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Instantaneous effects of resynchronisation therapy on exercise performance in heart failure patients: the mechanistic role and predictive power of total isovolumic time

T V Salukhe,1,2 K Dimopoulos,1,2 R Sutton,1,2 P Poole-Wilson,1,2 M Y Henein,1,2 M Morgan,2 J R Clague,2 D P Francis3

ABSTRACT

Background: Cardiac resynchronisation therapy improves peak oxygen uptake (peak VO2) 3–9 months after device implantation. In chronic heart failure, total isovolumic time (t-IVT) is a major determinant of peak VO2 and of cardiac output at peak dobutamine stress. In selected patients, resynchronisation can instantaneously shorten t-IVT. We sought to determine the acute effect of resynchronisation on exercise performance and determine, with pharmacological stress echocardiography, the mechanism underlying this effect.

Methods and results: Twenty-two patients with resynchronisation were studied within 3 months after device implantation. On a single study day, sequential cardiopulmonary exercise tests were performed during native activation (left bundle branch block) and resynchronisation (atrio-biventricular pacing) in random order. Total-IVT and cardiac output (at rest and peak dobutamine stress) were then measured in each activation mode. Resynchronisation acutely increased peak VO2 by 1.6 (SD 1.5) ml/kg/min (p<0.001) and shortened peak stress t-IVT by 10 (SD 7) s/min (p<0.001), with the effects in individual patients showing a correlation (r = −0.46, p<0.05). Amongst all measurements during native activation, the best predictor of gain in peak VO2 from resynchronisation was peak stress t-IVT (r = 0.71, p<0.001) with every increment of 5 s/min of peak stress t-IVT during native activation predicting an 8% gain in peak VO2. No conventional measures during native activation at rest or on stress (including QRS duration, Tei index, tissue Doppler intraventricular delay, and resting t-IVT) added significant additional information.

Conclusions: In eligible patients, resynchronisation can acutely augment peak VO2, possibly through a mechanism of t-IVT shortening. Under native activation, long t-IVT during peak stress is the single best predictor of acute resynchronisation-mediated increment in peak VO2.

In selected patients with heart failure, cardiac resynchronisation therapy can improve exercise tolerance (assessed by peak oxygen uptake (peak VO2)). This effect has consistently been shown to occur over a period of weeks or months, and hence the underlying mechanism is presumed to be a chronic process. Although LV cavity size reduction and ejection fraction increase follow a similar time course after resynchronisation, these changes cannot be assumed to account for improved exercise tolerance since LV cavity size and ejection fraction are known to have no direct relationship with peak VO2.

Total isovolumic time (t-IVT, when the ventricle is neither ejecting nor filling) has been found to be a major determinant of peak VO2 and of peak stress cardiac output. Resynchronisation can instantaneously shorten t-IVT at rest and during pharmacological stress. We therefore hypothesised, first, that resynchronisation therapy may augment peak VO2 more acutely than has previously been shown. Second, acute t-IVT reduction caused by resynchronisation (at rest or during stress) may be the underlying mechanism of peak VO2 gain from resynchronisation therapy. In addition, we investigated the possibility that t-IVT would provide an echocardiographic marker that might predict peak VO2 gain patients eligible for cardiac resynchronisation therapy.

METHODS

We studied 22 patients with a mean age of 66 (SD 7) years. All were selected to be in sinus rhythm, fulfil current ACC/AHA guideline criteria for resynchronisation therapy (patients with ischaemic or non-ischaemic dilated cardiomyopathy with NYHA III or IV symptoms, EF <35%, LVEDD >5.5 cm, QRS duration >150 ms, who received maximum tolerated medical treatment) and have had a successful implantation of an atrio-biventricular pacemaker or pacemaker-defibrillator. All patients were studied within 3 months after device implantation. The Royal Brompton and Harefield Ethics Committee approved the study protocol. All subjects gave written, informed consent.

