Title: The physiological effects of cardiac resynchronization therapy on aortic and pulmonary flow and dynamic and static components of systemic impedance

Short title: Physiological effects of CRT

Authors: Baldeep S Sidhu(PhD)[1,2], Simon Claridge(PhD)[1,2], Haotian Gu(PhD)[3], Ye Li(PhD)[3], Justin Gould(PhD)[1,2], Bradley Porter(PhD)[1,2], Mark K Elliott(MBBS)[1,2], Vishal Mehta(MBBS)[1,2], Tom Jackson(PhD)[1,2], Tiffany Patterson(PhD)[2,4], Natalia Briceno(MBBS)[2,5], Jack Lee(DPhil)[1], Simon Redwood(MD)[2,4], Shaumik Adhya(FHRS)[2], Steven A Niederer(DPhil)[1], Phil Chowienczyk(BSc)[3*] and Christopher A Rinaldi(FHRS)[1,2*]

Affiliations

[1]School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK

[2]Guy's and St Thomas' Hospital, London, UK

[3]British Heart Foundation Centre, King's College London, London, UK

[4]Cardiovascular department, King's College London, London, UK

[5]NIHR Biomedical Research Centre, School of Cardiovascular Medicine and Sciences, King's College London, London, UK

[*] These authors contributed equally

Corresponding author:

Dr Baldeep Singh Sidhu

School of Biomedical Engineering and Imaging Sciences, St Thomas' Hospital, London,

SE17EH, UK

Email: baldeep.sidhu@kcl.ac.uk

Conflict of interest

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Abstract

Background: Patients who improve following cardiac resynchronization therapy (CRT) have left ventricular (LV) remodeling and improved cardiac output (CO). Effects on the systemic circulation are unknown.

Objective: To explore the effects of CRT on aortic and pulmonary blood flow and systemic afterload.

Methods: At CRT implant patients underwent a non-invasive assessment of central haemodynamics including wave intensity analysis (n=28). This was repeated at 6-months after CRT. A sub-sample (n=11) underwent an invasive electrophysiological and hemodynamic assessment immediately following CRT. CRT response was defined as reduction in LV end-systolic volume ≥15% at 6-months.

Results: In CRT responders (75% of those in the non-invasive arm), there was a significant increase in CO (from 3 ± 2L/min to 4 ± 2L/min, P=0.002) and LV dP/dtmax (from 846 ± 162mmHg/s to 958 ± 194mmHg/s, P=0.001), immediately after CRT in those in the invasive arm. They demonstrated a significant increase in aortic forward compression wave (FCW) both acutely and at follow-up. The relative change in LV dP/dtmax strongly correlated with changes in the aortic FCW (R_s0.733, P=0.025). CRT responders displayed a significant reduction in afterload; decrease in systemic vascular resistance and pulse wave velocity acutely; there was a significant decrease in acute pulmonary afterload measured by the pulmonary FCW and forward expansion wave.

Conclusions: Improved cardiac function following CRT is attributable to a combination of changes in the cardiac and cardiovascular system. The relative importance of these two mechanisms may then be important for optimizing CRT.

Keywords: Aortic flow, Cardiac resynchronization therapy, Physiology, Pressure-volume loops, Pulmonary flow, Wave intensity analysis

