Acute haemodynamic effects of increase in paced heart rate in heart failure patients recorded with an implantable haemodynamic monitor

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Introduction

Cardiac resynchronization therapy (CRT) is recommended for patients with drug refractory, advanced heart failure (HF), and evidence of dyssynchrony. Programming of the basic heart rate (HR) remains largely empirical in these patients, although it is a parameter with potential important haemodynamic and clinical impact.

The stepwise increase in contractility with increased stimulation frequency [force frequency relationship (FFR)] originally described in the late 19th century is blunted in isolated muscle strips as well as during atrial and right ventricular (RV) pacing in HF patients. This is thought to contribute to the failure to maintain stroke volume (SV) and increase cardiac output (CO) in response to increased HR and may add to the reduced exercise tolerance in this patient group. Recently, acute haemodynamic studies showed that CRT partly restores the blunted FFR and improves the CO response to increased HR at rest as well as during exercise. These findings have, however, only been studied in the left ventricle. The relationship between biventricularly paced HR (pHR) and RV + dP/dt has not been studied previously. Furthermore, the acute effects of HR increase on RV pressures and pulmonary arterial and systemic vascular resistance remain unclear.

The aim of this study was to investigate the acute effects of different biventricularly paced heart rates (pHRs) on right ventricular (RV) haemodynamics in heart failure (HF) patients with an implantable haemodynamic monitor (IHM).

Methods and results

At rest, seven pHRs, range 60–120 bpm (steps of 10), were randomly programmed and maintained for 60 s in 10 patients (male, 65 ± 12 years, New York Heart Association II–III). Right ventricular systolic (RVSP) and diastolic pressures, estimated pulmonary artery diastolic (ePAD) pressure, and RV + dP/dt were recorded beat-to-beat using the IHM. Cardiac output (CO) was estimated from the RV pressure waveforms and arterial blood pressure was measured (Portapres). To compare the haemodynamic effects of increased pHR at rest to that of spontaneous, sinus-driven heart rate (HR) increase, patients also performed a symptom-limited bicycle exercise. At rest, RV + dP/dt increased significantly with elevated pHR (P, main effect, <0.001), whereas filling pressures (ePAD and RVSP) decreased significantly in the range 60–100 bpm (P < 0.03 and P < 0.003, respectively) but tended to increase or level out at pHRs >100 bpm. At a pHR of 100 bpm, ePAD was 1.4 mmHg lower compared with 60 bpm (P < 0.01). Cardiac output increased gradually with elevated pHR at rest (P < 0.001). Both total peripheral and estimated pulmonary arterial resistance significantly decreased with increased pHR. During exercise-induced maximum HR increase, RV + dP/dt, ePAD, and CO were all significantly higher compared with the corresponding pHR at rest.

Conclusion

During cardiac resynchronization therapy in HF patients, the force frequency relationship is present in the RV, as increasing the pHR in the range 60–100 bpm results in decreased filling pressures and increased CO.

Keywords
Cardiac resynchronization therapy • Heart failure • Heart rate • Haemodynamic
haemodynamic monitor (IHM) providing continuous central haemodynamic data derived from RV pressure measurements. Furthermore, we compared the haemodynamic effects of an increased pHr and spontaneous sinus-driven HR elevation during exercise.

## Methods

### Patient population

Ten CRT patients received an IHM (Chronicle®, Medtronic Inc., MN, USA). Patients were implanted with a commercially available atrioventricular pacing device (InSyncIII®, Medtronic Inc.) at least 3 months prior to the study and were considered treatment responders based on improvements in New York Heart Association (NYHA) class and/or 6-min walking distance (10%). The initial indication for CRT was drug-refractory NYHA class III HF with QRS duration of ≥130 ms with left bundle branch block pattern morphology. Patients with uncorrected congenital heart disease, tricuspid or pulmonic stenosis, a mechanical right heart valve prosthesis, a terminal illness unrelated to their HF with life expectancy <1 year, or subjects who were expected to undergo heart transplantation within 12 months were excluded from IHM implantation. The investigation conformed to the principles of the Helsinki declaration. The study was approved by the local Ethics Committee, and all subjects gave their written informed consent.