Exercise preconditioning

Before formal cardiopulmonary exercise testing, all patients underwent a practice treadmill exercise (modified Bruce protocol) with electrocardiogram and blood pressure monitoring. All patients were encouraged to exercise to exhaustion. All studied patients stopped exercise because of breathlessness and/or fatigue and none experienced chest pain or developed ST segment shift. Patients were allowed to rest and recover from preconditioning until they subjectively felt ready for formal exercise testing (typically 50–60 minutes). Exercise preconditioning and two formal cardiopulmonary exercise tests were all performed on the same day to exclude second window protection.
Cardiopulmonary exercise testing
All patients underwent two symptom-limited cardiopulmonary exercise tests—one during resynchronisation (atrio-biventricular pacing) and one during native activation (device programmed AAI with base rate at 30 beats/min). Patients were allowed to rest and recover fully between tests (typically 30–60 minutes). The order of tests was randomised (using a sealed envelope technique) for each patient. The order of tests was known only to the device programmer and the investigator monitoring the ECG. The patient and the investigator responsible for motivating the patient and analysing exercise data were blinded to the activation mode during testing.

During exercise testing a modified Bruce protocol was used with assessment of minute ventilation (VE), oxygen consumption (VO2), and carbon dioxide production (VCO2) every 10 s by mass spectrometer (Amis 2000, Innovision; MedGraphics Cardio O2 System, Odense, Denmark). Patients were encouraged to exercise to exhaustion (VCO2/VO2 >1.05). Continuous 12-lead electrocardiographic monitoring was used. All participants stopped exercise because of breathlessness and/or fatigue. None experienced chest pain or developed ST segment shift.

Heart failure and cardiomyopathy

Dodobutamine stress protocol
Dobutamine was administered through an infusion pump (IVAC 770 syringe driver, Alaris Medical Systems, Hampshire, UK), starting at a rate of 5 μg per kg of body weight per min, with similar increments every 3 min to a maximum of 40 μg/kg per min. Atropine (300 mg) was added to augment the heart rate in patients not reaching the predetermined stress end points by the end of stage 2. Systolic and diastolic blood pressures were recorded at each stage using a Critikon Dinamap monitor (Critikon Inc., Tampa, Florida). Predetermined stress end points were: 1) 85% predicted target heart rate (22.0 – age in years) or 2) development of symptoms, ventricular ectopic beats, 20 mm Hg drop in systolic arterial pressure, ST segment shift >2 mm, or T-wave inversion.

Stress echocardiography
Transsthoracic echocardiography was performed using a Philips Sonos echocardiograph and a multifrequency transducer. Cross-sectional, two-dimensionally guided M-mode recordings of the LV minor axis at rest were performed using the left parasternal long-axis view, with the cursor by the tips of the mitral valve leaflets. Left ventricular minor axis dimensions were taken at end diastole (onset of the QRS complex) and at end systole at the first high-frequency vibration of the aortic component of the second heart sound on the phonocardiogram (A2). A2 itself was identified as the sound synchronous with the onset of the closure artifact on the aortic Doppler image. The LV outflow tract diameter was measured from the parasternal long-axis view and subaortic area calculated during systole.9 The transaortic Doppler velocities were obtained from the apical five-chamber view with the sample volume below the AV valve leaflets. The LV ejection time was measured as the interval between the onset of forward aortic flow and the onset of the aortic closure artifact. Aortic velocity traces were digitised off line (100 Hz). Transmural flow velocities were recorded from the apical four-chamber view, and the filling time was measured from the onset of the E wave to the end of the A wave. Total ejection and filling periods were derived as the product of the corresponding time interval and heart rate, and these periods were expressed as seconds per minute. The t-IVT (also in s/min) was calculated as: 60 – (total ejection time + total filling time). These values are independent of the heart rate.10 The Tei index was obtained as previously described.11 Stroke distance was calculated as the time integral of aortic velocity; stroke volume as the product of stroke distance and subaortic cross-sectional area; and cardiac output as the product of stroke volume and heart rate.

Tissue Doppler assessment of intraventricular and interventricular dyssynchrony
Using the apical two-chamber and four-chamber views, tissue Doppler sample volumes were sequentially placed in four basal segments of the LV (anterior, posterior, septal, and lateral walls). For each segment, the time delay from the Q wave on the ECG to the peak systolic velocity was measured. Left intraventricular dyssynchrony was measured as the time delay between earliest and latest peak systolic velocities among the four walls of the LV.12 13

Stress protocol activation mode sequence
Transaortic and transmitral Doppler recordings, tissue Doppler recordings and LV outflow tract diameter were repeated at rest and peak stress during native activation and then resynchronisation. All tracings were acquired digitally at a speed of 100 mm/s, with an electrocardiogram (ECG lead II) and phonocardiogram superimposed. An independent investigator who was unaware of the clinical history, stress ECG results, and angiographic data acquired all echocardiographic images.