Introduction

Cardiac resynchronization therapy (CRT) improves symptoms and reduces mortality in symptomatic patients with left ventricular (LV) systolic impairment and electrical dyssynchrony, who are on optimal medical therapy.(1) However, even in carefully selected cases approximately 30% of patients fail to benefit.(1) In patients who improve following CRT there is evidence of ventricular resynchronization, reverse LV remodeling, increased cardiac output (CO) and increased external work achieved by the heart.(2) It is unknown whether these physiological changes result purely from improved LV contraction thus increasing CO or whether there are concomitant changes in loading conditions on the left ventricle and/or changes in systemic impedance following CRT. Previous studies have shown that CRT is associated with improved right ventricular function and reduced systolic pulmonary pressures(3) but the mechanism through which these effects are seen are not fully understood. In humans, it is understood that CRT improves coronary flow in the left anterior descending artery(4) but the effect of dynamic aortic and pulmonary pressure and flow changes on cardiac function requires further investigation. Wave intensity analysis enables the study of cardiovascular dynamics by representing pressure and velocity waveforms as successive wavefronts.(5) The forward compression wave (FCW) measures the increase in pressure and flow through an artery and characterizes blood flow during early systole.(5, 6) The forward expansion wave (FEW) measures the decrease in pressure and flow in late-systole. The backward compression wave (BCW) measures the increase in pressure and reduced flow through an artery and characterizes blood flow during mid-systole. These waves are present in both the systemic and pulmonary circulation.(6, 7) Determining whether there is a correlation between aortic flow and myocardial contractility helps understand how improved myocardial contractility seen with CRT may influence aortic flow in CRT responders and non-responders.

Although CRT is known to increase CO the effect on different components of afterload, namely systemic vascular resistance (SVR) and arterial stiffness, is not fully understood. Adjunctive medical therapy used in the treatment of heart failure alters afterload(1) and identifying whether CRT has additional effects of the vascular system is important in these patients. Aortic pulse wave velocity (PWV) is considered the gold standard for measuring central aortic stiffness and can be used to provide important prognostic information for a variety of conditions(8). A greater PWV is independently associated with incident clinical heart failure.(9) Therefore understanding whether CRT alters arterial hemodynamics has implications on potential therapeutic interventions.(10)

The purpose of this study was to explore the effects of CRT on aortic and pulmonary blood flow and afterload by comparing intrinsic rhythm with biventricular pacing. We hypothesized that response to CRT would be associated with cardiac changes, principally improved myocardial contractility and stroke work and also changes in the cardiovascular system, which together would facilitate an increased mean arterial blood pressure. We measured wave intensity invasively and non-invasively and used pressure-volume loops to accurately assess LV hemodynamics.

Methods

Study design

The study was approved by the London Research Ethics Committee (11/LO/1232), all patients provided written informed consent for participation in this study and the research in this study was conducted to the Helsinki Declaration guidelines on human research. The inclusion criteria involved patients with a guideline directed indication for CRT(11). Patients were excluded if they were under 18 years old, pregnant or unwilling to undergo non-invasive assessment at 6-months and patients were also excluded from the invasive arm of the study if they had significant aortic valve disease or a contraindication to heparin. A quadripolar LV lead was placed at the basal lateral wall via the posterolateral or lateral coronary vein, wherever possible and targeted to areas of latest electrical activation as assessed by the Q-LV time. The pacing vector that produced the narrowest QRS duration was chosen. Immediately following CRT, patients underwent an invasive and/or non-invasive assessment of cardiac function, pulmonary and systemic hemodynamics.

Non-invasive assessment of aortic flow and arterial stiffness

This was performed on the same day following CRT and repeated at 6-months, using a pacing protocol described below and using a similar protocol to previously published work.(7) Brachial blood pressure was measured by a validated oscillometric method (Omron 705CP; Omron Healthcare, Tokyo, Japan). Radial and carotid pressure waveforms were obtained using the SphygmoCor system (AtCor, West Ryde, Australia). Radial pressure was calibrated from the measured values of brachial systolic and diastolic pressure because these are assumed to be equal at both sites. Systolic pressure differs at the carotid and brachial sites and therefore the carotid pressure was calibrated from the mean and diastolic pressure which are similar at all three sites.(12) Mean pressure is derived from radial pressure integrated over

time. Femoral pressure waveforms were recorded by applanation tonometry using the SphygmoCor system. PWV was calculated from the transit time between the carotid to femoral pressure waveforms. The SphygmoCor device and transducer was used to record both pressure waveforms. The difference in the time of pulse arrival between these two sites was referenced to the R wave of the ECG and taken as the transit time. The path length was estimated from the distance between the sternal notch and femoral artery whereby the artery was applanated. PWV was then calculated as the path length divided by the transit time. Aortic flow was recorded from an echocardiographic Apical 5-chamber view using continuous Doppler.