### Baseline echocardiography

A baseline echocardiographic investigation was performed within 1 week before the study. Cardiac dimensions and systolic and diastolic functions were evaluated according to the guidelines. In addition, CRT treatment was optimized by tuning of the atrioventricular delay (AVD) according to the mitral valve inflow profile and selecting the ventricular-to-ventricular pacing delay (VVD) yielding the largest aortic velocity time integral (VTI). Mean optimized paced AVD was 138 ± 12 ms (range: 120–150 ms) and VVD optimization resulted in left ventricular pre-activation in all patients (mean: 22 ± 12 ms, range: 4–40 ms).

### Pacing protocol and data analysis

Patients were evaluated in the resting supine position. After a resting period of at least 10 min, seven different HRs (60, 70, 80, 90, 100, 110, and 120 bpm) were programmed in randomized order and maintained for 60 s. Each of these steps was preceded by a 60 s period of pacing at 70 bpm to allow for haemodynamic recovery. AVDs and VVDs were left unchanged throughout the protocol. To allow for haemodynamic adaptation after changing the pHr, the median haemodynamic values measured during the last 40 s of each programming step was used in the analysis. The protocol was repeated in the same way after 1 week, and all values were calculated as the mean of these two measurements.

### Exercise protocol

To compare haemodynamic effects of pHRs at rest with spontaneous sinus-driven HR elevation, symptom-limited bicycle exercise was performed after the pacing protocol at Visit 1. Baseline haemodynamics were recorded for 3 min in a resting seated position on the bicycle before exercise. The initial workload was set to 30 W (10 W in three patients with anticipated low exercise capacity) and maintained for 2 min. The workload was then increased with 10 W/min till exhaustion. Haemodynamics during exercise were assessed during three conditions: at baseline, at the last completed workload (HR_{MAX}), and at the workload yielding ~50% of the HR increase achieved at HR_{MAX} (HR_{50%}). Haemodynamics measured at HR_{50%} and HR_{MAX} were then compared with those measured at similar HR increases from baseline during the pacing protocol at rest. Similar to the protocol at rest, a median of haemodynamic values obtained during the last 40 s at each workload was analysed.

### Right ventricular haemodynamics

Right ventricular haemodynamic parameters were measured with an IHM (Chronicle®) in a beat-to-beat fashion. Briefly, this device consists of a memory device implanted subcutaneously in the subclavicular region, and a pressure sensor carrying lead that is passively fixed in the RV outflow tract. The IHM continuously stores the following parameters: RV systolic pressure (RVSP), RV diastolic pressure (RVDP), RV pulse pressure, systolic time interval (STI), pre-ejection interval (PEI), maximum rate of pressure increase in the RV (+dP/dt), and maximum rate of pressure decrease in the RV (−dP/dt). Moreover, the pulmonary artery diastolic pressure can be estimated (ePAD) by measuring the RV pressure at +dP/dt (occurring at the opening of the pulmonary valve). The ePAD correlates with actual pulmonary artery pressures under various haemodynamic circumstances. The system requires a brief pre-insertion calibration procedure at implantation. Previous validation of the sensor’s accuracy and precision using serial comparisons with simultaneously acquired balloon-tipped catheter values showed a small baseline error at 12 months that was similar to the error at the time of implantation (<1.0 mmHg). In addition, we computed the estimated mean pulmonary arterial pressure by applying the formula:

\[ e\text{MPAP} = (\text{STI} \times \text{RVSP}) + (\text{DTI} \times \text{ePAD}) \times \frac{1}{\text{RR}} \text{ (mmHg)} \]

where DTI (diastolic time interval) = RR-interval − STI (ms). During the acute study protocol, the IHM was programmed to high-resolution sampling (beat-to-beat pressure recordings from the RV).

### Cardiac output and pulmonary arterial resistance

We recently presented an algorithm for the estimation of changes in SV and CO from parameters stored by the IHM. In short, the algorithm is based on the transformation of peak pressure difference during the ejection phase (RVSP−ePAD) to maximal velocity using the simplified, reversed Bernoulli equation. This velocity difference is then multiplied by the ejection time (STI−PEI) to approximate a VTI. Conversion of this estimated RV VTl to CO requires information on each patient’s RV afterload, RV outflow tract cross-sectional area, and HR. For the purpose of this study, we considered the RV cross-sectional area and RV afterload to be a patient-specific constant and present %−changes in CO and CO-derived variables rather than the absolute values. The IHM-derived CO was also used to estimate pulmonary arterial resistance (ePAR) using the formula:

\[ e\text{PAR} = \frac{e\text{MPAP} \times 80}{\text{CO}} \text{ (arbitrary units)} \]

