We also did not control for or document physical activity in our study group during the CRT intervention period and thus cannot discount potential skeletal muscle adaptations or further cardiovascular benefits that may have occurred secondary to an improvement in physical function (36). We were also not able to have a control group. Additionally, cardiac imaging was performed in a single plane, and this could affect absolute values for cardiac volumes (50). Such error, however, would be systematic from our pre-CRT to post-CRT analyses and thus would not affect our study findings. To further increase the feasibility of our imaging technique, we used a commercial contrast agent, which has been shown to increase the accuracy and reproducibility of volume and LV EF determination (34).

An additional and obvious limitation that warrants discussion is the high incompletion rate that was due to mortality, HF complications, and clinical intervention. Our noted incompletion rate is not overly surprising given that the Pacing Therapies in Congestive Heart Failure study (53) reported a similar 40% dropout rate by their 6-mo followup period in their small cohort of 42 subjects. Furthermore, in the large Multicenter InSync Randomized Clinical Evaluation study, ~42% of 528 subjects who underwent device implantation did not complete the 6-mo followup Vo2 study (1). Compared with those studies, individuals in the present investigation were younger, with a slightly lower LV EF and peak Vo2, and were requested to undergo more intensive exercise testing (multiple gas exchange exercise tests and exercise contrast echocardiography) likely requiring greater physical effort and time commitment.

Conclusions. Chronic CRT improves Vo2 kinetics by increasing exercise SV via a reduction in LV ESV and by causing a functional speeding in HR kinetics. At peak exercise, CRT increases LV ESV reserve and subsequently increases peak and reserve SV and cardiac output. The greater reduction in exercise LV ESV post-CRT is independent of an increase in LV EDV reserve during moderate-intensity or peak exercise and may be the result of increased contractility and/or reduced LV afterload.
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DISCLOSURES
R. G. Haennel is listed as the principle investigator on the grant from St. Jude Medical, and I. Paterson, M. J. Haykowsky, A. Pantano, and S. Gulamhusein are listed as co-investigators. C. R. Tomczak, A. Pantano, R. Lawrance, A. Martellotto, A. Pantano, S. Gulamhusein, and R. G. Haennel have attended a meeting regarding this study that was hosted by St. Jude Medical. St. Jude Medical was not involved in any step of this study, including its conception and design, data collection and analysis, data interpretation, manuscript preparation, or decision for publication. The authors declare no other perceived or real conflict of interest.

AUTHOR CONTRIBUTIONS

REFERENCES

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EFFECTS OF BIVENTRICULAR PACING ON V˙o2 KINETICS


