# Haemodynamic optimization of Cardiac Resynchronization Therapy

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A thesis submitted to Imperial College

for the degree of

Doctor of Philosophy

International Centre for Circulatory Health

Imperial College NHS Trust

National Heart and Lung Institute

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Re-submitted with minor revisions on 06/06/14

Words: 57,008

# Abstract

Heart failure carries a very poor prognosis, unless treated with the appropriate pharmacological agents which, have been evaluated in large randomized clinical trials and have demonstrated improvements in morbidity and mortality of this cohort of patients. A significant proportion of these patients develop conduction abnormalities involving both the atrioventricular node and also the specialised conduction tissue (bundle of His and Purkinje fibers) of the ventricular myocardium which is most commonly evidenced by the presence of a wide QRS, typically left bundle branch block. The net effect of these conduction abnormalities is inefficient filling and contraction of the left ventricle. The presence of these conduction abnormalities is an additional strong marker of poor prognosis. Over the last 15 years pacing treatments have been developed aimed at mitigating the conduction disease. Large scale randomized multicentre trials have repeatedly demonstrated the effectiveness of cardiac pacing, officially recognized as cardiac resynchronization therapy (CRT). This mode of pacing therapy has undoubtedly had a positive impact on both the morbidity and mortality of these patients.

Despite the large advancement in the management of heart failure patients by pacing therapies, a significant proportion of patients (30%) being offered CRT are classed as non-responders. Many explanations have been put forward for the lack of response. The presence of scar at the pacing site with failure to capture or delayed capture of myocardium, too much left ventricular scar therefore minimal contractile response, incorrect pacing site due to often limited anatomical options of lead placement and insufficient programming i.e optimization, of pacemaker settings such as the AV and VV delay are just some of the suggested areas perceived to be responsible for the lack of patients' response to cardiac resynchronization therapy.

The effect of optimization of pacemaker settings is a field that has been investigated extensively in the last decade. Disappointingly, current methods of assessing the effect of optimization of pacemaker settings on several haemodynamic parameters, such as cardiac output and blood pressure, are marred

with very poor reproducibility, so measurement of any effect of optimization is close to being meaningless.

Moreover, detailed understanding of the effects of CRT on coronary physiology and cardiac mechanoenergetics is equally, disappointingly, lacking.

In this thesis, I investigated the acute effects of cardiac resynchronization therapy and AV optimization on coronary physiology and cardiac mechanoenergetics. This was accomplished using very detailed and demanding series of invasive catheterization studies. I used novel analytical mathematical techniques, such as wave intensity analysis, which have been developed locally and this provided a unique insight of the important physiological entities defining coronary physiology and cardiac mechanics.

I explored in detail the application and reliability of photoplethysmography as a tool for non-invasive optimization of the AV delay. Photoplethysmography has the potential of miniaturization and therefore implantation alongside pacemaker devices.

I compared current optimization techniques (Echocardiography and ECG) of VV delay against beat-to-beat blood pressure using the Finometer device and defined the criteria that a technique requires if such a technique can be used meaningfully for the optimization of pacemaker settings both in clinical practice and in clinical trials.

Finally, I investigated the impact of atrial pacing and heart rate on the optimal AV delay and attempted to characterize the mechanisms underlying any changes of the optimal AV delay under these varying patient and pacing states.

In this thesis I found that optimization of AV delay of cardiac resynchronization therapy not only improved cardiac contraction and external cardiac work, but also cardiac relaxation and coronary blood flow, when compared against LBBB.

I found that most of the increase in coronary blood flow occurred during diastole and that the predominant drive for this was ventricular microcirculatory suction as evidenced by the increased intracoronary diastolic backward-travelling decompression wave.

I showed that non-invasive haemodynamic optimization using the plethysmograph signal of an inexpensive pulse oximeter is as reliable as using the Finometer. Appropriate processing of the oximetric signal improved the reproducibility of the optimal AV delay. The advantage of this technology is that it might be miniaturized and implanted to provide automated optimization.

In this thesis I found that other commonly used modalities of VV optimization such as echocardiography and ECG lack internal validity as opposed to non-invasive haemodynamic optimization using blood pressure. This finding will encourage avoidance of internally invalid modalities, which may cause more harm than good.

In this thesis I found that the sensed and paced optimal AV delays have, on average, a bigger difference than the one assumed by the device manufacturers and clinicians. As a significant proportion of patients will be atrially paced, especially during exercise, optimization during this mode of pacing is equally crucial as it is during atrial sensing.

Finally, I found that the optimal AV delay decreases with increasing heart rate, and the slope of this is within the range of existing pacemaker algorithms used for rate adaptation of AV delay, strengthening the argument for the rate adaptation to be programmed on.

# Declaration

I confirm that the work within this thesis is my own work and that I have appropriately acknowledged the work of others.



Dr Andreas Kyriacou

# Dedication

I dedicate this thesis to my wife, Laura, who has stood by me and supported me throughout this time, and to my children, Liliana and Louis, whose love has been an important catalyst to my work.

I deeply thank my parents, Theodora and Loizos, for their lifelong support and love throughout my studies.

# Acknowledgements

I owe my deepest gratitude to the many people who have supported and guided me through my time in research at the International Centre for Circulatory Health. Their day to day involvement in my work, at all levels, has shaped my research into a body of work, which I will be immensely proud of, for the rest of my life.

Dr Darrel Francis has guided me and taught me the fundamentals of carrying out research, supported and constantly improved any ideas that had arisen throughout the time of this work. His admirable constant attention to detail and his constructive critique have enormously helped me carry out experiments of essence and clinical usefulness. He has been truly inspirational and instrumental to every aspect of this thesis. I also thank:

Dr Zachary Whinnett who has been an invaluable mentor and his extensive experience in the same field of research has been an immeasurably unique advantage for the completion of this thesis.

Dr Punam Pabari who has been a great colleague and friend to work with. She has always been immensely helpful and supportive.

Professors Jamil Mayet and Alun Hughes and Dr Prapa Kanagaratnam and Dr Justin Davies who provided the support and clinical training, central in allowing me to carry out this research. Dr Wyn Davies and Professor Nicholas Peters who have been tremendously supportive throughout my work

Keith Willson who spent endless hours making custom made equipment essential to the success of this thesis.

I am very grateful to the British Heart Foundation for providing me with a Clinical Research Training Fellowship over the three years of my research.

Finally, my gratitude is owed to our patients who generously volunteered to participate in my studies.

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# 1 Backround

Heart failure (HF) is a complex syndrome where the heart is not able to produce sufficient cardiac output to meet the metabolic demands. This is the final common pathway of a number of aetiologies and the mortality from this syndrome is approximately 50% in 5 years.

The injury to the cardiac muscle with loss of a critical quantity of functional tissue can be a result of many diseases but the causes most commonly identified are ischaemic heart disease, hypertension and diabetes (Roger VL. 2011, Lloyd-Jones DM. 2002). Less frequent causes of heart failure include the cardiomyopathies, infective insults, toxins, incessant arrhythmias and valvular heart disease.

The symptomatology and clinical findings are a result of the reduced cardiac output and inefficient venous return. Symptoms of breathlessness, cough, peripheral oedema, tiredness and lethargy and cachexia are just some of the symptoms attributed to the redistribution of blood volume and accumulation of extravascular fluid.

The severity of heart failure can be classified using the New York Heart Association (NYHA) with Class I implying no symptoms with ordinary activity and Class IV being at the most severe end of the spectrum with patients having symptoms at rest. This classification has been shown to be predictive of mortality rates (MERIT-HF Study Group. 1999).

In addition to the severity of heart failure, the QRS width, and specifically left bundle branch block (LBBB) type morphology, had been recognised as an independent marker of poorer prognosis. In fact there seems to be a 15% increase in the mortality with QRS width above 120ms, thought to be a consequence of the mechanical dyssynchrony caused by the delayed ventricular activation from the electrical conduction disease.

Electrical conduction and mechanical synchrony have an intricate association. In the normal heart electrical activation starts endocardially and at the apex with propagation of the wavefront to the

epicardium and base of the heart. This efficient mechanical pump function is facilitated by the distribution His-purkinje system. Therefore any conduction abnormality that would disturb the fine balance of the mechanical activation of the myocardial complex fibre structure will compromise cardiac efficiency. In specific, the electrical consequence of the LBBB is the initial activation of the septal region with very slow propagation via the myocardial (and not the specialised conduction) tissue to the lateral left ventricular segments. At the same time, with the right bundle being intact, there is rapid activation of the right ventricle. The effect of this electrical dyssynchrony is discoordinate left intraventricular myocardial contraction and also interventricular contraction delay. In addition to ventricular dyssynchrony there is also atrial electrical abnormalities with delayed left atrial contraction; the atrial and ventricular dyssynchronies both contribute to a loss of optimal atrioventricular synchrony which negatively affects ventricular filling and stroke volume, exacerbating pump inefficiency.

Dyssynchrony in the failing heart may also occur in the absence of electrical abnormality as a result of the abnormal loading conditions, but treatment by cardiac resynchronization is not appropriate in this scenario (Wang J. 2007, Yano M.1994).

Cardiac resynchronization therapy became a standard therapy for patients who are refractory to optimal medical therapy and fulfil the criteria of QRS >120ms, ejection fraction < 35% and NYHA class III or IV. Cardiac resynchronization therapy improved morbidity and mortality outcomes of these patients (Cleland J.G. 2005, Young J.B. 2003, Abraham W.T. 2002, Cazeau S. 2001, Bristow M.R. 2004, Fox M. 2007). More recent studies (RAFT, REVERSE and MADIT-CRT) have highlighted the importance of the extent of the QRS width, the morphology of the QRS and the severity of heart failure by NYHA class. (Tang AS. 2010, Linde C. 2008 and Moss AJ. 2009).

Patients with wider QRS (>150ms) or LBBB are more likely to benefit from CRT especially so if the severity of heart failure symptoms is mild (NYHA II). The findings of these more recent trials are now reflected by the most recent ESC Guidelines 2012 and 2013 (McMurray JJ. 2012, Brignole M. 2013).

Cardiac resynchronization has demonstrated a mean relative reduction in mortality in the region of 30% and a similar relative reduction in morbidity. Recent data suggest that lifespan gained from CRT follows

a non-linear trend and the benefit is larger in the longer term especially in those patients with lower risk (Finegold JA. 2013).

Unless there is some other heretofore unrecognised effect of pacing, the benefits of CRT on hard outcomes observed in randomised trials can only be attributed to the physiological changes it induces such as increases in cardiac output and possibly a reduction in myocardial oxygen consumption leading to an improvement in cardiac function efficiency, which have been demonstrated in a number of small studies over the last 15 years.

The term "Cardiac Resynchronization Therapy" for biventricular pacing presupposes that restoration of synchrony (simultaneity of timing) between left and right ventricles, and/or between walls of the left ventricle is the mechanism of benefit. But could a substantial proportion of these benefits arise not from ventricular resynchronization but from favourable shortening of AV delay ("AV optimization") which cannot be termed "resynchronization" unless the meaning of the word is stretched to cover any change in timing, thus rendering the word almost meaningless.

It is therefore, far from clear whether the beneficial effects of CRT are a result of the inter/intra ventricular resynchronization or a result of the shortening of the long intrinsic AV interval, very commonly present in these patients, or indeed a varying combination of the two.

Moreover, it is not clear how optimization of AV delay affects the cardiac mechanoenergetics and coronary flow, and whether the modalities used for optimization of CRT in clinical research are valid and sensitive enough to identify the true optimal AV or VV delay and in addition investigate the effects of heart rate and atrial pacing (in sinus rhythm) on the optimal settings.

## 1.1 Pathophysiology of the failing heart

The heart typically pumps blood somewhere between 4-8 L/min. This cardiac output is determined by the stroke volume and the heart rate. Factors such as synergistic ventricular contraction, ventricular integrity and the competence of valves can affect this cardiac output.

Heart failure ensues when there is a reduction in the cardiac output. It can be divided in systolic dysfunction where there is impaired ventricular contraction and ejection of blood volume and in diastolic dysfunction where there is impaired relaxation and filling of the ventricle.

The reduction in the cardiac output leads to systemic hypoperfusion, increase in systolic and diastolic left ventricular volumes and raised LV end-diastolic pressure, increasing left atrial pressure and elevated lung capillaries pressure. Elevated pulmonary capillary pressure leads to pulmonary congestion. Ultimately this leads to right ventricular failure with the presence of oedema in the peripheries.

A number of compensatory mechanisms are activated in heart failure. The reduction in the mean arterial pressure and tissue perfusion are the drivers for the compensatory response. The numerous compensatory mechanisms, neurohormonal and mechanical, are chronically activated in heart failure and the long term effects of these serve to worsen heart failure in a vicious cycle. The Frank- Starling effect and especially the neurohormonal activation play an important role, initially, in maximising compensation. These, along with the increased sympathetic tone, synergistically increase the mean arterial pressure.

The circulating catecholamines and the increased expression of β1, β2, and α1 receptors lead to myocardial toxicity, the effects of which are a further reduction in the ejection fraction which also leads to a higher incidence of tachyarrhythmias.

The chronic haemodynamic stresses on the cardiac muscle lead to remodelling with alterations in geometry such as in size and shape (more spherical) and function of the ventricle.

With time, hypertrophy and/or apoptosis occur in response to this increased stress and myocardium is replaced by fibrotic tissue (Weber K.T 1983). As the function decreases further, filling pressures rise resulting in congestion and mitral filling adopts a restrictive pattern (Salo R.W. 1997).

Unlike a healthy heart with isolated conduction disturbances, in which suboptimal efficiency may impair its function but not lead to impairment of physical capacity or survival, the dilated failing heart may be operating on a knife-edge in which even apparently minor inefficiency is compounded by adverse

feedback processes in a way that impairs capacity and worsens survival. Suboptimal AV and VV conduction are examples of such additional inefficiencies (Salo R.W. 1999).

Therefore development of conduction abnormalities contributes to this vicious cycle by regional desynchronization. The effect of inter-atrial and inter-ventricular conduction delays is to generate ineffective left and right heart atrioventricular delays. This decreases efficiency of transport of blood from atrium to ventricle, and precipitates mitral and tricuspid regurgitation. Interventricular conduction abnormalities also cause paradoxical septal motion; meanwhile extensive intraventricular delays, such as LBBB, result in reduced global ventricular function and impair both systolic and diastolic behaviour.

Clearly, to maximise efficiency of function, the four-chamber heart requires not only synchrony within and between ventricles, but also optimal atrioventricular delay. The latter cannot rationally be termed synchrony (simultaneous timing) because the intention is definitely not to have simultaneous atrial and ventricular contraction. Although it might be argued that the "synchrony" should be stretched to accommodate any change in time (not specifically making timing simultaneous), there are two reasons not to do so. First, using a word in science, in this case of Greek origin, whose etymology (synchronization = same time) does not fully describe the therapy that is delivered by atriobiventricular pacing should be avoided because science demands accuracy and transparency. Second, patients benefit when clinicians understand words and concepts when they read or hear them. When the procedure of biventricular pacing is superseded by the (longer) name cardiac resynchronization therapy, a clinician might reasonably suppose that the newer name must have been adopted because it is more precise, and so conclude that the purpose of the procedure is to bring the ventricular walls into a closer timing relationship with each other. If this turns out not to be the dominant benefit of biventricular pacing, the choice to impose the name "resynchronization" is doing patients a disservice.

## 1.2 Consequence of a long AV interval and ventricular dyssynchrony on mitral flow and effective LV filling time

In prolonged AV conduction, mitral regurgitation can occur in late diastole (Rutishauser W. 1966). This "presystolic mitral regurgitation" was initially observed in patients with complete heart block and normal ventricles. It occurs because atrial systole finishes but ventricular systole does not start immediately: this occurs whenever the AV interval is long.

Doppler echocardiography detects this atrioventricular valve regurgitation in the last diastolic or presystolic period, in patients with complete or first-degree heart block (Rokey R. 1986). Tricuspid and mitral regurgitation are equally common (Panidis I.P. 1986, Schnittger I. 1988).

Patients with wide QRS, can also have presystolic mitral regurgitation as a consequence of prolonged isovolumic contraction and relaxation times. Wide QRS due to LBBB, prolongs mitral regurgitation, by sometimes over 100ms, in patients with EF<35% beyond that caused by a long AV interval alone (Xiao H.B. 1991, Xiao H.B. 1992, Xiao H.B. 1994, Xiao H.B. 1993) .

***Impact of prolonged AV and wide QRS on ventricular filling time***

Xiao et al, cast a spotlight on left ventricular filling time in heart failure. Prolonged AV and wide QRS each decrease LVFT: and thereby reduce stroke volume (Xiao H.B. 1991, Xiao H.B. 1992, Xiao H.B. 1994, Xiao H.B. 1993).

A prolonged AV interval reduces net volume of blood pumped by the ventricle by 2 mechanisms. First, it allows presystolic mitral and tricuspid regurgitation to take place, which means that net forward flow across those valves is smaller than it might otherwise be. Second, long AV time causes fusion of the E and A waves reducing LVFT and thus cardiac output (Figures 1.1 and 1.2).

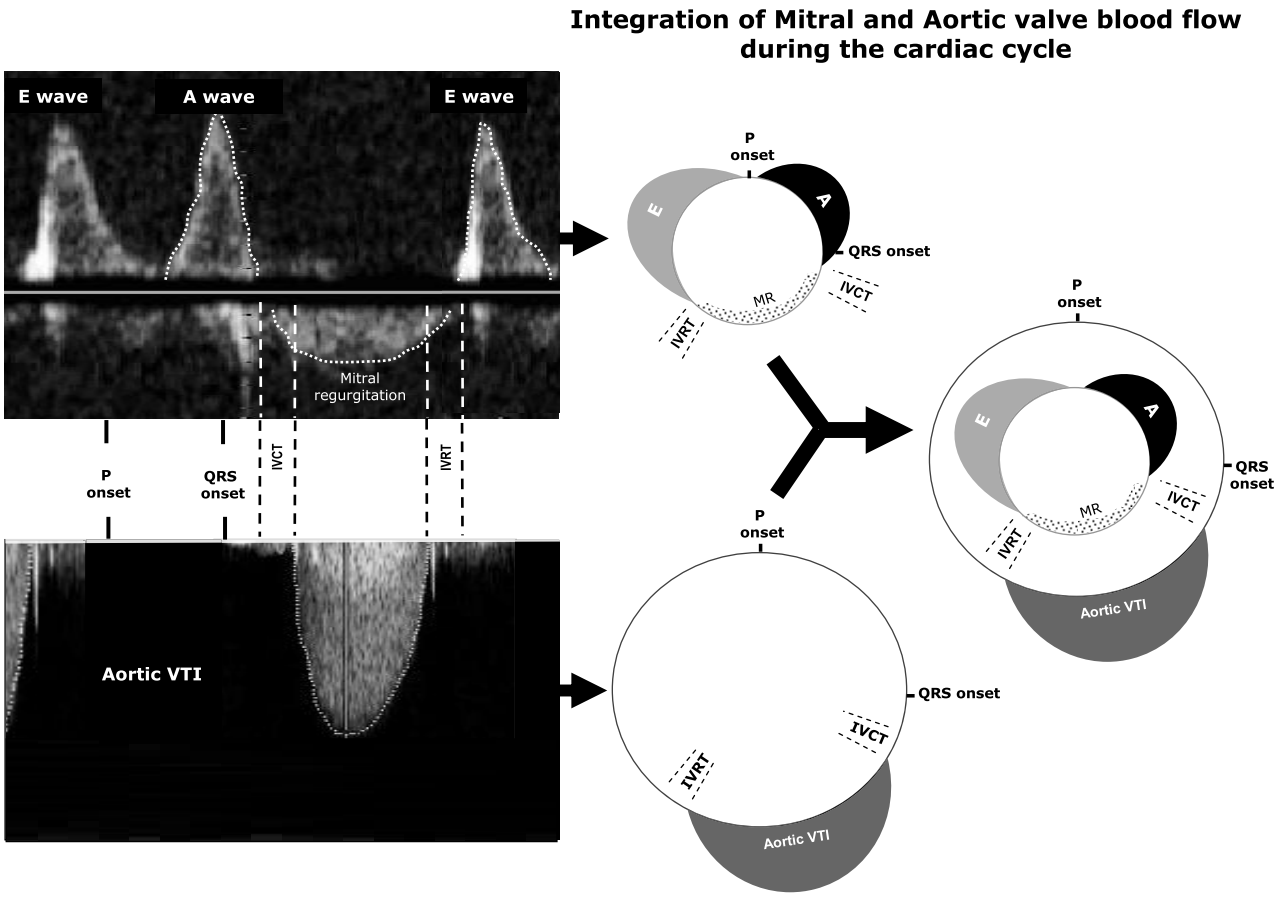


**Figure 1-1. A schematic illustration combining the transmitral and aortic flow during the cardiac cycle**

To simplify understanding of Doppler flows (left), they can be sketched wrapped into a circle, representing the cardiac cycle, starting with atrial activation ("P onset"). The mitral (top) and aortic (bottom) flow traces are inscribed upon inner and outer circles which can be combined into a single diagram (right). This allows clear demonstration of the interaction between timings of activation, forward flow, mitral regurgitation and isovolumic contraction and relaxation times (IVCT and IVRT).