Invasive protocol

Simultaneous invasive hemodynamic and electrophysiological measurements were performed immediately following successful CRT. Successful CRT was defined as evidence of biventricular pacing following LV lead placement and narrowing of the QRS duration. A pressure-volume loop conductance catheter (CD Leycom, Netherlands) was placed within the left ventricle and the tip of a 0.014-inch dual pressure-Doppler sensor wire (ComboWire 9500; Volcano Corp) within the ascending aorta for aortic flow and a pacing protocol undertaken. The pressure-Doppler wire was then re-sited in the main pulmonary artery for pulmonary flow and the pacing protocol repeated.

Processing waveform data and PWV

Non-invasive ensemble averaged carotid pressures were used as a surrogate for ascending aortic pressure and together with aortic flow velocity were processed using MATLAB (MathWorks, MA) for wave intensity, pulse wave and wave decomposition analysis.(7)

Invasive waveform data was processed using a similar protocol to previously published work.(2, 4) Data was imported into CardiacWaves (King's College London, UK). Wave intensity analysis was performed using previously described methods.(4, 13) A polynomial filter was used to refine the derivates of aortic/ pulmonary pressure and velocity signals, using a Savitzky-Golay convolution method.(13) The chosen 3-5 beats were gated to the R wave on the ECG, with ensemble averaging of the aortic/ pulmonary pressure, average peak velocity and heart rate.

Wave intensity (dI) was calculated from the time derivatives (dt) of ensemble-averaged aortic/pulmonary pressure (dP) and flow velocity (dU) as shown: $dI = dP/dt \times dU/dt$.(5, 13) Corresponding forward and backward propagating waves were separated assuming a blood density of 1050 kg/m^3 and estimating aortic/ pulmonary wave speed using the sum of squares method.(13) The peak energy carried by the 3 most prominent wave energies were analyzed and recorded in this manuscript; the FCW, FEW and BCW *(Figure 1).*

Processing invasive hemodynamic data

Simultaneous LV pressure and volume were measured and volume calibration was performed off-line post data acquisition using three dimensional echocardiography to obtain LV ejection fraction, LV end-diastolic volume and LV end-systolic volume. Hemodynamic data was recorded on Conduct NT (CD Leycom). Data was sampled at 250Hz and exported into SimpleWires (King's College London). At least ten consecutive cycles were selected, with ensemble average of at least five beats for analysis. The resulting pressure-volume loop was exported to provide invasive hemodynamic data.(14)

Pacing protocol

Biventricular pacing at baseline heart rates was compared with intrinsic rhythm at baseline heart rates. Measurements for patients in sinus rhythm were made in AAI mode, atrial fibrillation in VVI mode and complete heart block in DDD mode. Baseline heart rates were 10bpm above the patient's intrinsic rate or at 70bpm in patients with complete heart block.(4) The atrioventricular delay was set to 120ms and simultaneous ventricular activation.

Definition of CRT responders

Patients were defined as CRT responders if they had a reduction in LV end-systolic volume ≥15% at 6-month follow-up.(1, 15)

Statistical Analysis

Discrete data is presented as n values with corresponding percentages in parentheses and continuous data as means±standard deviation. Responses in the same participants at different pacing settings were compared using a paired 2-sided Student *t* test for normally distributed data and Wilcoxon signed-rank test for non-normally distributed data. A two-sided *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using Prism (GraphPad Software Inc., Version 8, CA) and SPSS (IBM Switzerland, Version 25, Switzerland).

Results

Patient recruitment is shown in *Figure 2,* a flowchart of the study in *Figure 3* and baseline demographics in *Table 1.* All 28 patients underwent successful CRT with a quadripolar LV lead placed in a lateral or posterolateral vein in 25 (89.3%) patients. All patients survived to 6-month follow-up and had >99% biventricular pacing delivery confirmed at 6 months. *Appendix A* provides a sub-group analysis of patients who were in sinus rhythm only and left bundle branch block at baseline.