Stress ECG
A standard 12-lead ECG was recorded at rest and at each stage of stress using a Hewlett-Packard Pagewriter Xli. The frequency response of the electrocardiograph was 0.05 to 150 Hz, with the baseline filter (0.4 Hz) inactivated. The ECG intervals were determined directly using built-in software and registered on a printed chart at a speed of 25 mm/s. The ST segment shift was measured manually 80 ms after the J point.

Data analysis
Data are expressed as the mean value (SD in brackets). Rest and stress values within each activation mode were compared using paired Student t test. A correlation was performed by linear regression analysis, and the standard deviations of the intercepts and slopes were determined. The 95% confidence limits of correlation coefficients were determined by Fisher’s r-to-z transformation.

Reproducibility
Reproducibility of echocardiographic measurements of our data have been described in a previous study,14 in which duplicate measurements of ejection and filling times were made. The intraobserver coefficient of variability ranged from 3.5% to 5.2%, and the interobserver variability ranged from 4.2% to 6.4%. The reproducibility of ECG data and cardiopulmonary testing in our department has been previously reported (difference between two tests: 0.95 ml/kg/min; SD of the difference: 3.07 ml/kg/min; coefficient of variability: 17.5%).14
RESULTS
Of 22 eligible patients, two patients were excluded from the study; one patient could not be weaned off ventricular pacing and hence native ventricular activation could not be achieved, and the other was found to be in atrial fibrillation on the day of study. The clinical and pacemaker profiles of the remaining 20 patients are displayed in table 1. Prior to implantation, all patients had NYHA class III or IV symptoms, an ejection fraction of 35% or less and a cardiac output showed no correlation with peak VO₂ gain. None of the measurements at rest correlated with gain in peak VO₂ from resynchronisation. However, the percentage gain in peak VO₂ correlated with peak stress t-IVT during native activation (r = 0.71, p < 0.001, see fig 2), and inversely correlated

<table>
<thead>
<tr>
<th>Variable (n = 20)</th>
<th>Rest</th>
<th>Native activation</th>
<th>Resynchronisation</th>
<th>Stress</th>
<th>Native activation</th>
<th>Resynchronisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 (14)</td>
<td>72 (13)</td>
<td>110 (11)§</td>
<td>111 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV filling time (s/min)</td>
<td>27 (5)</td>
<td>29 (5)†</td>
<td>22 (4)</td>
<td>30 (4)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection time (s/min)</td>
<td>18 (3)</td>
<td>19 (4)</td>
<td>21 (3)</td>
<td>23 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total isovolumic time (s/min)</td>
<td>15 (5)</td>
<td>11 (5)*</td>
<td>17 (6)</td>
<td>7 (4)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tei index</td>
<td>0.41 (0.09)</td>
<td>0.40 (0.08)</td>
<td>0.49 (0.04)</td>
<td>0.43 (0.05)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraventricular delay (ms)</td>
<td>69 (42)</td>
<td>77 (48)</td>
<td>71 (47)</td>
<td>65 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>154 (16)</td>
<td>150 (15)</td>
<td>150 (19)</td>
<td>154 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>77 (29)</td>
<td>80 (26)</td>
<td>70 (26)</td>
<td>78 (24)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.4 (1.8)</td>
<td>5.6 (1.7)</td>
<td>7.6 (2.4)*</td>
<td>8.4 (2.2)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean (SD).

*p < 0.001, †p < 0.01 for comparisons with native activation within same state, §p < 0.001, p < 0.01 for comparison with native activation at rest. All comparisons with paired t test.
with peak stress LV ejection time, filling time and cardiac output during native activation \((r = -0.61; \ p < 0.01, \ r = -0.59; \ p < 0.01\) and \(r = 0.49; \ p < 0.05\) respectively). Peak stress Tei index, QRS duration and intraventricular delay during native activation showed no such correlation.

On univariate analysis, peak stress t-IVT, LV filling time, ejection time and cardiac output during native activation were the significant predictors of percentage gain in peak VO\(_2\) from resynchronisation. However, when a multivariate model was developed in a stepwise process with these variables, peak stress t-IVT during native activation was identified as the single best independent predictor of peak VO\(_2\) gain \((p < 0.001, \text{see table 4})\).