Wide QRS (causing or worsening mechanical dyssynchrony) also impairs LVFT additional to the effect of long AV delay. Wide QRS prolongs isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) by impairing the rate of rise and fall of pressure in the ventricle. Since LVFT is the remnant of the RR interval after the 'bites' taken by ejection time (ET), IVCT and IVRT, all three of which may be prolonged, LVFT has three reasons to be compressed in patients with poor cardiac timings.

Finally, long IVCT and IVRT also prolong the potential for mitral regurgitation to occur while blood is not being ejected forward, thus worsening the balance of blood ejected forward versus backwards, from the ventricle.

***Physiological impact of shortening AV delay by Atrio-biventricular pacing***

CRT can both shorten AV delay and reduce any ventricular dyssynchrony. Pacing by programming the AV delay to a shorter interval alters timing of ventricular contraction with respect to the onset of atrial contraction and ejection. This timing, and its effects on LVFT, has been shown to be important (Meisner J.S. 1985) and it is unlikely to be less important in patients with failing hearts. Shortening a prolonged intrinsic AV interval by pacing, increases ventricular preload at the onset of systole and reduces regurgitation. This manifests as increased stroke volume and cardiac output and optimization of the AV delay will therefore provide maximum benefit.

***Physiological effect of improving ventricular dyssynchrony by atrio-biventricular pacing***

Resynchronising the ventricle should improve the contractile efficiency manifesting as an increase in the rate of change of LV pressure. This reduces IVCT and IVRT: the time the ventricle spends achieving nothing. So on the one hand LV filling time improves and on the other both presystolic and systolic mitral regurgitation decline. These mechanisms improve stroke volume. By optimizing VV delay (in other words maximizing resynchronization by achieving as much simultaneous contraction of left ventricular segments as possible) it is plausible that the physiological effects of resynchronization can be further improved, maximizing therefore benefits for the patients.

The relative contributions to the increment in stroke volume and to the ultimate clinical benefits of shortening the AV delay versus ventricular resynchronization is currently unclear. Figure 1.2 is a sketch illustrating the separate effects of long AV delay and wide QRS on the blood flow across the mitral valve

during the cardiac cycle, and how abnormalities of either or both can disturb effective left ventricular filling time.

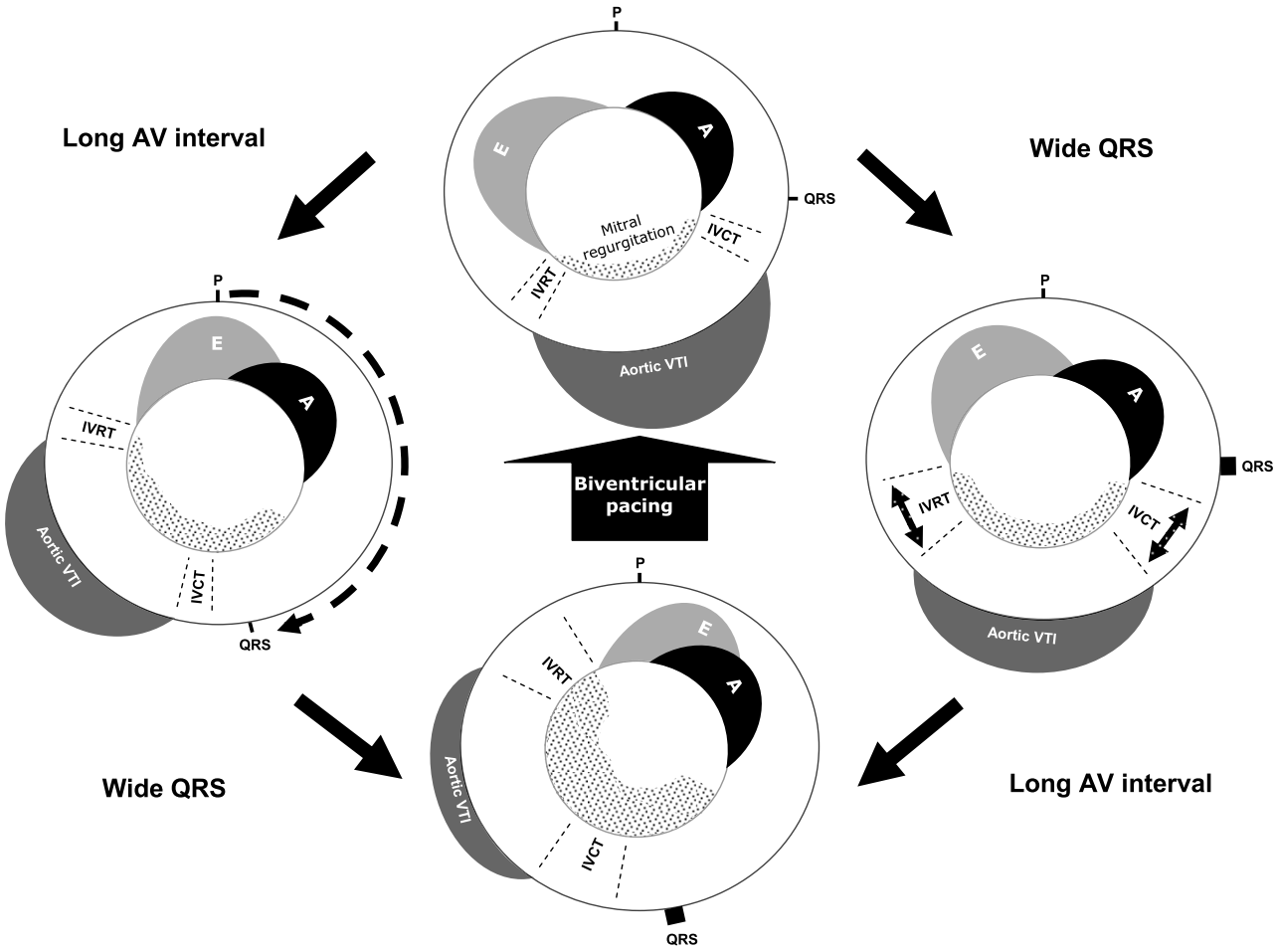


**Figure 1-2. A schematic illustration of the effects of long AV interval, wide QRS width and biventricular pacing on stroke volume**

Each sketch shows transmitral (inner circle) and transaortic (outer circle) blood flow, with in each case atrial activation fixed in time at the top ("P"). The top sketch illustrates blood flow in a subject with normal AV delay and narrow QRS. A prolonged AV interval (left sketch) delays aortic ejection thereby permitting presystolic mitral regurgitation and delaying E wave onset resulting in fusion with the following A wave. A wide QRS (right sketch) causes prolonged IVCT and IVRT, reducing left ventricular filling time and worsening MR. When prolonged AV interval and wide QRS co-exist (bottom sketch), their effects on MR are additive and devastating. Atrio-biventricular pacing corrects both electrical abnormalities and thereby improves stroke volume.

### *Effect of heart rate on LV filling time*

Patients with LBBB and long intrinsic AV interval have critically short LVFT at low heart rates (Mbassouroum M. 1992); LVFT, therefore, does not significantly worsen with increasing heart rate.

Patients with a long intrinsic AV interval but with a narrow QRS have a better LVFT for the same heart rate. However, in these patients, with increasing heart rate LVFT falls more dramatically and stroke volume drops significantly (Mbassouroum M. 1992).

So, once ventricular resynchronization has occurred the LVFT improves but when patients are, for example, exercising and heart rate increases, the LVFT may start to fall (Mbassouroum M. 1992) dramatically. This rate of fall in LVFT with increasing heart rate can be slowed down by adjusting the AV delay (rate adaptive pacing); although the most logic approach is to shorten the AV delay, interestingly, a review (Bogaard M.D. 2010) of the very few studies available, has suggested that this is not universally true; in some patients the AV delay may need to be prolonged or left unchanged for best cardiac output.

Nevertheless, if AV is not adjusted as the heart rate increases, the fall of stroke volume and consequently blood pressure becomes progressively larger (Whinnett Z.I. 2006, Whinnett Z.I. 2008, Whinnett Z.I. 2008, Whinnett Z.I. 2006).

To cast light on which of the two components of biventricular pacing (AV optimization or ventricular resynchronization) is more dominant in improving haemodynamics, cardiac mechanoenergetics and clinical endpoints, one has to look carefully at the existing evidence from (a) small invasive studies that assessed the acute haemodynamic benefits of CRT and (b) large randomised clinical trials.

## 1.3 Results from acute studies

Shortening a prolonged AV interval in dilated cardiomyopathy by atrially sensed RV pacing was demonstrated to be beneficial (Hochleitner M. 1990) long before biventricular pacing was introduced as a mode of treatment. In patients with heart failure and sinus tachycardia with fused E and A waves, shortening of the AV delay during atrial-sensed RV pacing reduced the duration of mitral and tricuspid regurgitation and lengthened the LV filling time (Brecker S.J. 1992). Shortening the AV interval also raised exercise duration and maximum oxygen consumption and reduced the sensation of breathlessness

at peak exercise. Another group of investigators performed atrially sensed RV pacing in patients with severe LV dysfunction and long intrinsic AV delays. The benefit of AV shortening was only evident in those patients with very prolonged intrinsic AV intervals (Nishimura R.A. 1995).

A study which looked at the response of patients paced in AAI and with an intrinsic wide QRS and very long AV delays, showed that atrially-sensed RV pacing increased the cardiac index by 18%, which was half as much as the increase (35%) that atrially-sensed biventricular pacing produced at the optimal AV delay. With RV pacing, left ventricular dyssynchrony is clearly not being corrected (and may actually be aggravated) yet there was a significant haemodynamic improvement suggesting that AV shortening, in that group of patients, was responsible for approximately 50% of the improvement (Leclercq C. 1998).

The PATH-CHF (Aurrichio A. 2002) investigators found that shortening AV delay of patients by with RV pacing achieved improvements in LV $dP/dt_{max}$, aortic SBP and pulse pressure that were ~25-50% of the improvements achieved with full biventricular pacing. Although the improvement in haemodynamics by RV pacing was less than by biventricular pacing, it was far from zero, suggesting that shortening AV delay (which is always part of biventricular pacing) could contribute importantly in the haemodynamic improvements seen during biventricular pacing.

Others found less convincing evidence that atrially-sensed RV pacing offers any acute benefits at all when compared with baseline. In a study (Gold M.R. 1995) of 12 patients with narrower QRS there was no benefit from atrially sensed RV pacing. However, in such patients with narrow QRS, RV pacing induces LV dyssynchrony and therefore impairs LV function, as demonstrated in that study. When the AV delay was shortened there were progressive improvements in haemodynamics, with the optimal AV delay reaching the values of the intrinsic haemodynamics: just managing to compensate for the ventricular dyssynchrony caused by the RV pacing.

Another group of investigators (Kass D.A. 1999) reported that in patients with wide QRS and prolonged AV delay, atrially-sensed biventricular or LV pacing showed significant improvements in LV $dP/dt_{max}$. Atrially sensed RV pacing, although it showed a trend to improved haemodynamics (at the optimal AV delay) of approximately 30-50% of that of biventricular pacing, this was not statistically significant. I

cannot tell from that study alone whether atrially-sensed RV pacing makes a substantial contribution, due to a limited statistical power.

So far I have discussed the impact of atrially-sensed RV pacing versus atrially-sensed biventricular/LV pacing on acute haemodynamics in patients with EF <35%, long intrinsic AV intervals and evidence of dyssynchrony (wide QRS, commonly LBBB).

Therefore, looking at the effects of atrially sensed RV pacing, which is not favourable (in fact, potentially aggravating) for correcting ventricular dyssynchrony, can give insights of the contribution of optimization AV delay. In the studies above it seems that the acute improvement by atrially sensed RV pacing at the optimal AV delay, for example in LV $dP/dt_{max}$, can be 30-50% of that achieved by complete biventricular pacing: AV optimization may not be the dominant component, but neither is it trivial.

Even though in most of the invasive studies mentioned above the optimal AV delay tended to be between 100-120ms shorter than the intrinsic AV interval, assessing the pure effect of shortening AV delay during biventricular/LV pacing is difficult. This is because during the process of AV shortening there are, initially, changes in the LV pre-excitation pattern and therefore ventricular resynchronization.

The two are so closely linked that it is very difficult to decide at which point the 'ventricular resynchronization' is maximal and subsequent effects are purely due to AV shortening.

In reality, both AV optimization and VV synchrony contribute simultaneously; the relative balance is likely to be different between patients, due to different intrinsic AV intervals, severity of ventricular dyssynchrony, and pacing site (RV apex/septum, LV anterior/postero-lateral (Butter C. 2001) etc).

Haemodynamic curves shown in many of the studies described above support this impression.

Whether LV and biventricular pacing are different is less certain. In theory, appropriately timed LV pacing can create fusion with intrinsic conduction, giving a similar effect as biventricular pacing. If intrinsic AV delay is long, this ideal timing of LV pacing may also be long, and so shorter delays such as 80-100 ms might be too short, causing the QRS to widen again, the ventricles to become more

dyssynchronous and haemodynamics to worsen (Derval N. 2010). As a result any benefits from AV optimization, by shortening the AV delay may be offset by ventricular desynchronization.

In atrially sensed biventricular pacing however, ventricular resynchronization is not as dependant on intrinsic conduction because the two pacing leads in RV and LV mean there is less reliance on an intrinsic contribution to activation. With biventricular pacing, greater shortening of the AV delay can be achieved without there being an obligatory cost of inducing ventricular dyssynchrony (Van Gelder B.M. 2005).

Therefore, by observing the haemodynamic effects during progressive shortening of AV delay of biventricular pacing, from intrinsic to very short AV delay, would be another approach to evaluate the effect of optimal AV interval versus the effects of VV synchrony.

During atrially sensed biventricular pacing, the haemodynamic improvement at an AV delay long enough to avoid effects of intrinsic conduction, approximately 30ms short of intrinsic AV interval, should be mostly due to VV synchrony. Any further improvement of haemodynamics with progressively shorter AV delays would be more of a result of improved AV delay.

A number of invasive and non-invasive studies provide this information. In PATH-CHF (Aurrichio A. 2002, Aurrichio A. 2006) when patients were BIV DDD paced 30ms shorter than their intrinsic AV interval, the LV dP/dt and pulse pressure improved on average by 5% and 4%, respectively. Shortening the AV further by on average 50% resulted on average to an additional 10% in LV $dP/dt_{max}$ and 5% in pulse pressure. The initial small increment is mostly from VV synchronization, whereas the subsequent much larger increment can be explained mostly by AV optimization. These findings would suggest that AV optimization may play just as an important role in acute haemodynamic improvements, as VV synchrony does.

## 1.4 Do the results from the clinical trials support AV optimization to be an important determinant of CRT benefits?

There are no clinical trials to date allowing us to assess the efficacy of RV DDD versus BIV DDD, in patients with existing dyssynchrony and ejection fraction of <35%.

PACE (Yu C.M 2009), a small randomised study, of patients with low normal EF (*no* dyssynchrony) and with indications for conventional brady-pacing, compared the effects of atrially sensed RV apical versus biventricular pacing. It reported that 50% of RV paced patients developed dyssynchrony, and at six months RV paced patients had an absolute reduction in ejection fraction by 7.1%, but no observed differences in functional tests, such as 6MWT and QoL (SF-36) questionnaire, were found between RV and biventricular pacing. However, this study was small and of short duration, therefore underpowered to find any true differences between the two study arms. More importantly, it did not address the clinical effect of AV optimization by atrially sensed RV pacing versus biventricular pacing in an *already* dyssynchronous ventricle.

The much larger trial, BLOCK-HF (Curtis AB. 2013), recruited patients with bradypacing indications and with systolic dysfunction (EF <50%) but dyssynchrony was not present in the majority of patients (mean QRS of 124ms). Patients were randomised to conventional RV-apical versus biventricular pacing. A significant less of proportion of patients with biventricular pacing met the primary endpoint (time to death from any cause, an urgent care visit for heart failure that required intravenous therapy, or a 15% or more increase in the left ventricular end-systolic volume index) of the study. This finding undoubtly strengthens the argument of the detrimental effect of apical pacing, which causes dyssynchrony, but unfortunately as with the PACE trial, it is not possible to know from this study the clinical effect of AV optimization by RV apical versus biventricular pacing in an already dyssynchronous ventricle.

Another trial, BIOPACE, will release its results in the next 12 months and may help to provide an insight to the clinical effects of AV optimization.

As a result, it is not yet possible to use this approach, as I have done with the smaller acute studies above, in order to quantify the difference in benefits of AV optimization in a dyssynchronous

ventricle (during atrially sensed RV pacing) from the benefits of both AV optimization and VV synchronization (during atrially sensed biventricular pacing).

The only other current approach of attempting to assess how important AV optimization is versus VV synchrony is to compare the effect of CRT in patients in AF (no AV delay to be impaired, so pure VV resynchronization) versus patients in SR (AV optimization with VV resynchronization). Bigger effects of CRT in SR than in AF would suggest that in SR a substantial element of AV optimization is involved.

Although there are, multiple randomised controlled trials evaluating of CRT in SR, these are lacking for AF. It is therefore a challenge to try and establish the true benefits of CRT in the AF population. A meta-analysis (Upadhyay G.A. 2008) of the few prospective cohort studies looking at the effects of CRT between AF and SR patients suggests that there is clinical improvement in both AF and, as expected, in SR patients when compared to baseline. However, the AF CRT group of patients showed a relative improvement in the 6-min walk test 50% of that of SR CRT, Minnesota quality of life 73% and NYHA class 90% of that of SR CRT.

Ejection fraction, was relatively slightly higher in AF by 5%. However, the authors noted that there was a significant degree of heterogeneity for this outcome.