Non-invasive protocol

Overall, 21 (75.0%) patients were CRT responders and 7 (25.0%) CRT non-responders. Patient demographics include a mean age of 72.9±8.0 years, 53.6% had ischemic heart disease, 85.7% had left bundle branch block, with a mean QRS duration of 158±19ms and a severely reduced LV ejection fraction of 30±8%.

In CRT responders at 6-months, biventricular pacing resulted in a significant increase in the systolic blood pressure (106.8±18.4 vs. 97.9±18.3mmHg;*P*=0.015), mean arterial pressure (84.2±12.3 vs. 77.7±13.7mmHg;*P*=0.046) and central pulse pressure (38.8±15.2 vs. 35.1±14.9;*P*=0.031) but not the diastolic blood pressure (68.0±10.7 vs. 62.8±13.0mmHg;*P*=0.083). There was no significant difference in CRT non-responders at 6-months in the systolic blood pressure, mean arterial pressure or central pulse pressure.

Non-invasive aortic wave intensity at baseline heart rates

In CRT responders, biventricular pacing compared with intrinsic rhythm resulted in an immediate increase in the FCW (2.1[1.3-2.8] vs. 1.4[1.1-2.0]W/m^2/s^2×10^6;*P*=0.006) but not the FEW and BCW *(Figure 4 and Table 2).* There was no significant difference in the timing

of the FCW wave (35.7 vs. 37.9ms;*P*=0.255). These findings were maintained at 6-months, with a significant increase in the FCW (*P*=0.025). These effects were not seen in CRT non-responders.

PWV

In CRT responders, biventricular pacing resulted in a significant reduction in the PWV acutely (0.5±1.2m/s;*P*=0.021) and a non-significant reduction at follow-up (0.7±1.6m/s;*P*=0.086) when compared with intrinsic rhythm. There were no significant differences in changes from baseline in PWV in CRT non-responders.

Invasive protocol

The invasive study was used to validate the major findings of the non-invasive study. 11 patients underwent an invasive protocol with 11 aortic and 7 pulmonary electrophysiology recordings. Acquisition of pressure-volume loop data was attempted in all cases but successful in 9 patients since there was significant interference during data collection in 2 patients preventing reliable recordings. There were no acute complications arising from this study.

Overall, 7 (63.6%) patients met the study definition for CRT response. Patients demographics include a mean age of 68.1±9.1years, QRS duration of 151±18ms and severely impaired LV ejection fraction of 27±9% (*Table 1).* In CRT responders, biventricular pacing resulted in a significant increase in the CO (4±2 vs. 3±2L/min;*P*=0.002) and reduction in SVR (26±10 vs. 44±26mmHg min/L;*P*=0.040) (*Table 3).* There was no significant difference in CO nor SVR in CRT non-responders. All CRT responders showed an acute hemodynamic improvement in LV dP/dt_{max} >10% which was not seen in any of the non-responders.

Invasive aortic wave intensity and correlation between aortic flow and myocardial contractility

In CRT responders, biventricular pacing compared with intrinsic rhythm resulted in a significant increase in the FCW acutely (8.3[4.4-8.4] vs. 4.8[3.0-7.0]W/m^2/s^2×10^5;*P*=0.023) *(Appendix B)* and shorter time to peak FCW (50.0 vs. 55.0ms;*P*=0.020). These effects were not seen in CRT non-responders. The relative change in LV dP/dt$_{max}$ strongly correlated with the change in aortic FCW (R_s 0.733;*P*=0.025).

Invasive pulmonary wave intensity following CRT

There were 4 (57.1%) CRT responders and 3 (42.9%) CRT non-responders who underwent pulmonary flow assessment *(Appendix B).* In CRT responders, biventricular pacing resulted in a significant reduction in the FCW (0.8[0.4-1.2] vs. 1.2[0.8-1.6]W/m^2/s^2×10^5; *P*=0.004) and FEW (*P*=0.030) (*Appendix B*). Biventricular pacing resulted in a significantly longer time to the peak FCW (72.5 vs. 47.5ms;*P*=0.009) and FEW (268.8 vs. 212.5ms;*P*=0.014). These changes were not seen in CRT non-responders.