### Arterial blood pressure and total peripheral resistance

Arterial systolic (ASBP, mmHg), diastolic (ADBP, mmHg) and mean (mmHg) blood pressure were measured beat-to-beat using a Portapres® device (Finapres Medical Systems, The Netherlands).
Total peripheral resistance (TPR) was calculated by the formula:

\[
TPR = \frac{AMBP \times 80}{CO} \text{ (arbitrary units)}
\]

**Statistical analysis**

Statistical analysis was performed using Statistica\textsuperscript{TM}, release 7 (Statsoft, Inc., Tulsa, OK, USA). Repeated-measures ANOVA was used to analyse changes in haemodynamic parameters with different HRs both over the whole range of tested HRs (60–120) as well as in the ‘clinical relevant’ range (60–100). If a significant main effect was found, post hoc analysis was performed with Fisher’s least significant difference. However, if data did not conform to the assumption of sphericity, planned comparisons were performed instead. A two-way repeated-measures ANOVA was used to analyse the haemodynamic effects of paced vs. spontaneous sinus-driven HR increase. To correct for repeated measurements, significance was accepted at \( P < 0.01 \) and trends were considered at \( 0.01 < P < 0.02 \). However, for comparison between paced and spontaneous sinus-driven HR increases, significance was accepted at \( P < 0.025 \). The correlation coefficient between pHR and RV + dP/dt was calculated with the least-square approach. Both linear and second-degree polynomial equations were tested for best fit. Data are shown as the mean ± SD. However, for clarity, results are shown as the mean ± SEM in Figures 1 and 2.

**Results**

Patient characteristics are presented in Table 1. Mean age of the 10 male patients was 65 ± 12 years. Seven of the patients had ischaemic cardiomyopathy and three had idiopathic dilated cardiomyopathy. Patients were on optimal medical therapy according to the HF guidelines\textsuperscript{1} and had been treated with CRT for on average 16 months (range: 4–62 months). All patients completed the protocol on both occasions without complaint. Two patients had an intrinsic HR >70 bpm (mean: 72 and 74, respectively).

**Haemodynamic effect of increase in paced heart rate at rest**

There was a positive correlation between RV + dP/dt and pHR in the total range of tested HRs (Figure 1). A second-degree polynomial equation provided the best fit of the trend line (RV + dP/dt = 0.02 × HR\textsuperscript{2} – 2.2 × HR + 361, \( R^2 = 0.95 \)). Compared with that at 60 bpm (304 ± 106 mmHg/s), RV + dP/dt was significantly higher at 110 bpm (379 ± 123 mmHg/s, \( P = 0.004 \)) and 120 bpm (384 ± 118 mmHg/s, \( P = 0.001 \)), and there was a trend towards increased RV + dP/dt at 100 bpm (347 ± 107 mmHg/s, \( P = 0.01 \)).

The effects of different biventricularly pHRs on CO, ePAD, and RV pressures are summarized in Figure 2. Cardiac output increased significantly with increase in biventricularly pHR in the range 60–120 bpm (\( P \), main effect, <0.001). This increase in CO was attributed to increased HR since SV decreased significantly from 80 bpm and above (Table 2). Estimated pulmonary artery diastolic pressure decreased significantly in the range 60–100 bpm (\( P \), main effect, <0.03) and was significantly lower at 90 bpm (17.8 ± 7.4 mmHg, \( P = 0.004 \)) and 100 bpm (17.7 ± 7.6 mmHg, \( P = 0.005 \)) compared with 60 bpm (19.1 ± 7.7 mmHg). Similar to ePAD, RVDP and RVSP also decreased significantly with increase in pHR in the range 60–100 bpm. When HR was further increased (>100 bpm), there was a tendency that the initial decrease in ePAD, RVDP, and RVSP levelled out or even reversed (Figure 2).

Both ePAR and TPR decreased significantly in the whole range of tested HRs (\( P \), main effect, <0.001 for both). The acute effects of increase in biventricularly pHR on other haemodynamic variables are presented in Table 2.