One other meta-analysis (Wein S. 2010) has also shown that the benefit from CRT obtained by patients with SR was greater than that obtained by patients with AF with respect to 6-MWT and quality of life. No difference in benefit was detected between the SR and AF patients for NYHA class improvement or for ejection fraction.

There are however, a number of limitations from these meta-analyses. Selection criteria and baseline characteristics of patients in different groups varied between the studies. As much as 20% of SR patients developed AF, who in the medically treated SR group were not reliably identified. Also rate control of AF patients in the CRT group, varied from just medical management to AVN ablation.

Perhaps the most convincing evidence that SR CRT may be superior to AF CRT comes from a subanalysis (Hoppe U.C. 2006) of CARE-HF. The same consistent trend, albeit statistically non-significant, is seen in CARE-HF. Some patients spontaneously developed AF post randomization, which was unrelated to which arm they were randomised to. The two post-hoc groups, AF and SR, happened to have very similar baseline characteristics, making it possible to informally compare the effect of CRT between the AF and SR patients. As shown in Table 1-1, the AF group showed a consistent trend to weaker effects of CRT than in SR patients. For example, the numerical value of mortality or unplanned hospitalization for a cardiovascular event reduction was in AF 64% of that of SR, emergency hospitalisation from cardiovascular causes 47%. Improvement of ejection fraction in AF was 50% of that in SR, and elevation in pulse pressure 40% of that of SR.

**Table 1-1. Calculation of the proportion of the benefit seen in sinus rhythm (SR) patients that is seen in atrial fibrillation (AF) patients, in the CARE-HF trial**

| Outcome | Medical Therapy Alone | | Medical Therapy Plus CRT | | Improvement in SR (%) | Improvement in AF (%) | Proportion of the full benefit obtained in AF (%) |
|---|---|---|---|---|---|---|---|
| | SR | AF | SR | AF | | | |
| Primary outcome of main trial, n (%) | | | | | | | |
| Death or unplanned hospitalization for a cardiovascular event | 51.2 | 81 | 34.1 | 63.6 | 33.4 | 21.5 | **64.3** |
| Unplanned hospitalization for a cardiovascular event | 41 | 72.4 | 25.1 | 59.1 | 38.8 | 18.4 | **47.4** |
| Secondary outcome of main trial, n (%) | | | | | | | |
| Death from any cause | 28.3 | 37.9 | 19.2 | 24.2 | 32.2 | 36.1 | **112.4** |
| Death from any cause or unplanned hospitalization with worsening heart failure | 44.2 | 65.5 | 26 | 43.9 | 41.2 | 33.0 | **80.1** |
| Unplanned hospitalization with worsening heart failure | 30.1 | 50 | 14.9 | 31.8 | 50.5 | 36.4 | **72.1** |
| Continuous outcome at 18 months, mean | | | | | | | |
| NYHA class | 2.9 | 2.9 | 2.3 | 2.6 | 20.7 | 10.3 | **50.0** |
| Minnesota Living with Heart Failure score | 39.3 | 41.4 | 30.9 | 38.8 | 21.4 | 6.3 | **29.4** |
| **Variables at 18 months** | | | | | | | |
| Left ventricular ejection fraction, % | | | | | | | |
| Median | 26.4 | 25.9 | 33.7 | 30.1 | 27.7 | 16.2 | **58.6** |
| 25th and 75th percentiles | 22.2/32.3 | 21.6/31.0 | 27.7/41.7 | 25.3/35.3 | | | |
| Pulse pressure | 46.7 | 46.6 | 52.2 | 48.8 | 11.8 | 4.7 | **40.1** |
| Systolic blood pressure, mm Hg, mean±SD | 120.1±19.4 | 116.9±20.0 | 126.2±19.7 | 121.2±15.4 | | | |
| Diastolic blood pressure, mm Hg, mean±SD | 73.4±28.8 | 70.3±9.4 | 74.0±10.6 | 72.4±10.5 | | | |

### *Predictors of Response: QRS, Echocardiographic dyssynchrony or long PR?*

Although QRS width, "electrical dyssynchrony" is at best a crude proxy for mechanical ventricular dyssynchrony, it has been shown in MADIT CRT (Moss A.J. 2009), REVERSE (Linde C. 2008) and PROSPECT (Chung E.S. 2008, Van Brommel R.J. 2009) trials to be a predictor of response to CRT. Conversely, in the PROSPECT trial, mechanical dyssynchrony by various echocardiographic markers, was not found to be predictor of response.

There are two potential reasons why QRS may be a better predictor than echocardiography. Firstly, QRS width is a simple and highly reproducible measure, when carried out automatically, whereas the echocardiographic measures used for dyssynchrony assessment may suffer from poor reproducibility and also from variability in methods between test centres (Chung E.S. 2008, Van Brommel R.J. 2009)

Second, it could be argued that ventricular resynchronization by pacing is an electrical intervention attempting to reorganise electrical conduction and this occurs immediately after implantation (Bleeker G.B. 2007). Prerequisite to success is the presence of adequate viable myocardium and anatomically suitable placement of the LV pacing lead. If there is echocardiographic evidence of ventricular dyssynchrony but its origin is not electrical dyssynchrony then it is possible that pacing might be fundamentally unable to correct the ventricular dyssynchrony.

Most trials which showed endpoint benefits of CRT used only wide QRS as a marker of mechanical dyssynchrony, and did not require confirmation by echocardiographic measures.

The RETHINQ trial (Beshai J.F. 2007), in contrast, enrolled patients with narrow QRS (<130ms) but with mechanical dyssynchrony on echocardiography, failed to show any difference between the CRT group and the control arm. Within this trial, patients with QRS width of 120-130ms had a significant benefit over the control group, compared to the non significant change in patients with QRS less than 120ms; strengthening the argument of using QRS for better predicting the response of CRT, an electrical intervention.

Similarly, the larger trial ECHO-CRT (Ruschitzka F. 2013) recruited patients with a QRS <130ms and evidence of echocardiographic mechanical dyssynchrony. The patients were randomised to CRT on versus CRT off but the study was stopped prematurely due to a higher death rate in the CRT on group. This finding again highlighted the fact that CRT is an electrical treatment for an electrically caused mechanical abnormality (mechanical dyssynchrony).

A sub-analysis of CARE-HF (Gervais R. 2009) also suggested that a long intrinsic AV interval at baseline is a strong predictor of more unfavourable outcomes and this was still the case after three months of CRT. This would suggest that shortening of intrinsic AV interval (i.e more effective AV optimization) is coupled with more successful CRT.

***Chronic studies of VV optimization***

There are three studies that appear to provide data on long term effects of optimization of VV delay of CRT pacemakers. However, all these studies were conducted in sinus rhythm and therefore I do not know for certain that the changes observed are purely due to changes in VV delay and not from the simultaneous effects on AV delay (on one side of the heart or the other).

First, the Decrease-HF (Rao R.K. 2007) study provided a comparison of a fixed zero VV delay against a VV delay determined by a formula based on electrical measurements during intrinsic conduction, and found that in some characteristics there was no difference, and others, there was a trend for the formula to give worse outcomes.

Second, the Rhythm II ICD (Boriani G. 2006) study used echocardiographic maximization of LVOT VTI to identify a VV delay as optimal. No difference was found between groups, although the study did not report whether the method of optimization had good test-retest reproducibility. Without confirmation that test-retest reproducibility is high, it is very possible, given the known beat-to-beat variability of VTI, that the allocation amongst VV delay settings in the optimized group largely the play of chance rather than identification of a true optimum setting for that patient (i.e. one that persists over at least a few minutes, or ideally months). The hazards of uncritically hoping that an apparent optimum is a consistent optimum has been quantified recently (Pabari P.A. 2010).

Finally, the Insync III (Leon A.R. 2005) study showed that with VV optimization, a population of CRT patients showed a greater increment in exercise capacity than a similar group of historical controls (MIRACLE study), and a modest improvement in stroke volume compared to the nominal VV delay. In other respects including symptom class and QoL score there were no differences. Interestingly, although the distribution of observed optima between LV-first, RV-first or simultaneous, remained unchanged between the start and the end of the study, it is not reported whether individual patients retained the same optima. Without this information on whether patients retested had the same optima as before, or only just drawn from the same distribution, it is again unfortunately not possible to tell whether the optimization

process was identifying a persistent feature of each individual, or drawing from a random distribution with a mean of approximately zero.

Overall, the VV optimization trial outcomes seem woefully unsupportive of the belief that VV timing is the critical benefit of CRT. The only way they might be supportive of an important role of VV timing, is if zero ms (typically used as a control setting) is in fact a very good value for most patients, and the various apparent optimization methods through being unreliable are selecting suboptimal settings.

But even still, it is difficult to discount the precise measurements of haemodynamic effects that have been made during AV and VV optimization conducted in the identical patients in acute studies, which show that the AV adjustments have many times larger an effect on blood pressure than VV adjustments. With haemodynamic techniques, where high numbers of replicates are easily obtained, the error bars are small. The effect of adjustment of VV delay is therefore easily verified to be much smaller (by several fold) than the effect of adjustment of AV delay (Whinnett et al, 2006). Neither the VV optimization trials nor the high-precision optimization studies, therefore, support an important role for resynchronization of the ventricles as the main benefit of biventricular pacing.

## 1.5 Unanswered Questions

The direct effects of biventricular pacing are purely electrical i.e the mechanical effects (AV synchrony and VV coordination) of pacing occur only through responses to electrical activation. The relative contribution of AV optimization versus ventricular synchronization to the overall improvement in haemodynamics and clinical endpoints may vary between individuals, and may depend on QRS width and intrinsic AV interval.

However, there are still a number of unanswered questions that unless they are addressed, the field of cardiac resynchronization therapy and optimization of AV and VV settings may fail to progress and fail to provide the full benefit of such a modality of therapy in the heart failure population.

### 1.5.1 Unanswered question 1: How does AV optimization affect cardiac mechanoenergetics?

Although one invasive study (Nelson G.S. 2000) has investigated the mechanoenergetic effects of biventricular pacing, this had several limitations. It only compared LBBB to biventricular pacing at one AV delay and did not investigate the effect of AV optimization on mechanoenergetics. Variability of heart rate may have introduced error in the estimation of the effect of atriobiventricular pacing on cardiac contractility myocardial oxygen consumption ($MVO_2$) *per beat*. A fall in $MVO_2$ was reported but since this was accompanied by a lower heart rate, it is not clear whether oxygen consumption per beat was altered, but overall efficiency seemed to improve with biventricular pacing.

Other studies using non-invasive estimation of $MVO_2$ using positron emission tomography (PET) have reported that regional $MVO_2$ changed with CRT with a more favorable redistribution of the pattern of oxygen consumption in the myocardium, (Ukkonen H. 2003, Lindner O. 2005). Although global $MVO_2$ was statistically unchanged, studies have indicated that biventricular pacing of LBBB (Ukkonen H. 2003) or absence of LBBB (Lindner O. 2005) shows a trend of higher $MVO_2$. Again these studies did not assess the mechanoenergetic effects of biventricular pacing at different AV delays.

Therefore from the current available data it is unclear whether the mechanoenergetic effects of CRT, during AV delay modulation, are preserved or whether they improve or worsen. Doubt exists because CRT is believed to primarily exert its haemodynamic and clinical benefits predominantly by improving the contractile timing (synchrony) between ventricular walls and only partly by shortening the AV delay; pure AV delay modulation may therefore give a different balance of mechanoenergetic effects than CRT overall.

### 1.5.2 Unanswered question 2: What happens to coronary physiology during biventricular pacing and which are the mechanisms responsible for any changes?

Surprisingly the effects of biventricular pacing on coronary physiology have been scarcely studied. Some authors (Nelson G.S. 2000) who allowed heart rate to change with CRT, found that CRT shows a nonsignificant trend to reduction in left coronary flow. Others (Lindner O. 2005) have suggested that

overall coronary flow shows the opposite, namely a nonsignificant trend to increase. All these studies measured coronary flow at one AV delay.

No study has investigated the instantaneous phasic (systolic and diastolic) changes in coronary blood flow over the cardiac cycle. In addition, the intracoronary pressure was not measured in any of the studies and therefore it was not possible to investigate the hemodynamic mechanisms of any changes in flow.

Therefore, from the current evidence it is unclear how ventricular resynchronization and AV optimization influence coronary flow and what mechanisms are behind any flow changes observed.

### 1.5.3 Unanswered question 3: Can non-invasive automated haemodynamic optimization be achieved reproducibly by a simple technology with the potential of co-implantation with the CRT device?

Invasive haemodynamics have been the cornerstone for assessing the response to CRT in many acute studies. However, obviously this approach cannot be used in routine clinical practice. Instead, non-invasive haemodynamic optimization using a beat-to-beat blood pressure (Finometer) device has been shown to accurately measure changes in blood pressure and has been validated against changes in invasive pressure measurements (Van Egmond J. 1985, Petersen M.E. 1995). This technology has been used for optimization of CRT devices and provides a very good reproducibility of the optimal AV delay (Whinnett Z.I. 2006, 2008).

However, the Finometer technology is expensive and not readily available in the typical clinical setting where CRT optimization is carried out. In addition this technology cannot be miniaturized and therefore be implanted with the pacemaker; an ideal scenario for any optimization technique.

Can simpler and cheaper haemodynamic technologies, more readily available than the Finometer device, be used in the routine optimization of CRT devices? It is not known from existing data whether the raw photoplethysmographic signal, which can be obtained from devices such as finger pulse oximetry, can be used for AV optimization. It is not known whether further automated processing of such a simple signal can improve the accuracy of optimization and match that of the Finometer.

### 1.5.4 Unanswered question 4: Are current modalities used for VV optimization internally valid and therefore applicable for large scale clinical research?

VV optimization is an exceptionally difficult aspect of CRT to be studied. In sinus rhythm, changing the VV delay it also, inevitably, causes a change in the AV delay and therefore any cardiac effects achieved are not purely VV delay change related. Also, the effect of changing the VV delay is found to be less than that of changing the AV delay, making it difficult to separate the genuine effect (signal) of changing a setting, from random variability (noise). Because the effect of VV optimization may be 5-10 times smaller than that of CRT implantation, an endpoint study would have to be 25-100 times larger any of the landmark CRT trials such as MIRACLE and CARE-HF. These, therefore, may be some of the reasons why to date any clinical trials assessing the benefits of VV optimization have been disappointing.

A rather more important, and more fundamental, aspect of VV optimization is the choice of optimization modality to measure the cardiac effects of this process. From the current data available no study has ever been performed to directly assess the internal validity of each of the optimization modalities proposed in the literature. It is not known if any of these modalities can be trusted to measure any effects of VV optimization. Unless such an evaluation has been carried out for each of the modalities, it would be inappropriate to use any of these in trials to measure the clinical effects of VV optimization.

### 1.5.5 Unanswered question 5: How does heart rate affect the optimal AV delay and does the difference between atrial sensed and paced optima change with heart rates?

It is unclear from the existing literature how the optimal AV delay is affected with changes in heart rate. The very few studies that have investigated rate adaptation of AV resulted in conflicting conclusions (Bogaard M.D. 2010). At elevated heart rate, the optimal AV delay has been seen to increase, stay the same, and decrease both during exercise (Mokrani B. 2009) and with atrial pacing (Whinnett Z.I. 2008). It is likely that several limitations in these studies' designs have not revealed the true response in the optimal AV delay as a result of change in heart rate. For example, many of the markers used for optimization suffer from poor reproducibility, preventing precise identification of an optimal AV delay.

In addition, the effect of atrial pacing is to prolong the optimal AV delay. The degree of prolongation in the CRT population has not been thoroughly investigated and has been assumed to be the same as in the bradypacing population without heart failure. Moreover, it is not known whether the difference in the optimal AV delay between an atrially sensed and atrially paced mode remains fixed or whether it changes with increasing heart rate.

These unresolved issues of CRT are of particular clinical importance since at elevated heart rates patients will receive additional benefit from a rate adaptive optimal AV delay. In addition patients with chronotropic incompetence (~ 40% of the CRT population) will rely on atrial pacing during exercise therefore more insight is required to understand the true relationship of the optimal AV delays between sensed and paced atria.

## 1.6 Aims of this thesis

To evaluate invasively the cardiac mechanoenergetic effect of biventricular pacing at three AV delays (40 ms, 120 ms, optimal AV) and intrinsic conduction (LBBB). The aims in this study were to study the relationship between external cardiac work and myocardial oxygen consumption during AV modulation and to investigate whether the celebrated improvement in cardiac mechanoenergetics with CRT is influenced by modulation of the AV delay.

To determine the effect of biventricular pacing on coronary physiology. Specifically, I tested the hypothesis that coronary flow is closely linked to cardiac mechanics and used wave intensity analysis to identify and quantify the waves acting on coronary blood flow. I aimed at identifying the predominant force driving the flow during biventricular pacing and whether affecting cardiac contractility beyond resynchronization, by modulation of AV delay, affects this predominant force.

To test the relative efficiency of two non-invasive haemodynamic technologies (finometer and simple photoplethysmography) for AV optimization of CRT devices. The aim of this study was to compare the reproducibility of the two tested haemodynamic technologies, and how this could be improved, and

whether the simple photoplethysmographic technology can be used as a reasonable alternative to finometer in routine clinical optimization.

To perform an acid test for the modalities used for VV optimization. I aimed at evaluating the internal validity (reproducibility, singularity and biological plausibility of the VV optimum) of each of three commonly used modalities (LVOT VTI, QRS width and non-invasive blood pressure) for VV optimization. The aim of such an evaluation was to bring to light the lack or presence of validity because it should be taken into consideration before using these modalities as a measure of the effect of CRT in large scale clinical trials.

To test the effect of heart rate on the optimal AV delay, during exercise and during overdrive atrial pacing. I also tested the effect of pacing (instead of sensing) the atrium on the optimal AV delay at rest and at faster heart rates. Finally, I explored whether the use of tissue Doppler echocardiography can explain the differences in optimal AV delays between a sensed and paced atrium.

# 2 Materials and methods

## 2.1 Equipment used

### 2.1.1 Non-invasive Arterial Blood Pressure Measurement

Throughout my research I used the Finometer device, Figure 2-1 (Finapres Medical Systems, Amsterdam, Holland), for the measurement of beat-to-beat non-invasive blood pressure.

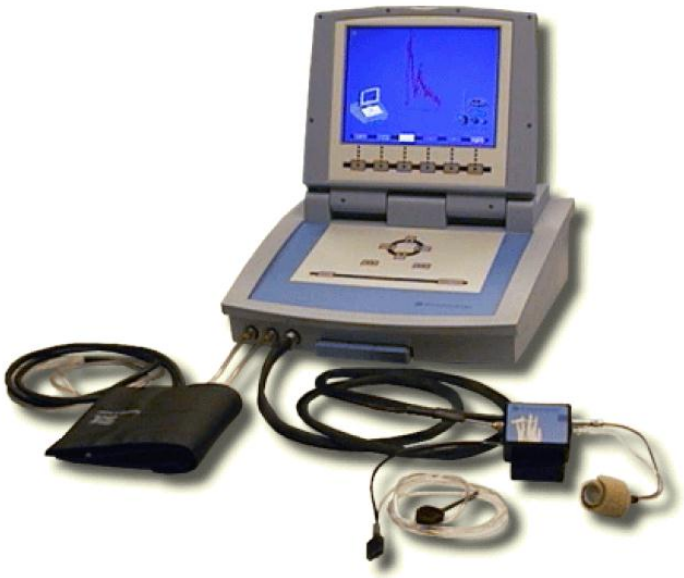

**Figure 2-1. A picture of the Finometer**

The finometer was used for measuring changes in beat to beat blood pressure when the pacemaker settings where changed during AV and VV optimization of CRT devices

The device includes a semi-rigid finger cuff with enclosing a balloon which is inflated to grip the extended finger. By doing so a measurement of the arterial blood pressure is obtained based on the concept of volume-clamp photoplethysmography (Penaz J. 1973, Imholz B.P. 1998). The sample rate of Finometer is 200Hz.