Discussion

To our knowledge, this is the first study to comprehensively examine the effects of biventricular pacing on aortic and pulmonary flow and determine its effects on SVR and PWV. Although wave intensity analysis has traditionally been measured invasively, we sought to determine the effects of CRT both acutely and chronically, requiring us to use a combination of invasive and non-invasive measurements. We found in CRT responders there was a:

1. Significant increase in CO and decrease in SVR. There was a significant reduction in the PWV acutely and a non-significant reduction chronically.
2. Significant increase in the aortic FCW both acutely and chronically.
3. Strong positive correlation between maximal rise in LV pressure and aortic FCW
4. Significant reduction in the pulmonary FCW and FEW.

This study demonstrates that in CRT responders there are significant changes to both the cardiac and vascular system. Principally, there is an increase in myocardial contractility and LV dP/dt_{max}, and vascular changes with a resulting decrease in afterload. These combined changes lead to an increased CO, stroke work and mean arterial blood pressure.

Effect of CRT on aortic pressure/ flow waves

The heart is part of an integrated system. Changes in cardiac contractility and perfusion are affected by preload and afterload, both of which dynamically respond to changes in cardiac function. The effects of CRT on coronary flow has previously been investigated,(2, 4) and demonstrate that biventricular pacing increases coronary flow in the left anterior descending artery by increasing the backward expansion wave and homogenizing wave timings that determine flow in the left anterior descending and circumflex arteries. The effects of CRT on

aortic flow are not well described. Fok et al. showed in hypertensive patients that dobutamine increased the FCW by a greater proportion than in normotensive patients.(7) Dobutamine partly exerts its effects through improving myocardial contractility and this improved contractility is evident in CRT responders. The current study demonstrates that in CRT responders there is a significant increase in the FCW both acutely and chronically. The relative change in acute LV pressure strongly correlated with the FCW at baseline heart rates suggesting that as LV pressure increases, from improved myocardial contractility, so does aortic forward flow in early systole. The aortic forward flow can only increase if systemic impedance does not rise in parallel with the rise in LV pressure. When measured invasively, the timing to the peak FCW occurred significantly earlier in the cardiac cycle which may enable longer diastolic filling and improved cardiac function.

Effect of CRT on pulmonary pressure/ flow waves

The effect of CRT on pulmonary wave intensity, to our knowledge, has not been previously described. In an invasive study of 31 patients investigating pulmonary flow, patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension were shown to have a significantly higher FCW and FEW compared with control subjects.(6) Severe LV systolic impairment is a common cause of post-capillary pulmonary hypertension. We demonstrated that in patients with severe LV systolic impairment who respond with CRT, biventricular pacing resulted in a significant reduction in the FCW and FEW. The time to the peak FCW and FEW was also significantly longer, in keeping with biventricular pacing allowing for more effective LV relaxation and filling, thereby increasing preload which in turn increases CO evidenced by a significant increase in the LV dP/dt_{min}.

Effect of CRT on afterload

The effect of CRT on afterload has not been comprehensively investigated to our knowledge. The two major components of afterload or impedance are PWV and SVR.(16) PWV determines the characteristic impedance which is afterload when pressure and flow are rapidly changing at the beginning of systole. However, SVR is the steady state afterload. Importantly, a greater aortic FCW can only generate greater flow if impedance remains constant or falls. In the current manuscript, we have shown that CRT responders have a significant increase in FCW with a concomitant reduction in SVR and PWV acutely and non-significant reduction in PWV at follow-up. Several studies have shown that increased arterial blood pressure is associated with an increase in PWV.(16) Our findings are in stark contrast to these studies where we have shown that CRT responders demonstrate a rise in mean arterial blood pressure, however this was not associated with a rise in PWV. Faconti et al. found a significant reduction in mean arterial pressure despite an increase in PWV after using lower-limb venous occlusion devices.(10) They postulated that these findings were explained by sympathetic activation leading to increased vascular smooth muscle. Our findings could be explained by the increased FCW seen with biventricular leading to greater pulsatility and CO which resulted in decreased baroreceptor activation of the sympathetic nervous system due to a higher pulse pressure and decreased activation of the renin-angiotensin-aldosterone system.