**Figure 1** Correlation between biventricularly paced HR and RV maximum pressure rise (RV + dP/dt). A second-degree polynomial fit best describes the correlation between pHR and RV + dP/dt. Data are expressed as the mean ± SEM. *\( P < 0.01 \) vs. 60 bpm; †0.01 < \( P < 0.02 \) vs. 60 bpm.
Haemodynamic effect of spontaneous sinus-driven heart rate increase during exercise

During exercise, HR increased by $16 \pm 6$ bpm at HR$_{50\%}$ ($50 \pm 21$ W) and $31 \pm 11$ bpm at HR$_{MAX}$ ($81 \pm 26$ W). The corresponding measurements during the pacing protocol at rest were performed at HR increases of $17 \pm 5$ and $33 \pm 10$ bpm, respectively. At HR$_{MAX}$, RV + dP/dt increased by $111 \pm 84\%$ during exercise compared with $14 \pm 12\%$ during pacing ($P < 0.001$; Figure 3). Estimated pulmonary artery diastolic pressure increased by $108 \pm 48\%$ during exercise ($P < 0.001$ HR$_{MAX}$ vs. baseline [BL]), whereas it significantly decreased during pacemaker stimulation ($-9 \pm 7\%, P = 0.001$). As expected, CO increased significantly more during exercise compared with pacing at rest. This was primarily due to the fact that SV increased during exercise, whereas it decreased during pacing at rest.

Table 1 Baseline characteristics

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<th>Patient number</th>
<th>Age (years)</th>
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<th>NYHA</th>
<th>Rhythm</th>
<th>CRT (months)</th>
<th>Medication</th>
<th>LVEDD (mm)</th>
<th>EF (%)</th>
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</table>

ICM, ischaemic cardiomyopathy; DCM, idiopathic dilated cardiomyopathy; SR, sinus rhythm; AF, atrial fibrillation; BB, beta-blockers; ACE-I, angiotensin-converting enzyme inhibitor; DIU, diuretics; SPIR, spironolactone; ARB, angiotensin receptor blocker; DIG, cardiac glycosides; LVEDD, left ventricular end-diastolic diameter; EF, ejection fraction.
The main finding in this study is that, during resting conditions, increased pHR improves haemodynamics in CRT-treated patients in the range 60–100 bpm. We found a reduction in left ventricular (LV) filling pressures (ePAD), an increase in CO, and reduced ePAR and TPR with a pacing-induced HR increase in the same range. However, when HR was further increased, RV \( \frac{dP}{dt} \)
and CO continued to increase, whereas filling pressures and RV pressures tended to level out or even increase. Vascular resistance decreased continuously even at higher HRs.

Previous studies using atrial pacing in HF patients showed no improvements in the FFR by high-rate pacing. In contrast, in recent years, it has been shown that simultaneous pacing in both chambers (CRT) improves the blunted FFR in the left ventricle at high HRs (70–140 bpm), whereas RV pacing does not. Our study extends these findings by demonstrating that, in CRT patients, a significant FFR is observed in the RV during biventricular stimulation. Notably, however, the slope of the FFR was smaller in the lower range of HRs. Increasing the pHR by 20 bpm between 60 and 80 bpm increased RV + dP/dt by 10 ± 27 mmHg/s, whereas a 20 bpm increase in the range 100–120 increased RV + dP/dt by 37 ± 25 mmHg/s. The second-degree polynomial equation best described the correlation between pHR and RV + dP/dt at a group level as evident by the close fit through mean values and a superior fit comparing individual data points in the majority of patients (6 of 10). However, three patients displayed a linear correlation in the range of tested HRs and one patient showed a flat response in the majority of patients (6 of 10). The explanation of these individual differences warrants further investigation.

Most studies describing the FFR in isolated muscle strips from failing hearts have shown that contractility increases from low to moderate frequencies and then levels off or decreases at HRs >90–100 bpm. In the experimental setting of isolated muscle strips, the contractility response to increased stimulation frequencies is preload independent. In the present study, the measurement of contractility was preload dependent, and it may be speculated that the less pronounced FFR at lower HRs was, at least partly, attributed to the concomitant decrease in filling pressures in the lower range of HRs.

We did not control for different pacing modes (i.e. RV- or atrial only pacing) and, therefore, further studies are needed to investigate how the RV FFR demonstrated in this study is affected by different pacing modes.