**DISCUSSION**

In this study we found, first, that resynchronisation can increase peak VO\(_2\) by 1.6 ml/kg/min acutely, and much earlier after device implantation than was previously thought. This acute increase represents a \(-15\%\) peak VO\(_2\) gain from native activation (left bundle branch block). Second, the mechanism of peak VO\(_2\) augmentation with resynchronisation may occur through reduction of t-IVT. Third, the t-IVT at peak stress during native activation is the single best predictor of percentage gain in peak VO\(_2\) from resynchronisation, and therefore has potential as a clinically applicable tool for identifying patients with the best prospect for improved exercise capacity from resynchronisation.

**ACUTE EFFECTS OF RESYNCHRONISATION ON EXERCISE PERFORMANCE**

Patients with chronic heart failure frequently have a limited exercise capacity. In such patients, left bundle branch block further reduces peak VO\(_2\) by 10.5 ml/kg/min.\(^4\) In selected patients with chronic heart failure and prolonged QRS, cardiac resynchronisation therapy has been shown to increase peak VO\(_2\) after 5–9 months, typically by 1.1–3.0 ml/kg/min (representing an 8–20% improvement).\(^{15,16}\) This occurs in association with a reduction in LV cavity size (reverse remodelling)\(^{17–19}\) and an increase in LV ejection fraction.\(^{20,21}\) In the present study, we showed that the acute gain in peak VO\(_2\) from resynchronisation (1.6 ml/kg/min) is similar in magnitude to that seen over the long term. This result has two implications. First, the mechanism underlying peak VO\(_2\) gain by resynchronisation occurs more abruptly than can be plausibly explained by LV reverse remodelling or increase in ejection fraction. Second, resynchronisation acutely recoups \(-15\%\) of the peak VO\(_2\) deficit specifically caused by left bundle branch block in patients with chronic heart failure.

**TOTAL ISOVOLUMIC TIME AND EXERCISE PERFORMANCE**

Longer peak stress t-IVT values during native activation were the best univariate and sole multivariate predictor of a larger percentage gain in peak VO\(_2\) from resynchronisation. Fall in peak stress t-IVT arising from resynchronisation was also related to the increment in peak VO\(_2\) from resynchronisation. A reduction in t-IVT implies an increase in either total LV filling time or ejection time or both. We found that peak stress t-IVT reduction due to resynchronisation was attributable to increases in both total LV filling time and ejection time. Although the increase in peak stress ejection time showed a correlation with peak VO\(_2\), that with fall in t-IVT was much closer \((-0.64)\). There were no resting measurements during native activation that predicted peak VO\(_2\) gain from resynchronisation. Peak stress LV filling time, ejection time and cardiac output during native activation also predicted peak VO\(_2\) gain, but all were eliminated on multivariate analysis by peak stress t-IVT during native activation, which emerged as the only independent predictor.

We therefore conclude, first, that the acute peak VO\(_2\) gain from resynchronisation may occur through t-IVT reduction.

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**Table 3** Cardiopulmonary exercise testing

<table>
<thead>
<tr>
<th>Variable (n = 20)</th>
<th>Native activation</th>
<th>Resynchronisation</th>
<th>First test</th>
<th>Second test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO(_2) (ml/kg/min)</td>
<td>14.6 (5.7)</td>
<td>16.3 (5.4)*</td>
<td>15.6 (5.7)</td>
<td>15.5 (5.5)</td>
</tr>
<tr>
<td>VE/VCO(_2) slope</td>
<td>39.9 (14.0)</td>
<td>41.4 (13.4)</td>
<td>42.3 (13.8)</td>
<td>38.9 (13.4)</td>
</tr>
<tr>
<td>RER (VCO(_2)/VO(_2))</td>
<td>1.11 (0.27)</td>
<td>1.05 (0.20)</td>
<td>1.06 (0.22)</td>
<td>1.10 (0.26)</td>
</tr>
<tr>
<td>exercise time (s)</td>
<td>237 (185)</td>
<td>266 (173)</td>
<td>240 (173)</td>
<td>263 (186)</td>
</tr>
</tbody>
</table>

*\(p < 0.001\) for comparison with native activation. All comparisons with paired t test.

RER, respiratory exchange ratio at peak exercise; VCO\(_2\), carbon dioxide production; VE, minute ventilation; peak VO\(_2\), peak oxygen uptake.

Data presented as mean (SD).
Second, the most significant t-IVT reduction from resynchronisation (and most pertinent in determining peak VO2 gain) occurs at high heart rates of exercise or pharmacological stress. Finally, peak stress t-IVT during native activation predicts the gain in peak VO2 from resynchronisation – an effect which can be quantified; every increase by 5 s/min of peak stress t-IVT during native activation predicted an 8% gain in peak VO2 from resynchronisation.