Clinical perspective

This study offers new explanations as to how CRT may exert its benefits in heart failure patients. Understanding the role of the cardiovascular system on CRT response supports considering the cardiovascular system as a whole in CRT patient selection. Therefore, it's important to examine both the cardiac and systemic haemodynamics to understand who will respond best to CRT and how to optimise response. It's possible, for example, that those who

show benefit in cardiac mechanics but not in systemic vascular responses could benefit from additional vasodilator therapy.

Limitations

The study size was small because patients were asked to undergo a rigorous and lengthy invasive and non-invasive protocol, therefore the results may not be generalizable to the whole CRT population. However, our sample size is in keeping with other published studies relating to invasive wave intensity analysis.(2, 4) The invasive protocol carried additional procedural risks and therefore is unlikely to be used in routine clinical practice, although the non-invasive protocol could be adopted. Both groups were matched in terms of sex, aetiology, presence of left bundle branch block, QRS duration and LV ejection fraction. The confidence intervals for hemodynamic and electrophysiology data in CRT non-responders was wide due to a small cohort and consequently we are unable to speculate why they have failed to improve. During the pacing protocol we fixed the patient's heart rate to control for the effect of changes in chronotropy can cause to inotropy, but it should be noted that this will prevent reflex heart rate regulation to alterations in inotropy. No variation in atrioventricular delay was assessed in the current study due to the complexity of the protocol and therefore we could not study the changes in acute hemodynamics which may have occurred with atrioventricular or ventricular optimization. Defining CRT response is heterogenous and can be based on hard and/or soft end-points.(1) The aim of this study was to further investigate the physiological effects of CRT on the cardiac and cardiovascular system and therefore we used patients who displayed evidence of LV remodeling to define CRT response. Although the present study suggests increased FCW in CRT responders, we are unable to provide a cut-off value for predicting response. Further studies with a larger sample size will be needed to determine whether this is possible. Furthermore, the study was underpowered to determine whether changes in FCW were different in patients with non-left bundle branch block and in CRT non-responders whether the FCW worsens or remains static with biventricular pacing. The sample size was too small to draw reliable conclusions from

368 the effect of rhythm (i.e. sinus rhythm versus atrial fibrillation) alone and optimal pre-load
369 was not possible for patients in atrial fibrillation.

Conclusion

This study demonstrates that response to CRT is characterised by an increased FCW, due to increased cardiac contractility, with a reduction in both dynamic (PWV) and steady state components (SVR) of afterload that results in an increased CO. Therefore, both cardiac and systemic vascular responses determine response to CRT which may be particularly important in optimizing therapy and informing patient selection.

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436 **Figure legends**

437 **Figure 1**. The predominant waves seen in aortic and pulmonary flow are displayed. The
438 forward travelling waves consist of the forward compression wave and forward expansion
439 wave. The backward compression wave is the predominant backward travelling wave. Key:
440 BCW=backward compression wave, FCW=forward compression wave and FEW=forward
441 expansion wave

442 **Figure 2**. Patient recruitment into non-invasive and invasive studies

443 **Figure 3.** Flowchart of invasive and non-invasive arms of the study

444 **Figure 4.** Box and whisker plot showing the non-invasive aortic wave intensity at baseline
445 rhythm before cardiac resynchronization therapy and at 6-months with biventricular pacing in
446 different patient groups. Tukey whiskers have been used to represent the data by displaying the
447 box consisting of the median, upper and lower quartiles and the whiskers consisting of the
448 maximum and minimum value followed by any outlining patient data represented by a dot.