Previous studies reported that cardiac filling pressures remain unchanged with biventricularly pHRs in the range between 80 and 120 bpm. In this study, ePAD and RVSP decreased significantly when HR was increased in the range 60–100, suggesting that filling pressures can be acutely lowered by increasing the pHR up to 100 bpm. Notably, the effect on filling pressures was predominately seen when HR was increased from a low level (i.e. 60 bpm). Similar to the findings by Steendijk et al., we found that filling pressures levelled out or even increased when HR was further increased to rates >100 bpm. This implies that the association between pHR and filling pressures is not linear over the entire range of HRs and that a decrease in filling pressures is only achieved with HR elevation within the lower HR range.

This deserves attention as the lowering of filling pressures represents a common goal in the management of HF patients. Thus, a temporary increase in the pHR may be considered to alleviate congestion in CRT patients with symptoms of decompensated HF.

Cardiac output gradually increased at higher pHRs due to the increase in HR, whereas SV did not increase and even dropped at and above the rate of 80 bpm. This finding is in line with a recent publication by Voss et al. using electrical velocimetry. A possible explanation of the CO increase is that increased contractility due to the restored FFR facilitated the maintenance of SV, although preload is reduced with a shortened diastolic filling time. In addition, higher pHRs were associated with a reduced afterload indicated by a decrease in both ePAR and TPR. This may also facilitate the maintenance of SV at higher HRs. The afterload reduction was observed along with decreasing LV filling pressures and increasing ADBP. The afterload reduction may be explained by a reflex sympathoinhibition induced by increased pHRs. Using a lower body negative pressure model in HF patients, Azevedo et al. elegantly showed that a selective reduction in LV filling pressures acutely decreases cardiac norepinephrine spillover, presumably attributed to reflex sympathoinhibition mediated by cardiopulmonary stretch receptors. Therefore, we may speculate that the CO gain with higher HRs is partly attributed to vasodilation due to reflex sympathoinhibition mediated by arterial baroreceptors. Therefore, we may speculate that the CO gain with higher HRs is partly attributed to vasodilation due to reflex sympathoinhibition mediated by arterial baroreceptors. To support this hypothesis, reflex sympathoinhibition by rapid pacing has been described previously in patients with depressed left ventricular function. However, further research is needed to elucidate the exact mechanisms behind the CO gain and vascular resistance decrease demonstrated in this study.

To put the findings obtained during pacing at rest into a physiological context, haemodynamic responses were compared with those measured during a similar HR increase induced by exercise. Owing to chronotropic incompetence in some patients, the mean HR increase achieved during exercise was small. As expected, the additional effect of sympathetic activation and increased preload caused substantially greater haemodynamic changes compared with corresponding increases in the basic HR at rest.

The usefulness of shortening the AVD with increased HR in CRT patients remains controversial. Therefore, we choose to maintain the same AVD at all tested HRs both at rest and during exercise. Although concerns may be raised about this strategy, a suboptimal AVD at elevated HRs would potentially have resulted in diminished preload and subsequent reduction in CO and RV + dP/dt. Therefore, we believe that the possibility of a suboptimal AVD at higher HRs did not significantly affect the results or conclusions presented in this study.

Our study also demonstrates that haemodynamic assessment of CRT patients can be performed by information that is generated by an implantable sensor. Such a concept may prove valuable for the haemodynamic optimization of device programming and the guidance of treatment during long-term follow-up in HF patients. However, in the future, haemodynamic sensors may be rather incorporated into CRT pacemakers or defibrillators, thus obviating a dual device implant.

**Limitations**

This study has several limitations. The limited number of patients included in this study and the acute setting of the protocol limit the clinical implication of the conclusions derived from this study. In this study, we used an implanted monitor for haemodynamic assessment. Although the long-term accuracy of the
pressure sensor has been validated against right heart catheterization, this method does not represent the gold standard. No data on left atrial pressures can be provided, and CO has been estimated from characteristics of the RV pressures curve. Of note, TPR and ePAR were measured without information about the central venous pressure, pulmonary capillary wedge pressure or left atrial pressure, and changes in these parameters might confound our results regarding the vascular resistance.

Conclusions

During CRT in HF patients, the FFR is present in the RV, as increasing the biventricularly pHr in the range 60–100 bpm results in decreased filling pressures and increased CO. These findings have possible implications for the programming of HRs in certain clinical settings. However, studies evaluating the impact on energy metabolism and clinical endpoints are required to better determine the ‘optimal’ pHr to be programmed in CRT patients on the short and the long terms.

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References

1. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008;10:933–89.