Volume-clamp photoplethysmography operates by using a rapid servo system with a finger cuff actuator. This continuously adjusts the volume of air in the finger cuff balloon to achieve a fixed volume of blood within the artery by keeping a reference photoplethysmographic signal constant throughout systole and diastole.

Therefore the pressure changes which are required to drive the volume changes, within the finger cuff's balloon, mirror the pressure changes within the artery; keeping a steady transmural pressure. Thus, the intra-arterial pressure is measured indirectly by assessing the cuff pressure required to exactly counteract the change in intra-arterial pressure.

The system is commercially produced and is widely accepted as valid for the measurement of changes of arterial blood pressure (Smith N.T.1985, Wesseling K.H.1995).

With time, due to variations in the smooth muscle behaviour and diameter, the servo system has to be adapted through an automatic physiological calibration.

The Finometer operated for at least 10 minutes prior to initiation of recording. This allowed sufficient time for a number of self-calibrations. When the blood pressure was stable within a reasonable range, over a period of ~½ minute, the self-calibration function was then disabled. This was disabled during the time of pacemaker settings changes, in order to allow continuous uninterrupted pressure measurements. Calibration was enabled periodically during the study, in between testing of pacemaker settings. This allowed as precise tracking of arterial pressure changes as possible.

The manufacturer's advice of fitting the finger cuff on the middle interphalangeal joint of the middle finger of the dominant hand (due to higher pressure), was followed. In the majority of cases this provided persistently satisfactory pressure traces. In the event of intermittently optimal pressure traces, the cuff was placed on a different finger; one that provided adequate quality of traces throughout the study. The patient was advised to keep the hand and finger still, in order to avoid hydrostatic induced pressure changes.

If the pressure traces were sub-optimal due to low hand temperatures during cold days or as a result of peripheral vascular disease causing vasoconstriction, every attempt was made to warm up the hand and keep it warm during the study period.

### 2.1.2 Photoplethysmographic Measurement

For some of the study I used additionally a transcutaneous photoplethysmogram signal using a modified finger probe pulse oximeter (Ohmeda Biox 3700e), Figure 2-2.

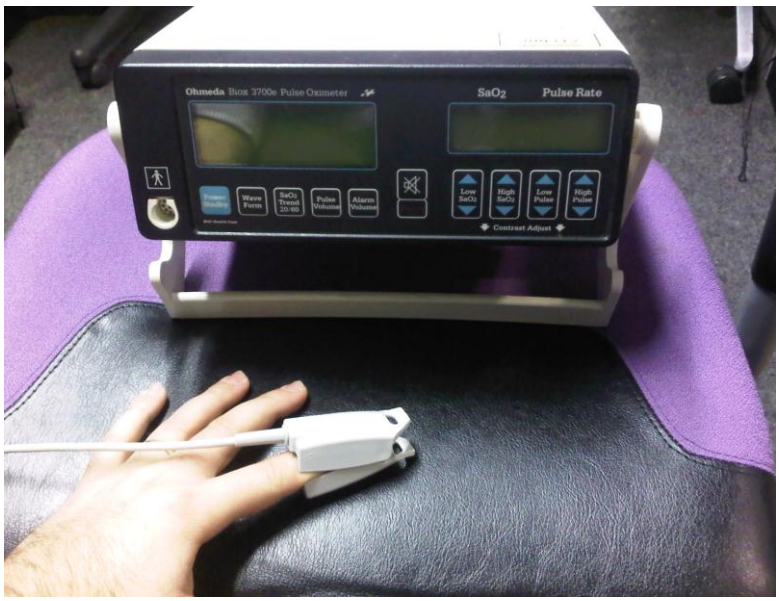


**Figure 2-2. Ohmeda Biox 3700e**

This pulse oximeter was used to measure the changes in the photoplethysmographic signal during the process of AV and VV optimization. The finger is illuminated with light by an LED and the change in intensity of the light is detected by the photodetector on the other side of the finger. Changes in light intensity reflect changes in blood volume

This provides a non-invasive index of blood volume change in the capillary bed. The photoplethysmogram signal changes were measured during optimization and its precision to identify an optimal pacemaker setting was compared to the Finometer, as discussed in detail in Chapter 5.

Pulse oximetry used photoplethysmography is a transmission mode plethysmography which works by using a light-emiting diode (LED) to illuminate the underlying tissue and measures the light intensity, by a photodetector, on the other side of the tissue. Light intensity would change depending on the depth of tissue it penetrates through. For example, increases in blood volume per unit cross-sectional area would result in a reduced light intensity. The sampling rate of the plethysmographic signal is 30Hz.

Standard clinical pulse oximeters have auto-scale circuitry which sets up operating levels of light outputs and amplifier gain automatically in order to cope with shifting probe position and tissue states in order to maintain a visible oximetry signal on the display screen.

However, for the purpose of optimization, it is important for the scale to be able to be held constant while the AV setting is changed, so that the impact of the change in AV delay is not confounded by changes in scale. On the other hand, the procedure is very much simplified if auto-rescaling is available because there is still the problem of wide between-patient differences in average light absorption. Rescaling is needed for the individual patient before the pacemaker settings tests begin.

So the pulse oximeter used for my research had to be modified slightly. A switch was added to give the option to freeze auto-control settings for duration of experiment, Figure 2-3.

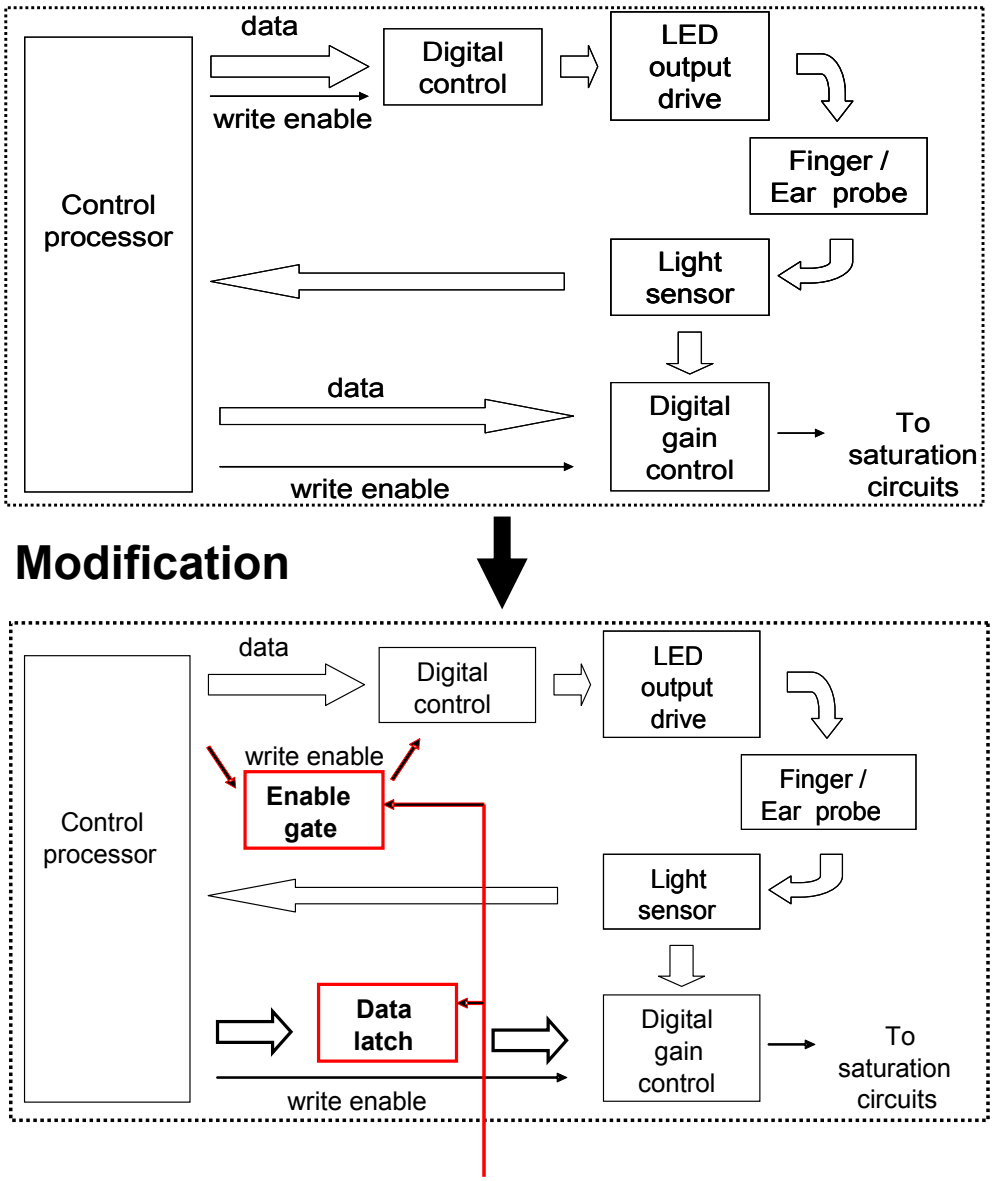


**Figure 2-3. A schematic presentation of the modification of a pulse oximeter**

A switch was added to control the auto control settings of the oximeter. This allowed 'freezing' of the auto-rescaling of the plethysmographic signal during optimization and allowed measurements of the change in the magnitude of the signal during changes of AV/VV delay

### 2.1.3 Invasive Haemodynamic Measurements

During the invasive assessment of the effect of changes in pacemaker settings on cardiac mechanoenergetics and coronary physiology, a number of invasive haemodynamic parameters were measured.

**Proximal aortic pressure measurement**

A fluid-filled hollow guide catheter (Judkins Right, 4mm diameter) was used to measure pressure in the ascending aorta. Pressure is transmitted through a fluid column to an external pressure transducer, to which the fluid-filled system is connected. A high level of quality of the pressure trace was achieved by keeping the minimum distance between the proximal end of the catheter and the pressure transducer and eliminating any bubbles within the catheter.

The pressure transducer was kept fixed to the catheter table to avoid erroneous readings of pressure due to height changes of the transducer.

Prior to use, the fluid-filled catheter was zeroed at the right atrial level with the patient supine. The pressure waveform was displayed continuously on a screen to be viewed by me together with minimum, maximum and mean values of aortic pressure.

**Pressure and flow measurements using sensors**

Pressure recordings from the left ventricle and left main stem (LMS) and flow velocity recordings from the LMS and proximal aorta were made by using 0.014-inch diameter PrimeWire 7900 and Flowire 1400 (Volcano Therapeutics, Inc), respectively.

***Pressure sensor.*** The pressure sensor uses the MEMS (MicroElectroMechanicalSystems) technology to form a thin silicon diaphragm over a reference pressure chamber. Tiny resistors are embedded in the diaphragm, and their resistances change when the diaphragm flexes in response to the changing blood pressure. The pressure electronics monitors the resistor values, using factory calibration coefficients to convert the resistance into a pressure reading.

This system is in contrast to other traditional pressure sensors where there are usually four resistors in a "Wheatstone bridge" configuration, with two resistors increasing with pressure while two resistors decrease with pressure.

***Doppler sensor.*** The Doppler sensor uses quartz crystals (piezoelectric crystals). Applying an electric current to these crystals, it induces a change in their shape rapidly. The change in the crystal shape, or vibration, generates sound waves that travel outward.

Conversely, when sound waves hit the crystal, it emits electrical currents. Therefore, the same crystals in the piezoelectric transducer can be used to send and receive sound waves.

The signal processing electronics uses the pulsed-wave Doppler method, generating the transmit burst waveforms and processing the frequency-shifted reflected signals to extract the blood flow velocity information from the received signal.

**ComboMap system (model 6800)**

The ComboMap system (Figure 2-4) processes the information it receives from the PrimeWire, Flowire, and pressure transducer (from the catheter table) and other external inputs.

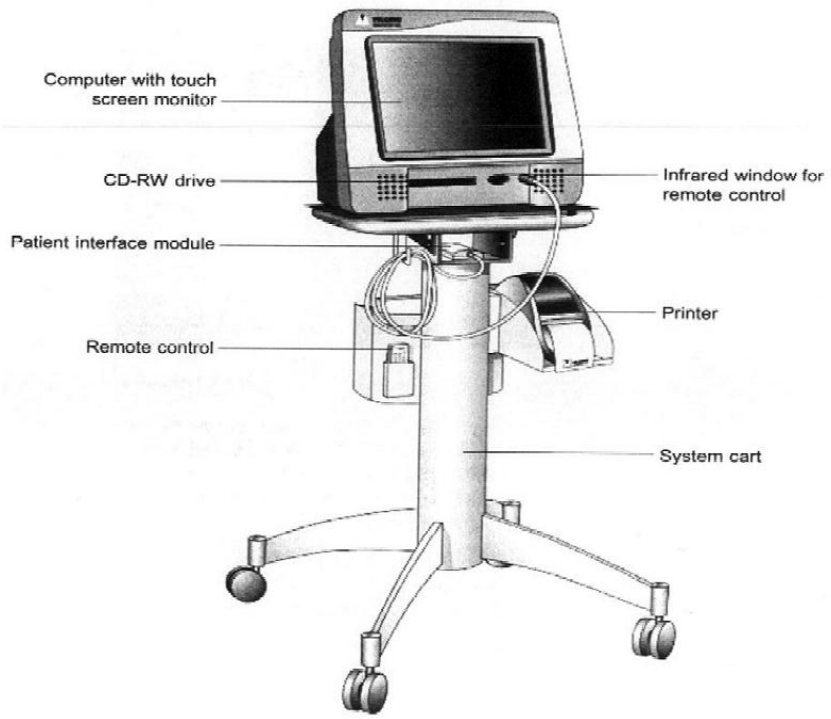


**Figure 2-4. The Combomap system**

A schematic presentation of the ComboMap system (taken from the ComboMap manual)

Intravascular blood pressure and blood flow velocity measured are displayed on the console screen in real time (Figure 2-5).

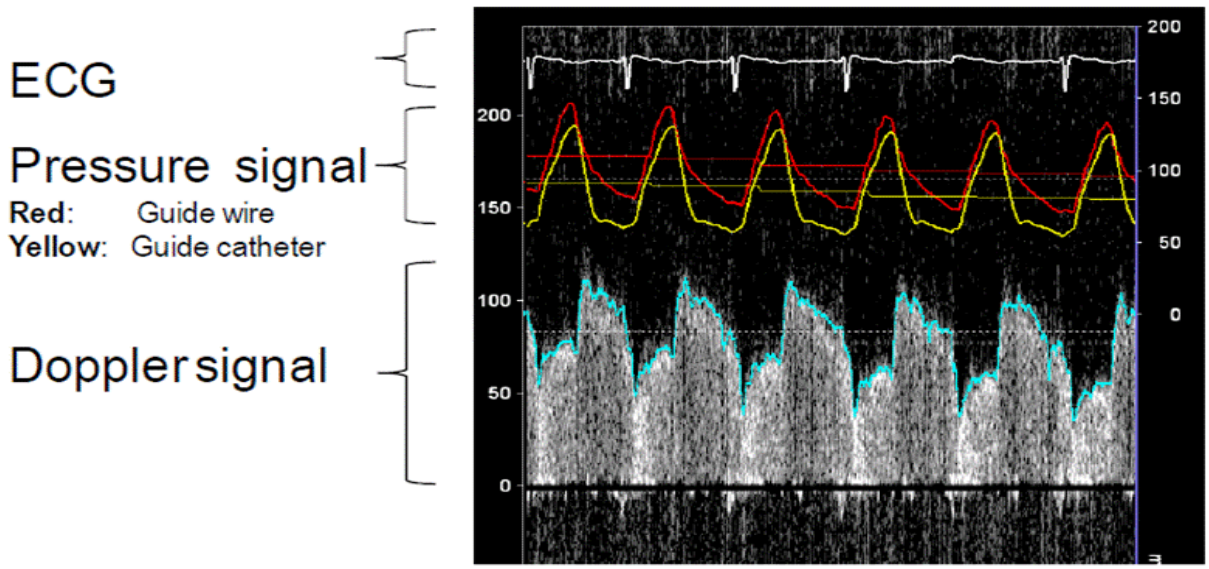


**Figure 2-5. ComboMap console live data screen**

The ECG, catheter and sensor pressures and flow are all displayed live on a touch screen

**Calibration before each study**

*Pressure* calibration:

(i) Input calibration. The two sources of pressure in the ComboMap were the guide catheter and the PrimeWire. When exposed to ambient pressure, small differences in the zero line for each of these pressure transducers may be present. For this reason, both pressure signals were compared at the zero mmHg signal. If there was a difference, it was corrected by touching the zero button.

(i) Output calibration. To test the output of each of the pressure signals, a calibration signal was sent to the acquisition computer screen via the output reference buttons.

*Doppler* calibration:

(i) Doppler spectrum input

*Wall filter*. At each location, proximal aorta and LMS, the use of the wall filter function allowed a reduction or elimination of low frequency noise returning together with signal when the transducer was near an artery wall. Available filter settings are 200, 400, 800 and 1600Hz; in most cases the best setting was found to be at 400Hz.

*IPV threshold*. The instantaneous pulse velocity (IPV) threshold is a signal to noise ratio, and establishes the signal threshold: signals below this level are considered noise and not displayed or used for flow measurements. The IPV threshold was set by optimizing the IPV envelope which is displayed as a blue envelope around the flow velocity spectrum. This was adjusted manually in all patients and all vessels studied to ensure that the blue tracking envelope matched the outer edge of the velocity spectrum.

(ii) Doppler spectrum output

To test the output of the Doppler signal, a calibration signal was sent to the acquisition computer screen via the output reference buttons. Output reference was available at selections of 0, 100, 250 and 500cm/s. The output voltage was in the range 0-5 volts which implied that the output reference was scaled

accordingly. For example, if a scale factor of 500cm/s is selected, the 5-volt output covers the range of 0-500cm/sec. i.e a flow velocity reference of 500cm/s is equivalent to 5 volts. So for example a recorded velocity of 200cm/s would be equivalent to 2 volts.

In all cases, a flow velocity reference of 250cm/s was set, which meant that there was 1 volt output per 50 cm/s of flow velocity.

### 2.1.4 Surface ECG

An ECG signal was recorded using the Hewlett-Packard 78351A monitor, Figure 2-6.


**Figure 2-6. The Hewlett-Packard 78351A monitor**

This ECG monitor was used for the whole duration of my work. The signal from the device was acquired via an analog output

The ECG electrodes were placed in the standard 3 lead configuration; right and left shoulder and abdomen. The signal was acquired via an analog output.

### 2.1.5 Pacemaker programmer

All patients recruited in the experiments had pacemakers implanted from two manufacturers; Medtronic and Boston Scientific. As a result, the programmers used in the study were the Medtronic CareLink® and Guidant Latitude®.