**MECHANISMS**

Prolongation of peak stress t-IVT during native activation proved to be a major determinant of gain in peak VO2 from resynchronisation. It is likely that this prolongation was due to ventricular asynchrony, which in left bundle branch block is the result of abnormal activation causing dispersion in the timing of local systole and diastole. It is ventricular asynchrony, rather than uniform depression of systolic or diastolic ventricular function, that prolongs t-IVT within the cardiac cycle, and determines maximum exercise tolerance in patients with heart failure. In dilated cardiomyopathy, left bundle branch block and coronary artery disease can both prolong t-IVT, albeit through different mechanisms: while left bundle branch block prolongs t-IVT at rest, coronary artery disease prolongs t-IVT during stress. When left bundle branch block and coronary artery disease coexist, these separate mechanisms amalgamate to severely prolong t-IVT, but are ultimately attributed to abnormalities of activation. The high prevalence of patients with coronary artery disease in the present study may partly explain the dominant predictive power and mechanistic role of peak stress t-IVT over resting t-IVT in the determination of percentage gain in peak VO2 from resynchronisation.

Peak VO2 is directly dependent on peak cardiac output, and therefore it is plausible that it responds promptly to changes in cardiac cycle efficiency. In contrast, VE/VCO2 slope (the ventilatory response per unit increase in carbon dioxide tension) is determined by as yet unclear mechanisms, which may include not only cardiac output but also pulmonary vasculature, ventilation-perfusion mismatching, chemoreceptor sensitivity and limb muscle ergoreceptor sensitivity. There is a certainly an inverse correlation in populations of heart failure patients between peak VO2 and VE/VCO2 slope, but the correlation is not perfect and it is not known how quickly (if at all) to expect VE/VCO2 to change in response to a change in peak VO2.

**STUDY LIMITATIONS**

Limitations in assessing stroke volume from aortic stroke distance are well recognised. They were minimised in the present study by using patients as their own controls and fixing the position of interrogation of the LV outflow tract. The effect of exercise training is well recognised and could account for incrementing peak VO2 measurements on sequential tests. The confounding effect of exercise testing was minimised first by preconditioning before formal exercise testing and second by randomising the order of activation modes. The success of this strategy is reflected in similar mean peak VO2 values between the first and second tests.

**CONCLUSIONS**

In eligible patients, cardiac resynchronisation therapy augments peak oxygen uptake much sooner after implantation of resynchronisation devices than was previously thought. At high heart rates, the instantaneous reduction of t-IVT by resynchronisation may have a mechanistic role in enhancing exercise capacity. Furthermore, the t-IVT at peak stress during native activation provides the best quantitative predictor of this favourable response to resynchronisation therapy with every additional 5 s/min of peak stress t-IVT during native activation predicting an 8% increase in peak oxygen uptake from resynchronisation. These findings underline the importance of cardiac cycle efficiency in determining exercise performance and bring to light the value of stress echocardiography and studying cardiac cycle time intervals to direct resynchronisation therapy more securely than has previously been possible.

**REFERENCES**

Intraoperative assessment of coronary grafts with fluorescent angiography

A 71-year-old man with triple vessel disease was treated with off-pump coronary artery bypass grafting (CABG). The following arteries were grafted: (a) left internal thoracic artery (LITA) to first diagonal branch (D1) and left anterior descending artery (LAD) sequentially (panel A); (b) free-radial artery to right ventricular branch and distal right coronary artery; and (c) saphenous vein to middle left circumflex artery. Immediately after all grafts were anastomosed, graft patency was assessed using a new intraoperative fluorescent imaging (IFI) system (SPY) using indocyanine green injected from a central venous line. The IFI system demonstrated rapid filling and emptying of the entire graft with indocyanine green. These results were confirmed by coronary angiography 10 days after surgery. Panels A and B (supplementary movies 1 and 2, respectively, available online) show representative IFI and angiography of LITA to D1 and LAD.

Compared with on-pump CABG, off-pump surgery potentially decreases the incidence of myocardial injury, renal damage and central nervous system complications. However, these clinical benefits of off-pump CABG are partly offset by a relatively higher rate of early graft failure. The IFI system may help to reduce procedure-related, early graft failures by enabling interactive evaluation of graft patency with images similar to conventional angiography but directly in the operating room before the chest closure.