The programmers were used to change the atrial rate and the AV and VV delay in various combinations, according to the type of the study performed. The initial programmed settings were printed at the start of each study and re-programmed prior to the patient leaving the area of the study.

In the invasive study, patients were only temporarily paced, extracorporeally. For the purpose of the study we used one type of pacemaker, Medtronic InSync III, which had attached custom made leads (by Medtronic Inc.) which could be connected to the temporary pacing electrodes (Figure 2-7)

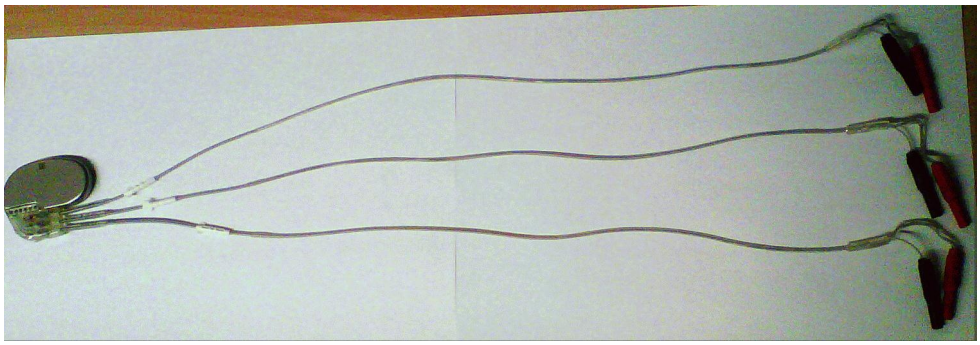

**Figure 2-7. Custom made pacing leads attached to a Medtronic InSync III pacemaker**

This pacing configuration was provided to us by Medtronic Inc and was used during an invasive study. The pacing leads were connected to 3 temporary pacing electrodes. AV optimization of atriobiventricular pacing was achieved extracorporeally.

This approach proved to be extremely reliable in achieving consistent temporary biventricular pacing due to its flexibility and speed of programming during the heavily time-pressured invasive experiments.

### 2.1.6 Purpose built transition-marker box

A transition-marker box was built locally for the purposes of AV and VV optimization.

The box was designed by Professor Darrel Francis and senior engineer Keith Willson. It was built, tested and validated thoroughly in the engineering department of St Marys Hospital, by Keith Willson.

This box was operated manually and simultaneously with the changes in the AV and VV delay. This purpose of the box was to mark the point of transition from one pacemaker setting to another, and this would be readily identifiable during the analysis of data.

The box (Figure 2-8) consisted of two channels, A and B. Channel A was used for changes in the AV delay and channel be for changes in the VV delay. Both channels had a continuous voltage signal output.


**Figure 2-8. Transition-marker box**

The marker box was built locally and it was used throughout my research work. This enables time stamping the change of pacemaker setting. The switch (toggle) on the box was pressed each time the setting of the pacemaker was changed. By pressing the switch the voltage magnitude outputted form the box would change and this serves as a signal of pacing setting change.

The magnitude of the voltage signal could be changed manually by pressing a switch on the box at the time of pacemaker setting changes. This would create a change in the voltage signal, which by design mirrored the corresponding in magnitude changes in the AV or VV delay. This voltage change was used as a marker of the equivalent change in pacemaker timings.

The box was designed so that the voltage signal change could be adjusted and reflect the equivalent numerical changes of the pacemaker timings. For example for changes in AV delay from 120 to 40 ms, the voltage signal would be adjusted to change, by pressing the switch, from 1.2 to 0.4 V. Likewise for a VV change of 0 to LV +40 ms (LV paced first) the adjustment in the voltage signal would have been from 0 to 0.4 V, Figure 2-9.

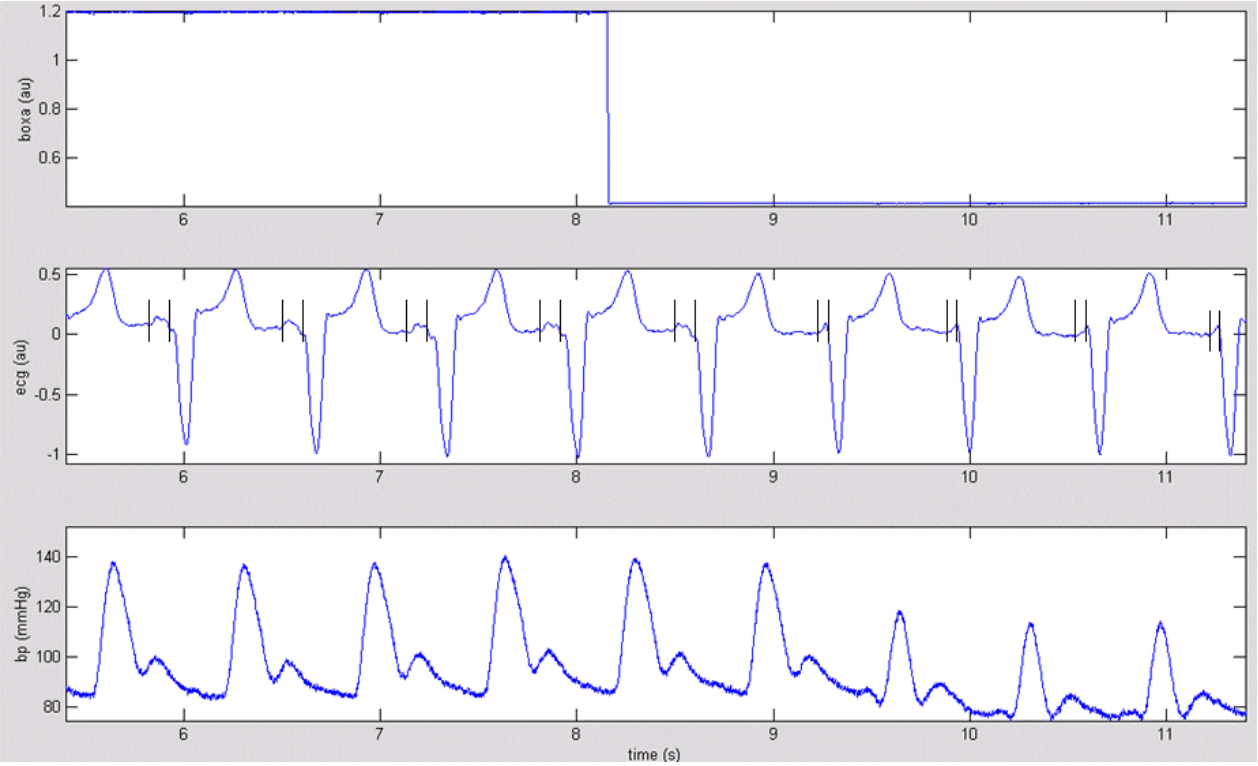


**Figure 2-9. Example of a trace from the transition-marker box**

The transition-marker box is pressed simultaneously with the pacemaker programmer and this is indicated by a change in the voltage in channel A ("Box A"). In this example the AV delay is changed from 120 ms to 40 ms (note the AV delay does not change until the second beat after the button on the programmer is pressed: this is typical of the delay between button pressing and the actual change to the AV delay pattern of the pacemaker). A voltage of 1.2 V represents a programmed AV delay of 120ms and 0.4 V represents 40 ms.

### 2.1.7 Acquisition system

Analog signals were taken via a National instruments, DAQ-Card AI-16E-4 (National Instruments, Austin, TX), and acquired in digital form using Labview (National Instruments, Austin, TX). The data were stored in text files in the corresponding zip folder of each tested AV or VV delay.

## 2.2 Algorithm for measuring haemodynamic effects of changing pacing parameters.

### 2.2.1 Sources of noise within the haemodynamic data

At an early stage of my research work, every effort was made to identify sources of noise within the haemodynamic data acquired by both the Finometer (volume clamp photoplethysmograph) and the pulse oximeter (simple photoplethysmograph).

I identified four main sources of noise:

**(i) Respiratory and cardiac variation.** Fluctuations in blood pressure occurred within a respiratory cycle, Figure 2-10. In addition, even after artificial elimination of respiration, by breath holding, there was still some blood pressure variation due to beat-to-beat variations of the cardiac contraction.

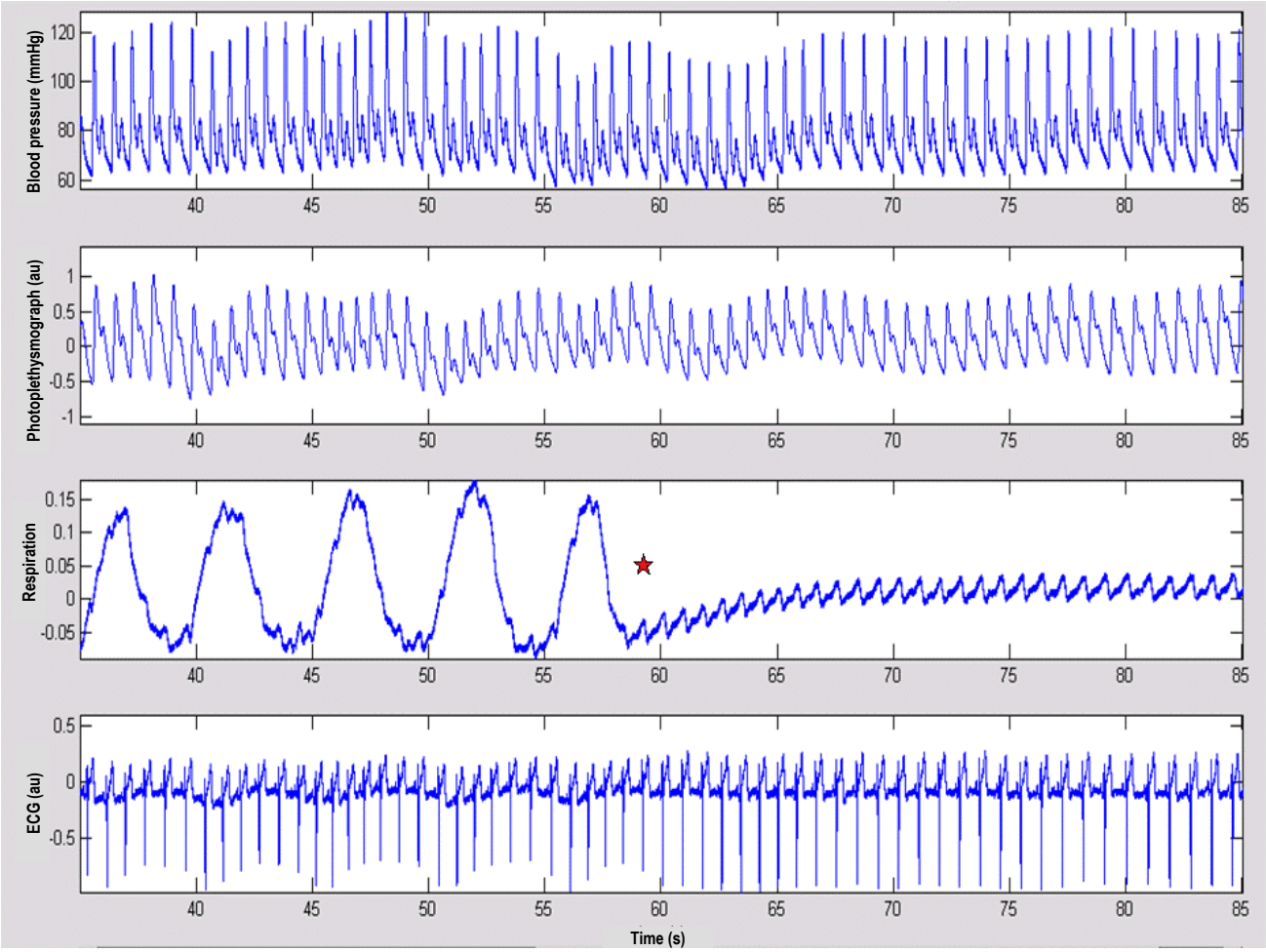


**Figure 2-10. Effect of respiration on the blood pressure trace**

Blood pressure and the photoplethysmographic signal fluctuate during respiration. Once respiration ceases (red asterisk) the spontaneous oscillations within the traces, are minimised. The remaining degree of pressure fluctuation is due to the varying beat-to-beat cardiac contractility.

**(ii) Hydrostatic changes due to movement.** Changes in the position of the hand or finger that the probe was attached to, can introduce immediate changes in blood pressure and therefore introduce a significant degree of noise, Figure 2-11. Patients were encouraged to keep their hand still and at the same level during the optimization session.

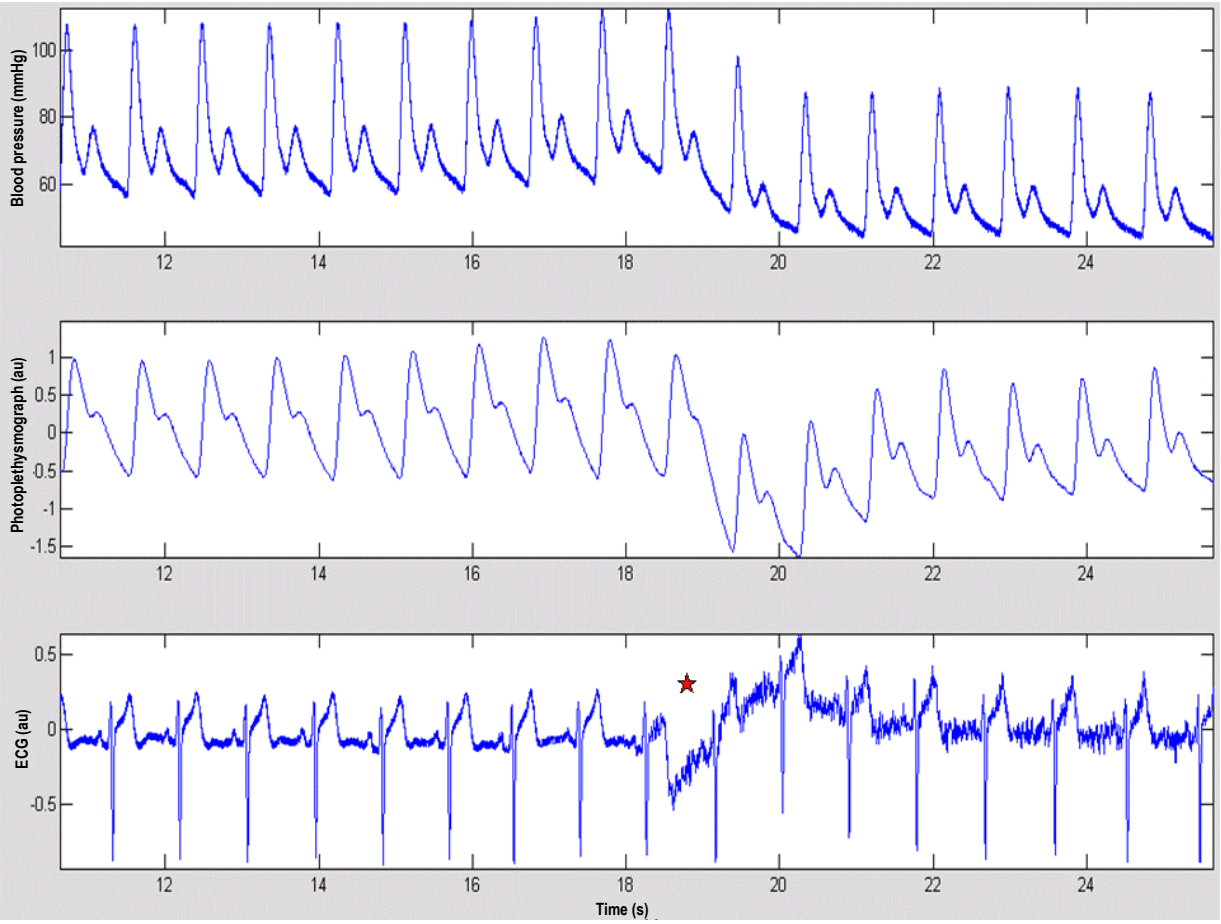


**Figure 2-11. Example of effect of hand movement on the haemodynamic traces**

Elevation (red asterisk) of the hand by 30cm immediately distorts the ECG signal and causes a drop in the blood pressure and photoplethysmographic signal. This source of noise was kept to a minimum by ensuring the patient kept their hand at the same level throughout the study

**(iii) Atrial or Ventricular ectopy.** Any ectopy, and especially that of ventricular origin had profound effects to blood pressure of that beat but also of the sinus beats following the ectopic, Figure 2-12. This "turbulence" effect on blood pressure lasted for at least 2 beats and might potentially be eliminated by future automated systems of haemodynamic acquisition.

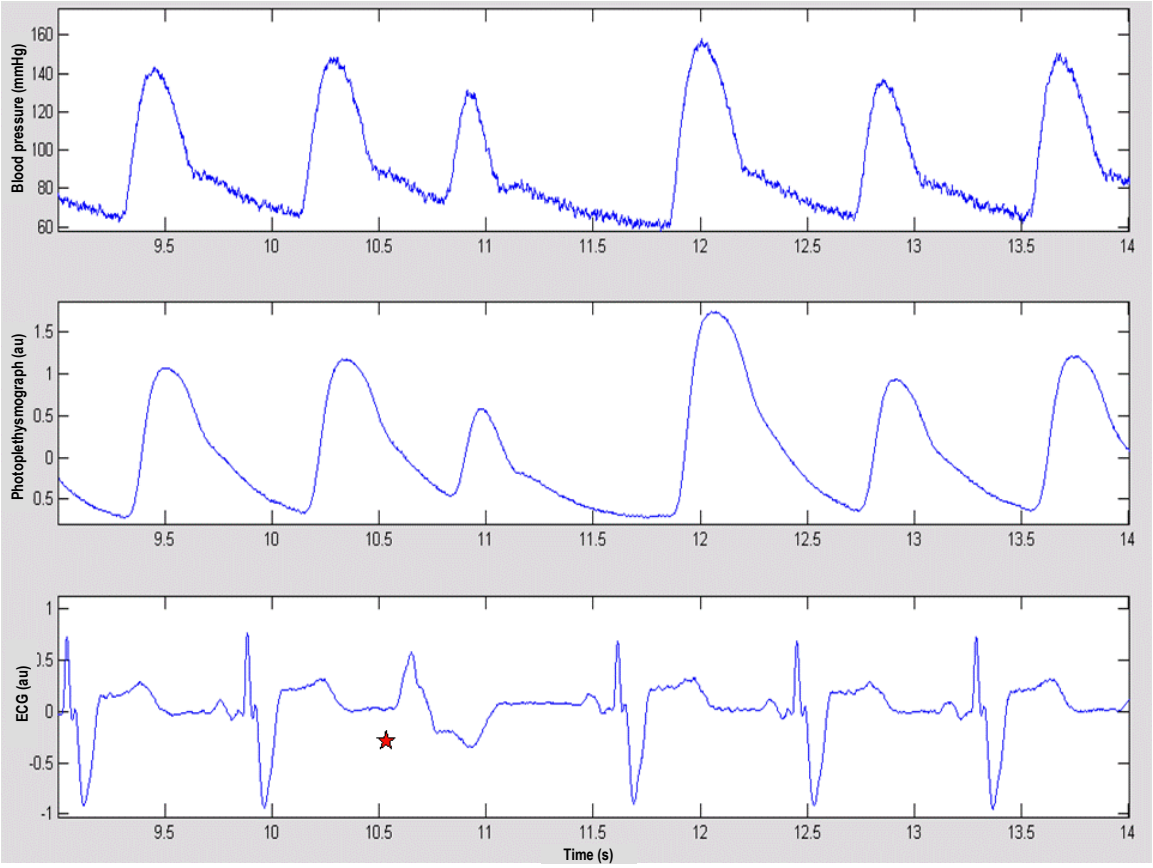


**Figure 2-12. Effect of ventricular ectopy on haemodynamics**

A ventricular ectopic (red asterisk) causes an immediate drop in blood pressure and photoplethysmographic signal. In addition it causes haemodynamic "turbulence" which affects the subsequent sinus beats. Blood pressure does not return to baseline until after at least the third sinus beat post ectopy (Davies L.C. 2001)

**(iv) Equipment drift.** A gradual drift of the blood pressure trace form the Finometer was often observed when the calibration function was disabled for a period of time. However, allowing calibration to occur at times of haemodynamic data acquisition would have resulted in a significant proportion of unusable data, therefore auto-calibration was only enabled periodically, in between testing of AV delays.

### 2.2.2 Strategies used to improve the signal to noise ratio (intraclass correlation coefficient - ICC)

As a result of the blood pressure changes occurring from physiological processes (respiration and cardiac influences), positional changes, ectopy and equipment related noise, measuring a genuine change in

haemodynamics from changes in the pacemaker settings may result in significant inaccuracy. The end result would be a reduction in our confidence in identifying the true optimal setting (in AV or VV delay).

To avoid inaccuracies and maximise the efficiency of optimization by improving the signal to noise ratio (ICC), I applied the following strategies:

**(i) Performing a series of alternations from a fixed reference AV/VV delay to a tested delay.** By comparing the haemodynamic changes from a fixed reference delay to a tested AV delay and measuring the relative changes, it ensured a more efficient exclusion of background fluctuations (noise) in haemodynamics as a result of the four principal sources discussed above.

In all patients I used an AV delay of 120 ms as my reference AV delay, and a VV delay of 0 ms or as close as possible depending on the pacemaker manufacturer (for example, the minimum VV delay on Medtronic pacemakers is 4 ms).

In order to minimise the potential effect of trending up (or down), of the haemodynamic trace, during the transitions, the protocol examined not only "forward" transitions from reference to tested AV delay, but also "backward" transitions (from tested AV to reference AV delay), Figure 2-13. This meant that, for example, from 3 transitions a total of 6 replicates of haemodynamic changes, between the reference and tested pacemaker setting, were available for averaging. This approach ensured that any uptrend or downtrend in the haemodynamic measure during the recording would be cancelled out.

Applying this protocol it meant that relative changes in haemodynamics between reference and tested setting were calculated and plotted, Figure 2-13**.**

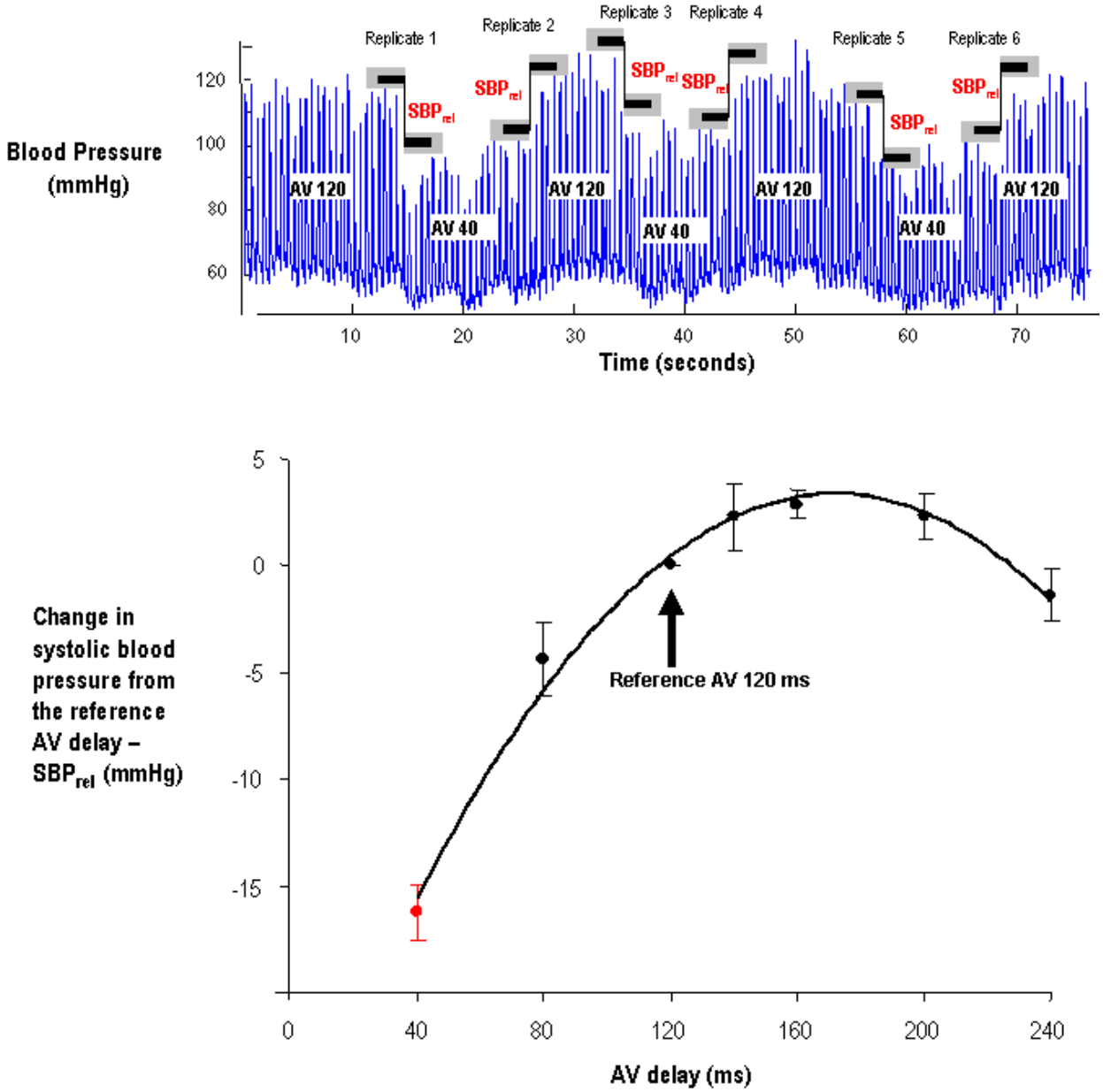


**Figure 2-13. Example of forward and backward transitions**

To minimise the noise I performed transitions from a reference AV delay of 120 ms to a tested AV delay such as AV 40 ms. A few transitions were performed for each tested pacemaker setting. By using both "forward" and "backward" transitions the effect of any drift within the haemodynamic trace is cancelled out

In addition, I tested whether using different reference AV/VV delays during successive optimization sessions, affected the ability to identify an optimal setting. Using for example an AV of 120ms during an optimization session and repeating the optimization process immediately after and using AV 200ms as a reference delay instead, it produced a very similar optimal AV delay, Figure 2-14.

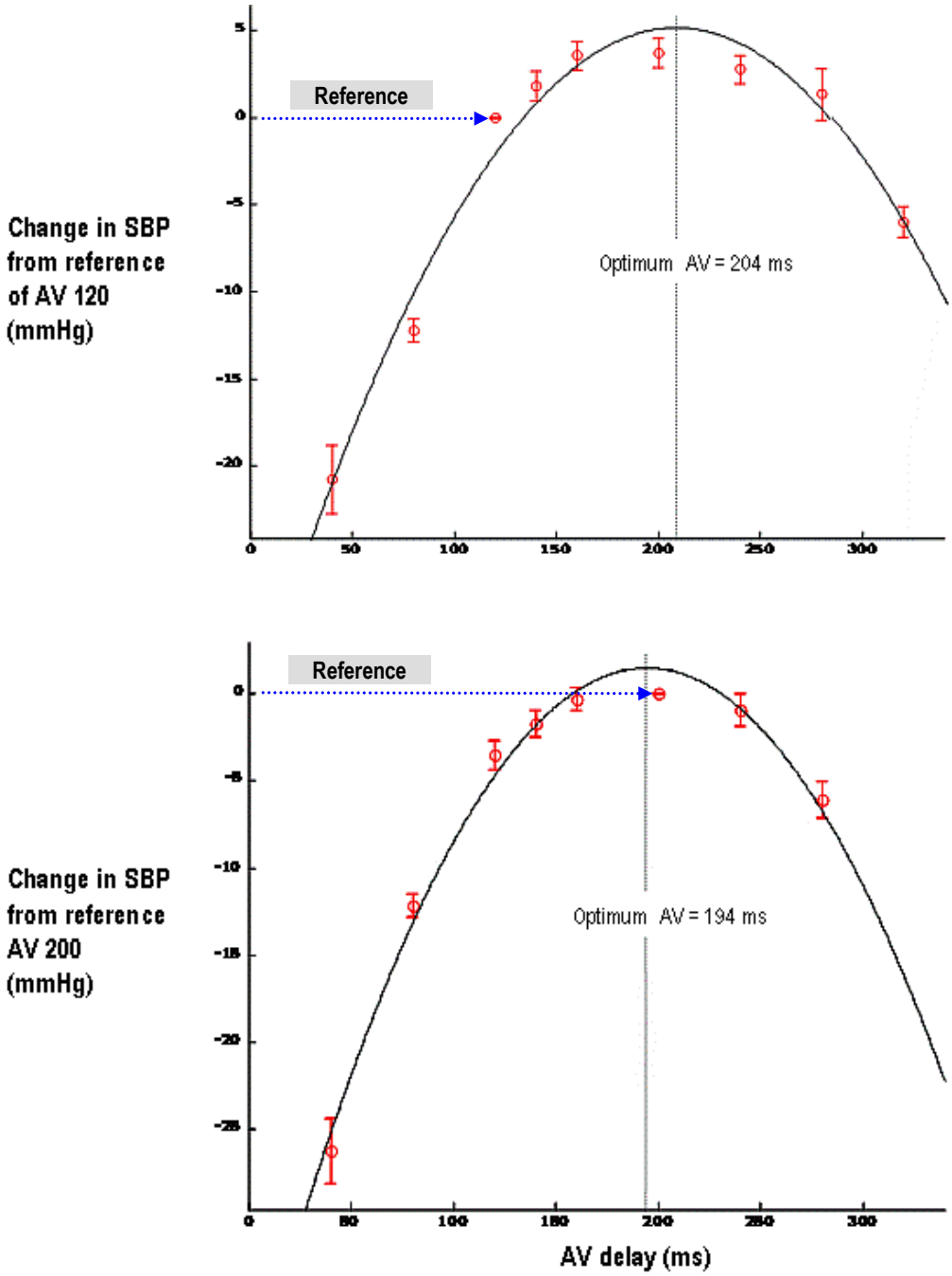


**Figure 2-14. Example of a patient optimized using 2 different reference AV delays**

This patient had one optimization session using a reference AV delay of 120 ms and an optimum of 204 ms was identified. Repeating the optimization shortly after but using a reference AV delay of 200ms, an optimum of 194ms was identified. The closeness of optima from different reference AV delays highlights the fact that the reference delay chosen should not affect the optimal pacemaker setting

I specifically did not use the intrinsic AV delay as the reference one, which would have meant alternating back and forth to LBBB. This is because the aim of the optimization was to measure haemodynamic changes as a result of changing a biventricularly paced AV setting to another, excluding any haemodynamic changes as a result of biventricular pacing.

This alternations protocol proved to be a more precise method of optimization than just performing steady state optimization whereby absolute, rather than relative, changes in haemodynamics were used to compare several AV/VV settings, Figure 2-15.

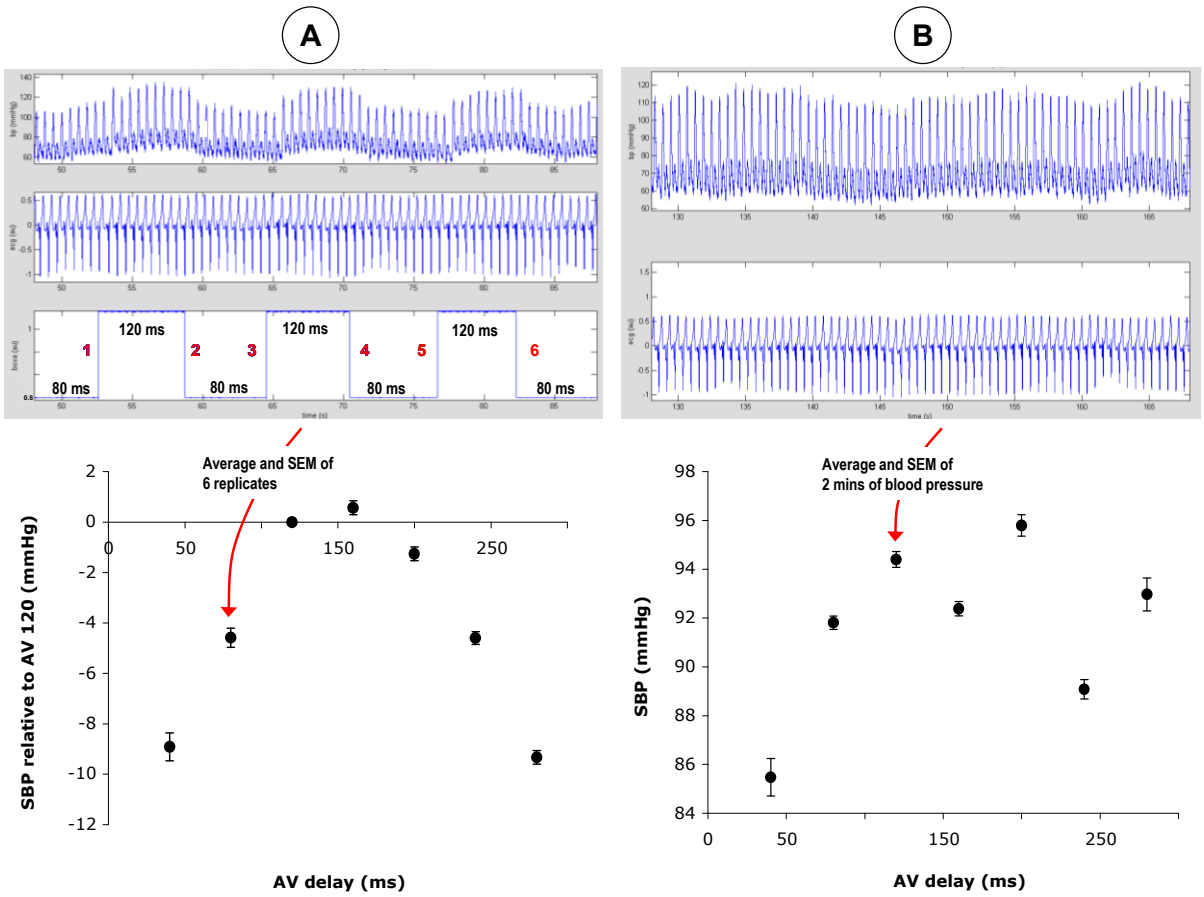


**Figure 2-15. Example patient whereby alternations and steady state optimizations were performed and compared**

In panel A the patient underwent AV optimization using the alternations protocol of forward and backward transitions from a reference AV delay of 120 ms and to a number of tested AV delays (such as AV 80 ms as shown in the top half). Plotting the changes in SBP relative to AV 120, across all tested AV delays a convincing parabolic curve was created with the peak (AV 150 ms) being the optimum. In panel B a number of AV delays were tested by measuring the SBP at each AV delay (such as AV 120 ms as shown) for 2 minutes, and these were plotted as shown in the bottom half of the panel; the haemodynamic relationship of AV delays was not parabolic and identification of the optimal AV delay was therefore less precise than the alternations protocol of optimizations

**(ii) Averaging multiple replicates.** A number of transitions were performed between the reference pacemaker setting and each of the tested settings. The number of transitions to be performed was determined at the start of my research. In a few pilot patients I spent considerable amount of time performing up to 30 transitions (= 60 replicates) for each of the tested settings, Figure 2-16.

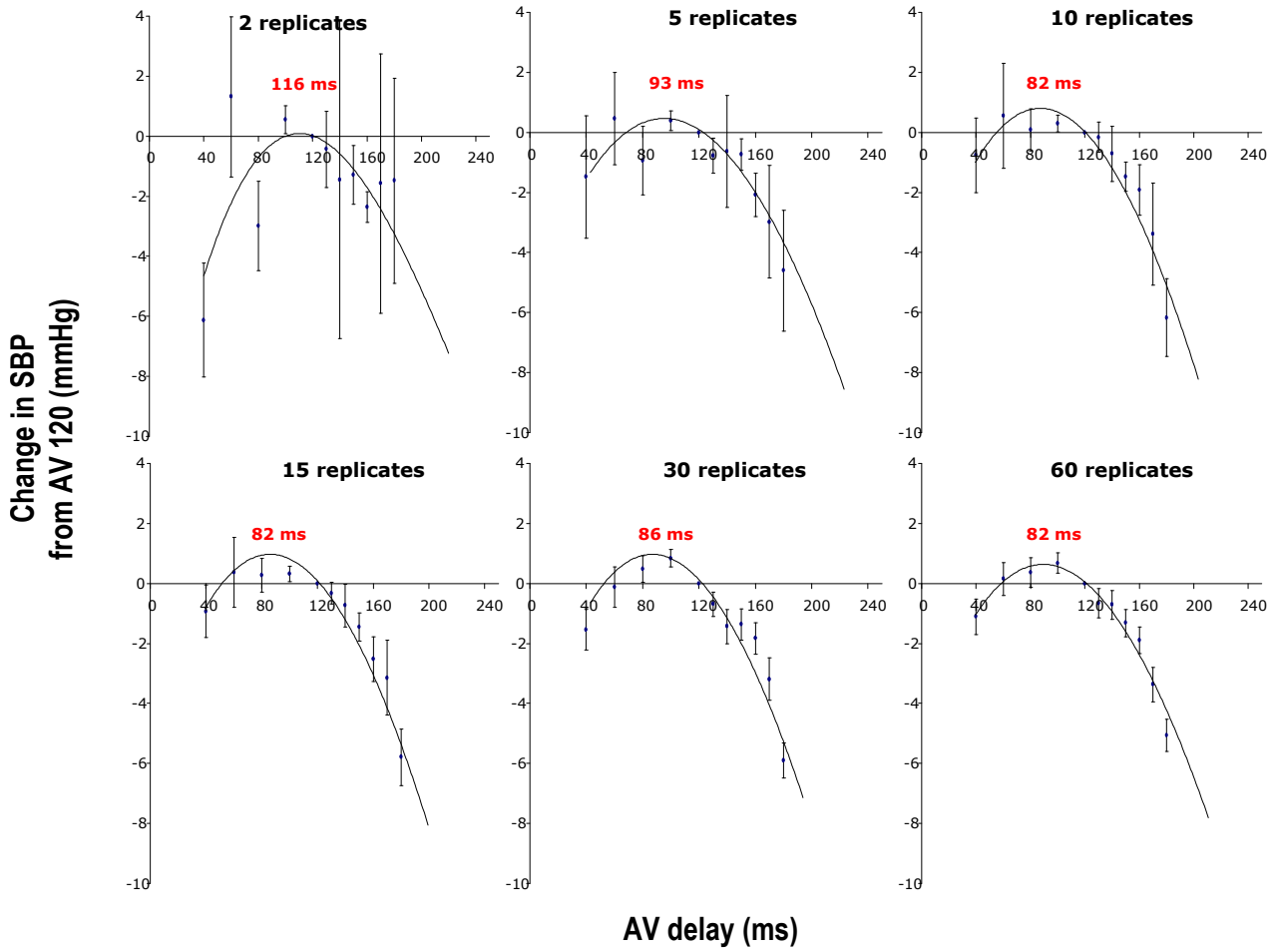


**Figure 2-16. Example of an AV optimization with varying the number of replicates averaged**

AV optimization was performed with a maximum of 60 replicates per AV delay tested. Increasing the number of replicates averaged from 2, 5, 10, 15, 30 to 60 the noise within the haemodynamic changes measured improves (smaller error bars).

This was a very prolonged optimization session, but necessary in order to assess the minimum number of replicates required to derive an optimal AV with a reasonably high level of precision.

I usually performed a minimum of 4-5 transitions (and therefore 8-10 replicates measured) per tested pacemaker setting; this usually took approximately 70-90 seconds. Occasionally, I performed more transitions if there were frequent ectopics or if for any other reason the haemodynamic signal was unusually noisy.

**(iii) Effect of heart rate and rate variability.** Patients were usually optimized at the resting sinus rate, and atrially paced rates of ~5 and 20bpm above the sinus rate. Whinnett Z.I. et al (2006, 2008), has reported that the signal to noise ratio of the optimization process, improves with increasing heart rates. I tested this at the start of my work and I found similar results with both the Finometer and the Pulse oximeter.

Additionally, I tested whether regularising the heart rate by atrially pacing just above (~ 5bpm) the sinus rate, contributed to a relatively significant level in the observed improvement in ICC of elevated heart rate achieved by atrial pacing, Figure 2-17.

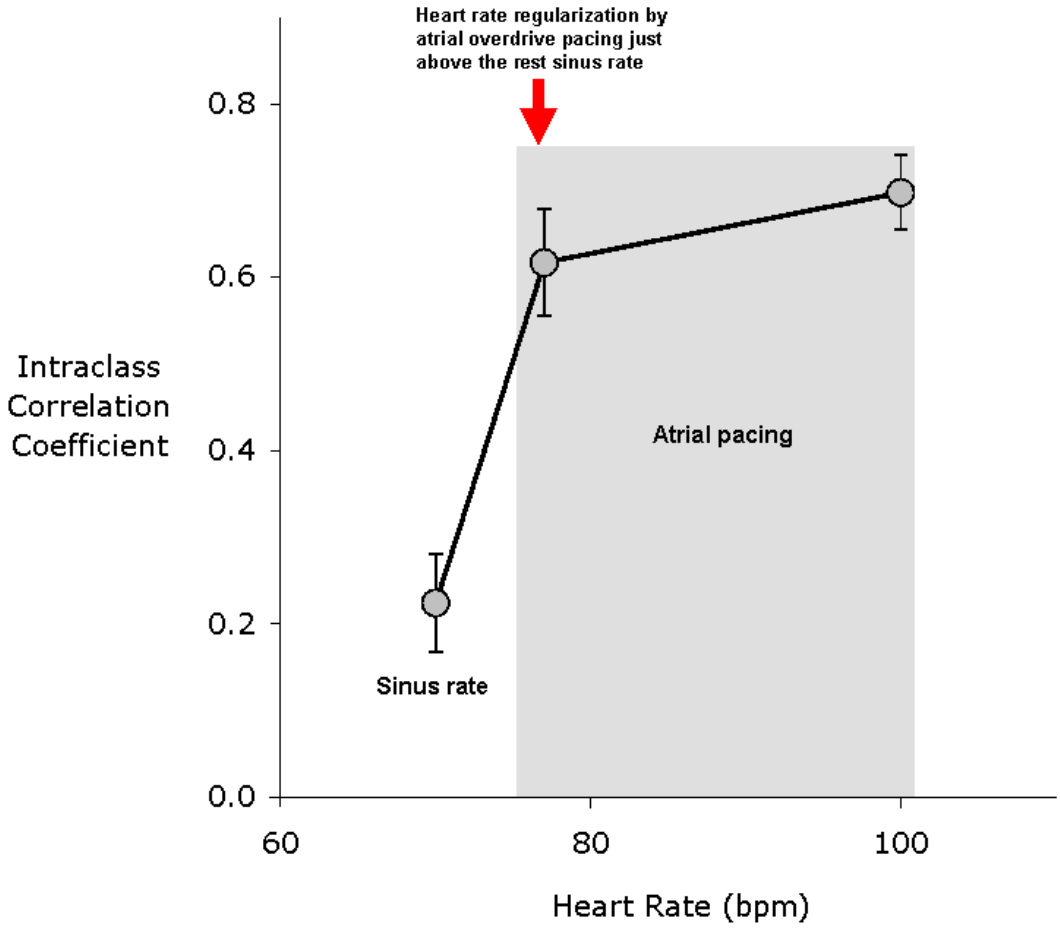


**Figure 2-17. Relative contribution of heart rate regularization to elevation of heart rate**

A measurement of the averaged signal to noise ratio (using the intraclass correlation coefficient) was made across a number of patients at three pacing rates. The ICC of the haemodynamic changes as a result of changes in the AV delay, increased as the heart rate at which optimization was performed was increased. However, the majority of the increase was due to the regularization of the RR interval and less so due to elevation of heart rate

**(iv) Averaging only the number of beats within one respiratory cycle.** Whinnett Z.I. et al (2006, 2008) demonstrated that the signal to noise ratio of optimization depended on the number of beats averaged immediately before and after a transition from the reference to the tested AV/VV delay. The ideal number of beats averaged was of one respiratory cycle's worth.

During my pilot work, I also found that averaging for beats of one respiratory cycle in general provided a better haemodynamic curve with an improved signal to noise ratio, Figure 2-18.

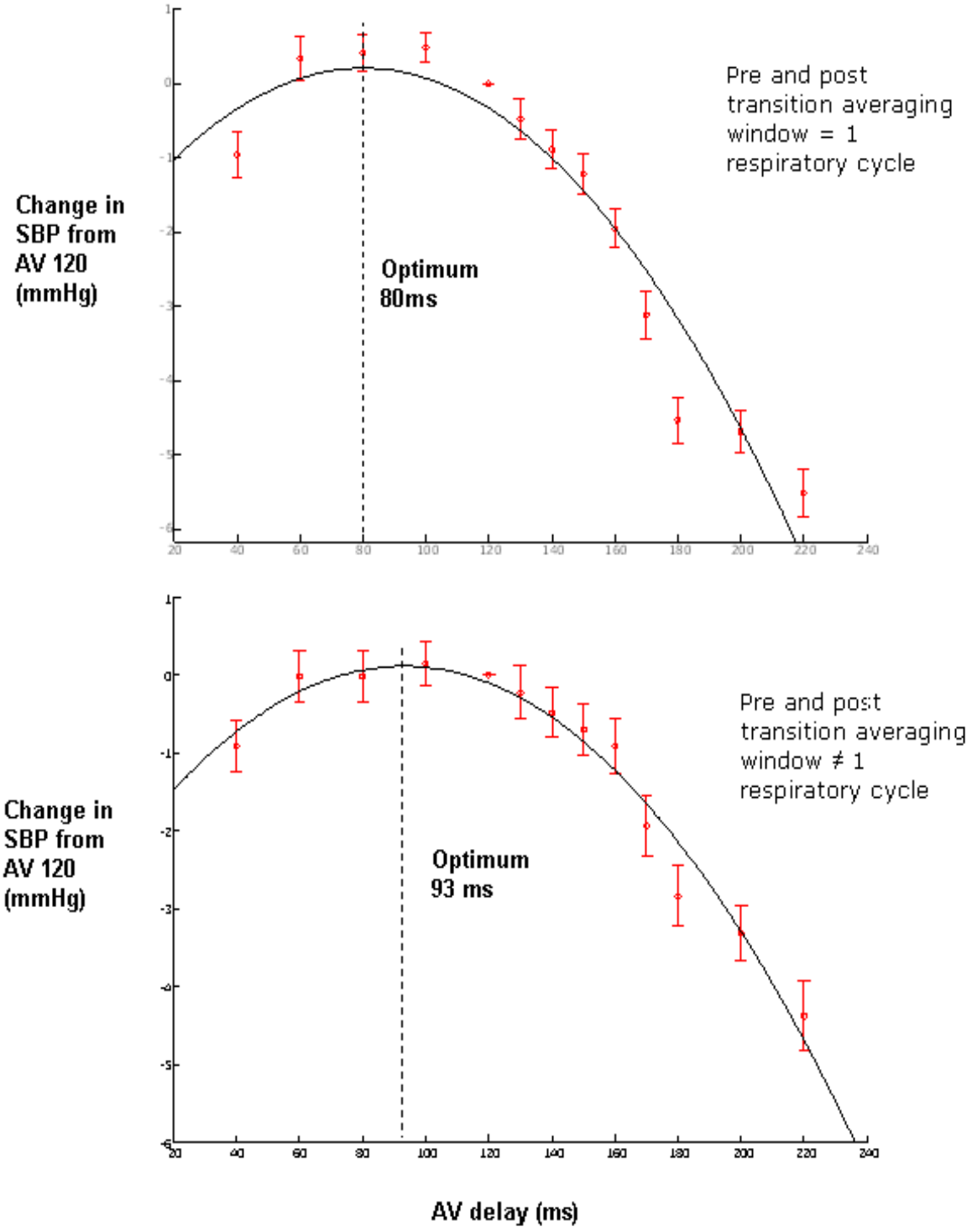


**Figure 2-18. Effect of the transition window width on signal to noise ratio**

For haemodynamic optimization curve at the top, the pre and post transition windows were each equal in duration of one respiratory cycle; approximately 6 beats. The transition windows for the optimization curve, at the bottom, were longer; approximately 9 beats averaged. The noise (width of error bars) of the measured haemodynamic changes is less in the top curve.

Consequently, the respiratory cycle of patients was measured at the beginning of each optimization session and the number of beats used for averaging in the pre and post transition windows varied only as a result of the heart rate at which optimization was performed; for example for the same respiratory cycle ~2/3 of beats would have been averaged at a heart rate of 60bpm rather than at a rate of 90bpm.

**(v) Processing of data**

**Slope versus peak of the waveform**. I found that processing of the haemodynamic (pressure or simple photoplethysmographic) waveform may add to the signal to noise ratio by eliminating some of the noise attributed to the respiratory caused fluctuations. By choosing to use the slope (maximum rate of change of haemodynamic; pressure or photplethysmographic signal) instead of the peak of the waveform, improved the reproducibility of the optimal pacemaker setting. This is discussed more extensively in Chapter 5.

**Avoidance of ventricular ectopics.** The presence of ventricular ectopy was avoided by not performing a transition for at least 8 beats after its occurrence. However, avoidance of ectopic beats was not always possible to achieve due to ectopy arising unpredictably within the first 8 beats after a transition. If this event occurred too often in a patient I opted to perform a lot more transitions and in the subsequent analysis of data I excluded the transitions which were affected by the ectopic beat(s). In patients where only infrequent ventricular ectopics occurred their exclusion was not pursued.

The presence of ectopy was most pronounced at the sinus rate, and its frequency seemed to decrease by atrial overdrive pacing.

## 2.3 Analysis software

The acquisition and analysis of the data was carried out off-line using custom software based on the Matlab platform (MathWorks, Natick, MA). This software analysed the data in a number of steps as summarised in Figure 2-19, and discussed in detail below.

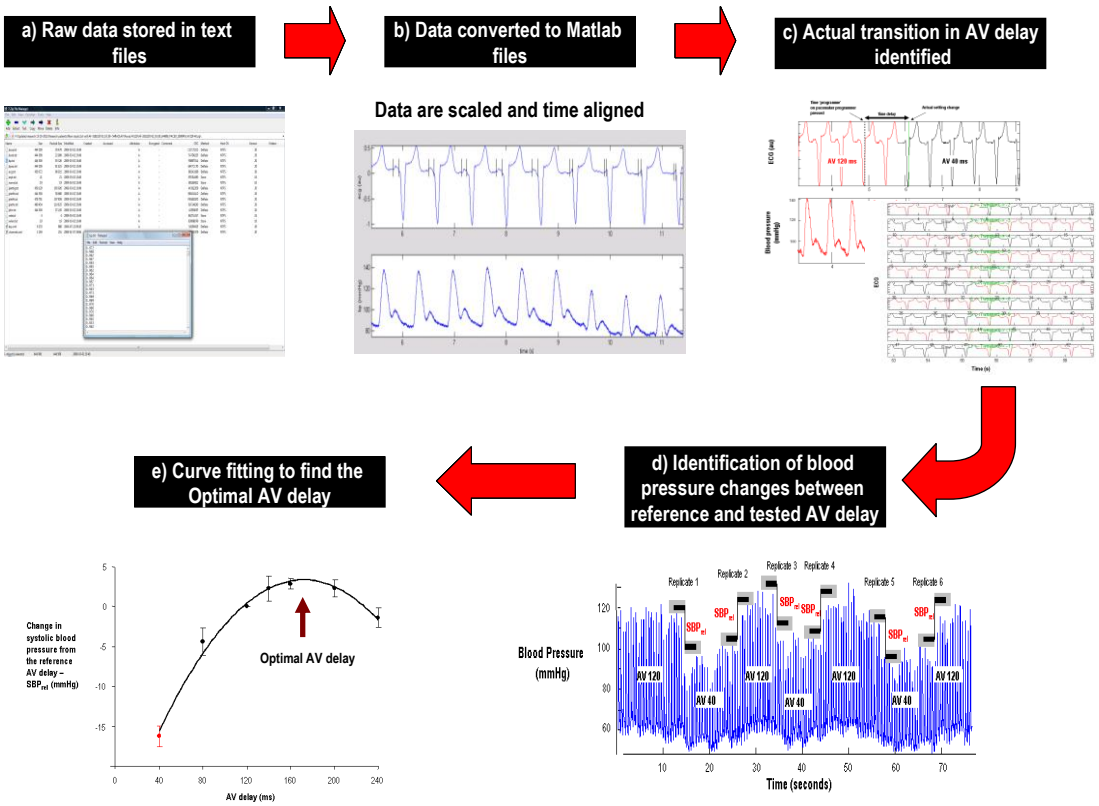


**Figure 2-19. Stepwise analysis of data by custom software**

(a) Raw data from the acquisition system, Labview, are stored in text files.

(b) During offline analysis, the text file are initially transformed to Matlab files and also time aligned and appropriately scaled.

(c) Automated identification of the actual transition from on AV to another takes place. Data are initially aligned according the time stamp by the transition-marker box, followed by actual transition identification by the ECG morphology correlation algorithm. Further manual correction of transition points is possible if needed.

(d) The optimization algorithm calculates the changes in systolic blood pressure ($SBP_{rel}$) between the reference AV or VV delays and all tested AV/VV delays.

(e) The $SBP_{rel}$ data are plotted for the AV and VV delays tested (AV delay data shown in figure) and a curve is fitted to identify the optimal setting.

### 2.3.1 Alignment of data

Alignment of data recorded was investigated at the start of my research work. I tried to establish that the data outputted by the various equipment (such as the Finometer and Ohmeda Biox 3700e plethysmograph) and acquired using Labview (National Instruments, Austin, TX), were released in 'real time'.

From the manufacturers specification I concluded that the Finometer unfiltered pressure waveform and the Ohmeda Biox 3700e plethysmogram were released without any time delay.

In order to confirm that the surface ECG was time aligned with the haemodynamic waveforms I observed, on Labview, the effects of movement on the various recordings, Figure 2-20.

I was able to confirm that the surface ECG is released without a significant time delay in relation to the pressure waveform from the Finometer.

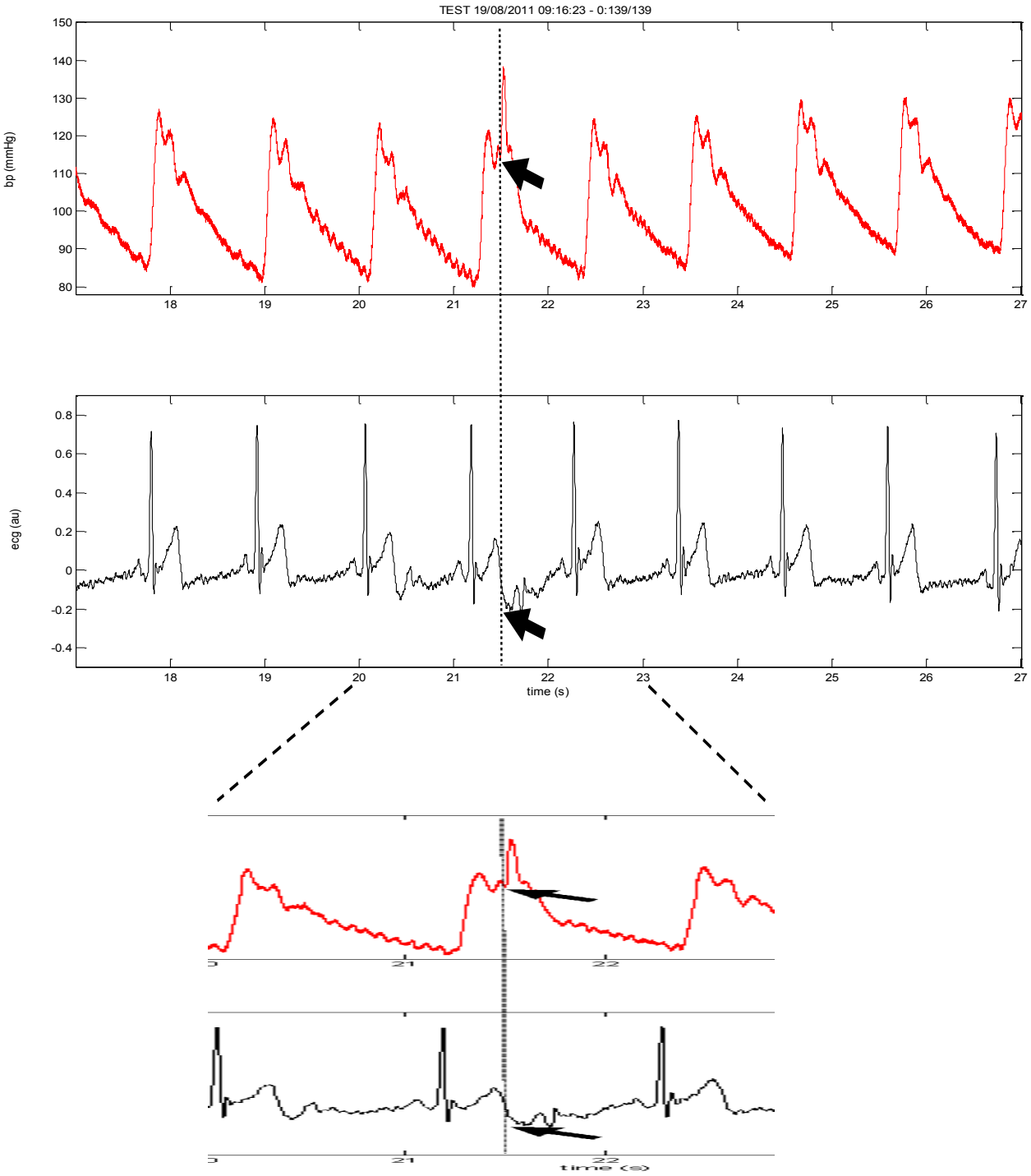


**Figure 2-20. Comparison of a blood pressure trace with a surface ECG**

A movement artefact was intentionally introduced to the pressure and ECG traces, by striking the ECG electrodes and the Finometer cuff simultaneously. This verified that there was no significant time delay (as seen clearly by the zoomed in area) between the output and subsequent acquisition, on Labview, of the two signals

### 2.3.2 Scaling of data

The haemodynamic data were not re-scaled when converted from text to Matlab files, as the right scale for each was correctly present during the recordings.

Re-scaling was introduced for data from the manual transition-marker box. This took place during the conversion of the text files to Matlab files.

The output from this channel is a continuous fixed voltage and is altered when the key on the box is pressed at times of transition form one pacemaker setting to another. For example, an AV change from 120 ms to 80 ms would have been represented by a voltage change from 1.2 to 0.8 Volts. A calibration factor of 100ms/Volt was applied prior to analysis.

### 2.3.3 Identification of the change in pacemaker setting

I noticed that there was a significant time delay between the actual pacemaker setting change and the 'time stamp' introduced manually using the transition-marker box. The key on this box was pressed at the same time as the change in the pacemaker setting was programmed. However, although the time stamp was almost immediately output and recorded, the pacemaker took some time to actually change the setting from the time the 'programme' button was pressed.

So the next step in the data analysis was to identify the point at which the actual transition in pacing parameter occurred, Figure 2-21. Not correcting for this time delay would introduce a very large amount of noise in the analysis with implication on the precision of the optimal pacemaker setting identification.

To prevent this, a number of steps were introduced in the analysis. The surface ECG was used as the cornerstone for identification of the actual transition.

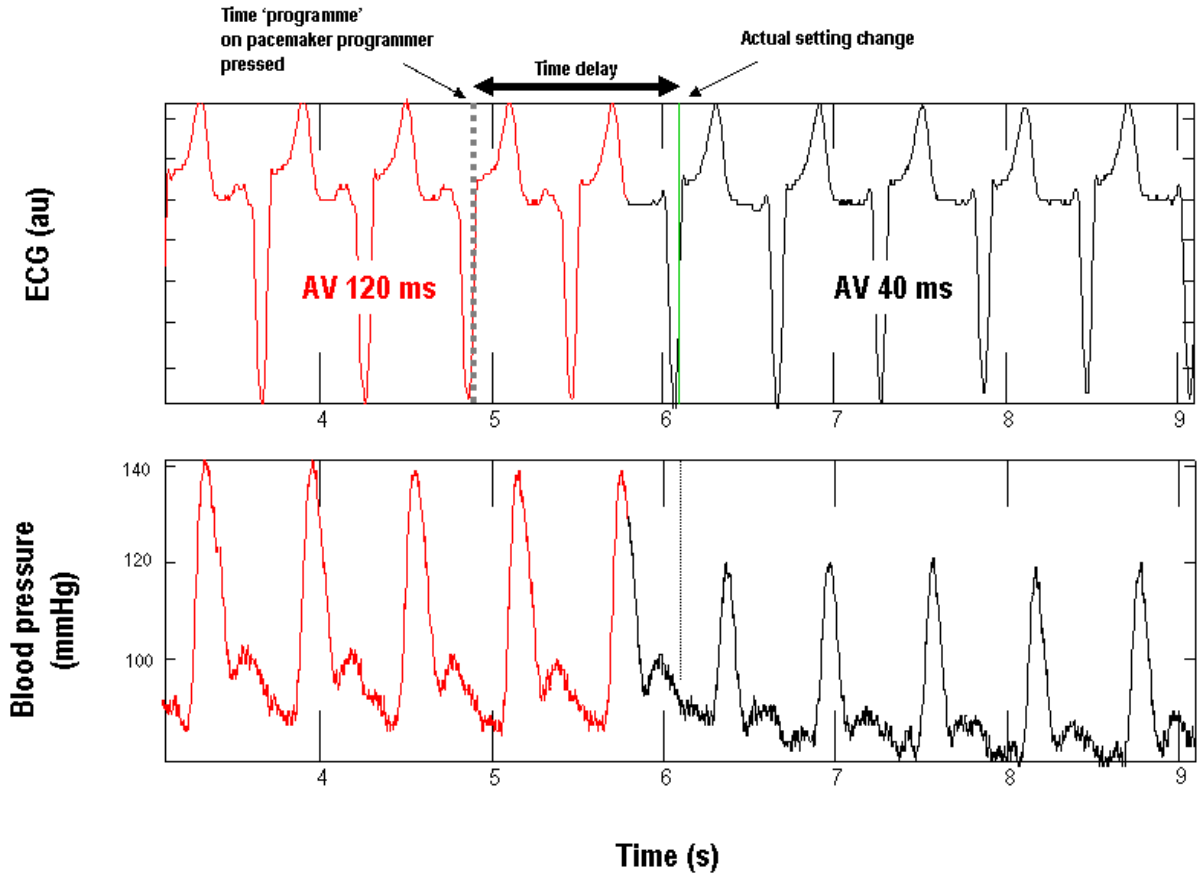


**Figure 2-21. Example of the time delay between pressing the 'programme' button and the actual change in the pacemaker setting occurring**

There is a time delay between the pressing of the programmer and the change on the AV delay occurring for 120 to 40ms. The number of beats it takes for this to happen depends on the heart rate; in this example the delay was of two beats

The software aligns the ECG segments and centres on the R wave. It then takes the first beat of the recorded data and examines the QRS complex a fixed time before and after the R wave. By doing so it gathers information about the PR segment and QRS morphology. Following this a rolling window of two beats compares (by plotting a correlation) the two successful beats and when the morphology of one of these two beats changes, the programme marks it as a change in the pacemaker setting. As a result during a recording of, for example transitions between the reference and tested AV delay, two distinct groups of beats are identified. This analysis is applicable for both AV and VV delay changes. The automatic

identification of changes in the AV delay is more challenging than changes in VV delay. The correlations between beats typically exceed 0.9, even between beats of different AV delays, because the QRS shape is large and essentially the same between different beats. Therefore, the algorithm transforms them on a logarithmic curve which "stretches out" these high correlations between 0.9 and 1.0.

The selections of the transition points are plotted on 2 charts. The first chart provides a visual presentation of the transition points, Figure 2-22. The appearance of this plot helps create an impression of the accuracy of transition identification by the software. A tartan like appearance (alternation of two discrete colours) suggests high degree of accuracy in the automatic selection of transitions by the software. A less discrete separation and presence of more than 2 colours, is very suggestive of unsatisfactory discrimination of ECG morphologies and less accurate marking of transition points.

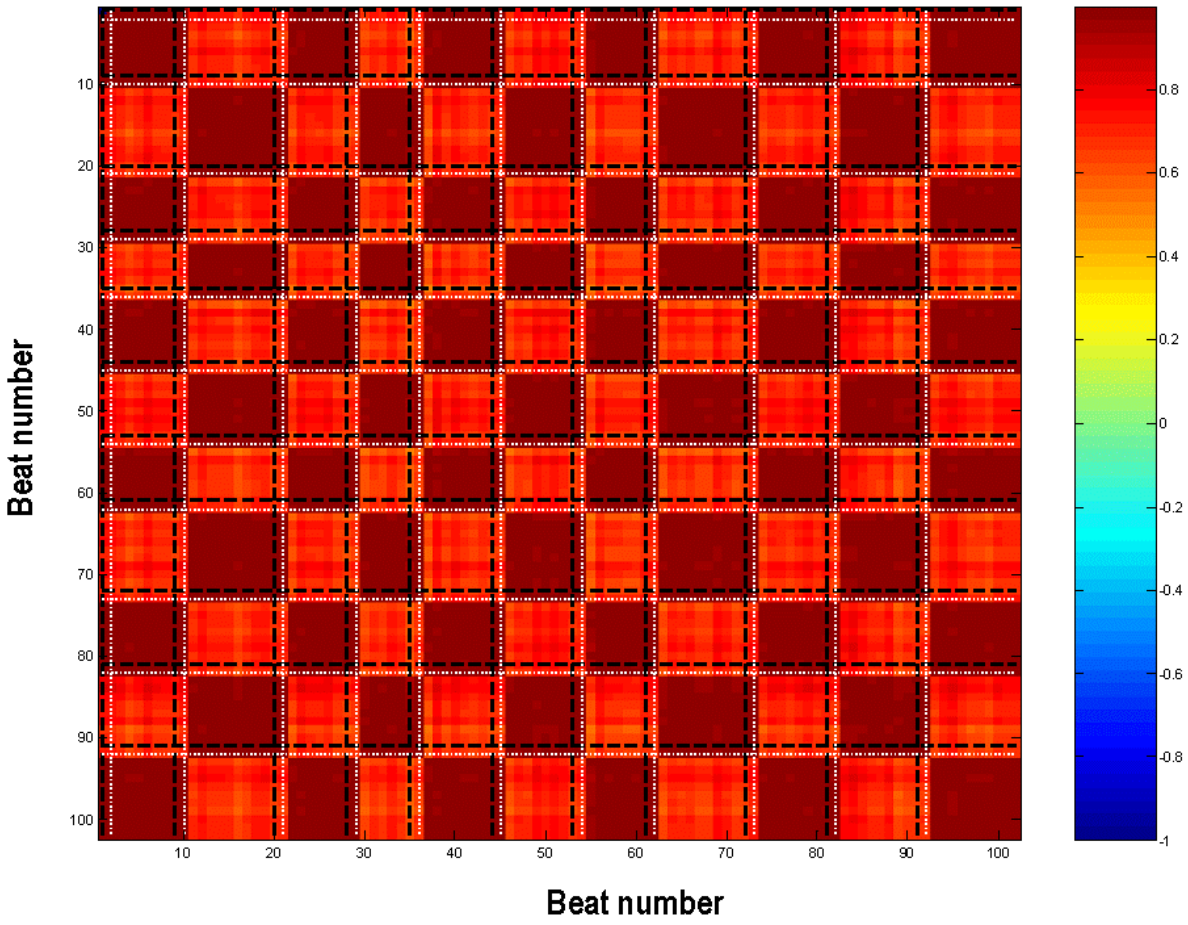


**Figure 2-22. Method for automated identification of transition point**

A rolling window of two beats compares the ECG morphology using an algorithm of correlations in order to identify a transition in pacemaker settings. The correlation coefficient is transformed in colour and shown here; the presence of two distinct colours represents the presence of two distinct ECG morphologies. The black line represents the time the pacemaker programmer was programmed ('stamped' using the transition-marker box) and the white line indicates where the automated analysis has identified the actual transition in AV delay.

The second chart presents the actual ECG and the automatically identified transition points. This provides preliminary information to the user that can help identify whether the selected transition points are the real ones or not, Figure 2-23.

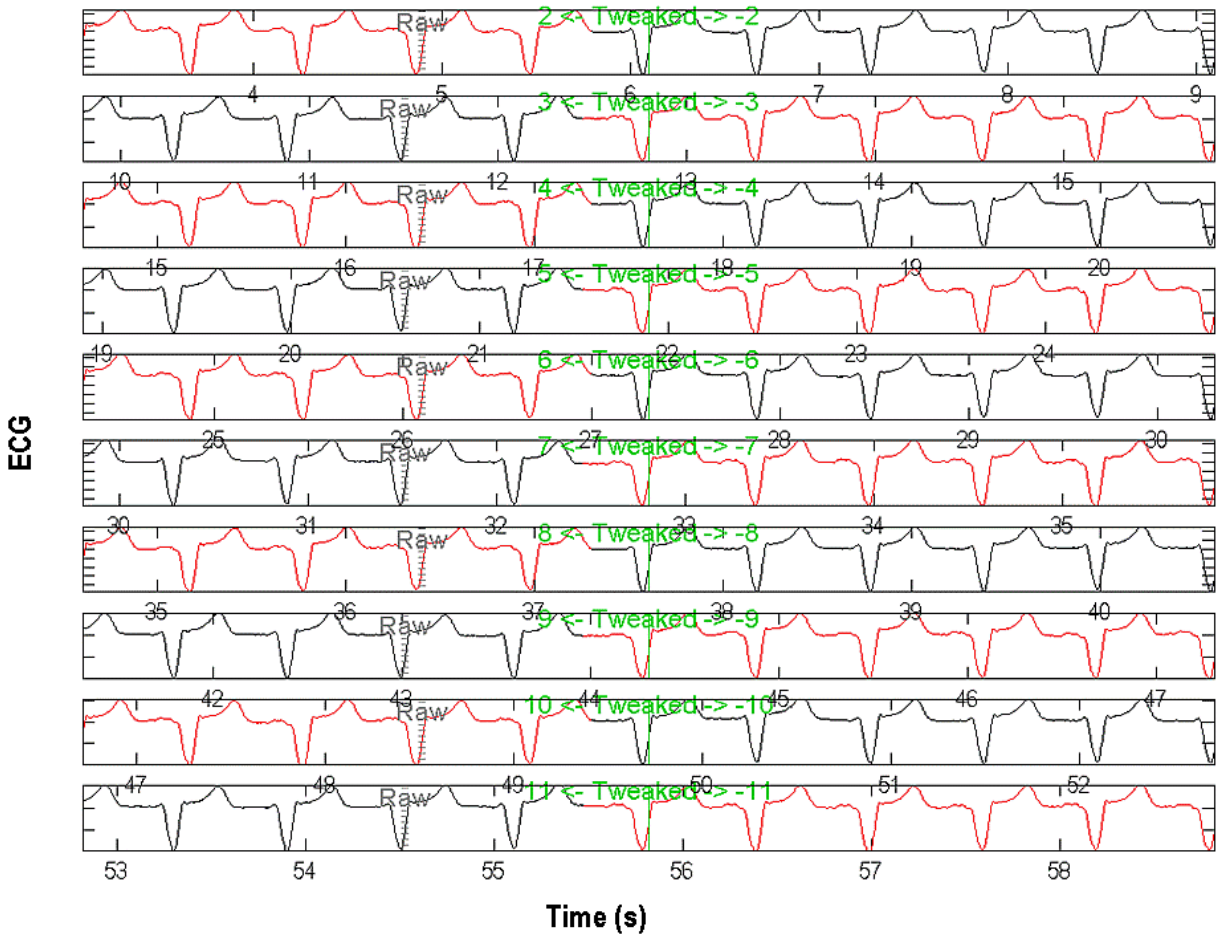


**Figure 2-23. ECG traces following automated identification of setting transition**

This is an example of transitions between AV 120 and 40 ms. The grey line marked 'Raw' represents the time stamp for the pacemaker programming. The green line marked 'Tweaked' indicates where the automated system has identified the actual transition. If on inspection the user identifies misplaced transition points, further tweaking can be manually performed. The numbers 1 to 11, and -1 to -11, represent the codes the user needs to enter to make the manual fine tunings to any of the automated 'Tweaked' transition identifications

If there is doubt regarding the accuracy of the transition point selection, the user has the option to examine the ECG trace to confirm that the software had correctly or not correctly identified each transition. Manual adjustments can be made as appropriate to ensure that the transitions in AV or VV delay are correctly marked. The ECG-aligned transition data is saved so that the next time the data is loaded they are automatically applied.

### 2.3.4 Algorithm for calculation of haemodynamic changes

Once the transition points for each of the tested AV/VV delays have been correctly identified the optimization algorithm can be applied. The algorithm calculates the relative changes, in the haemodynamic parameter measured (e.g $SBP_{rel}$), at each transition point and generates a number of relative haemodynamic changes equal to the number of replicates performed for each of the tested AV or VV delays.

It was possible to study a number of haemodynamic parameters such as non-invasive beat-to-beat blood pressure, invasive aortic and left ventricular blood pressures and invasive aortic and coronary blood flow velocities (all of these haemodynamic parameters were used for the experiments presented in Chapters 3-7). I was able to test a large number of various comparisons within and between haemodynamic parameters; for example the number of beats to be averaged before and after a transition in order to achieve maximal signal to noise ratio, the number of replicates to be included in the analysis and subsequent averaging in order to identify, with an acceptably high enough precision, the optimal pacemaker setting.

### 2.3.5 Export of data and curve fitting

The changes in the values of the haemodynamic parameter measured were automatically exported to an excel spreadsheet, which subsequently allowed determination of the mean change in the haemodynamic and its standard error, for each of the tested AV/ VV delays. Curve fitting identified the optimal pacemaker setting. These data were then saved for further analysis.

I employed curve fitting to identify the optimal setting (AV or VV) for two main reasons. First, this process was automated and therefore readily produced the best fit of a parabola, as described by the quadratic equation $y=ax^2+bx+c$ ($2^{nd}$ degree polynomial). By automating the process it immediately removed the need for the investigator to choose the highest/maximum value therefore mitigating an element of selection bias. The automation process of identifying the optimal value was especially

important when reproducibility of optimization of various technologies (echocardiography. ECG, and photoplethysmography) was assessed.

Second, picking the highest is not as straight forward as it is implied. Measurement of, for example, blood pressure changes from one setting to another has biological variability which serves as noise and makes identification of the optimal setting very challenging. To quash this noise sufficiently, and pick confidently the true optimal setting using the 'pick the highest' method, Francis DP (Francis DP. 2013) has mathematically demonstrated that an extraordinary number of replicates of data, with thousands of beats being acquired, will need to be averaged in order to deliver enough precision. This is not only feasible in clinical practice, due to time constraints, but also in the research environment when more time is available – but still hours of data will need to be acquired. Instead, application of a parabola (curve fitting) to choose the optimum reduces the number of replicates, and therefore time, required to perform a sufficiently reliable optimization.

### 2.3.6 Patient selection and Ethics

There were 3 groups of patients recruited for this study. All groups fulfilled criteria for cardiac resynchronization therapy. The specific inclusion and exclusion criteria for each group are described in the corresponding Chapters of the thesis.

The first group of patients were those who were recruited for the invasive studies (Chapters 3 and 4). They were all patients with current criteria of CRT implantation (LVEF<35%, NYHA II-IV, QRS>120ms and on maximal medical therapy) and were undergoing coronary angiography as part of their clinical investigation to determine the cause of their heart failure. The same patient cohort was used for the acquisition and analysis of the data presented in both Chapters 3 and 4.

The second group of patients had already a CRT device implanted and were patients in sinus rhythm. They were recruited for the non-invasive studies described in Chapters 5 and 7. Separate cohorts of patients were recruited for each of the two studies.

The third group of patients also had a CRT device already implanted but these were patients in permanent atrial fibrillation. They were specifically recruited for the non-invasive study described in Chapter 6.

All of the patients recruited for the investigations were provided with a Patient Information Sheet (PIS) and they all signed a specific consent form as approved by the local ethics committee. The ethics committee's approval letter, containing a list of all the documents reviewed and approved by the committee, is found in the Appendix.

# 3 The mechanoenergetic advantage of CRT arises from both ventricular resynchronization and atrioventricular optimization

## 3.1 Abstract

**Background**

The acute mechanoenergetic (i.e the extent of external 'useful' cardiac work and the quantity of energy consumption) effects of optimization of atrioventricular delay (AVD) during atriobiventricular pacing (cardiac resynchronization therapy, CRT) are not known. I studied these invasively, in a contemporary cohort of patients i.e patients with systolic heart failure and left ventricular ejection fraction (EF) of less than 35%, New York Heart Association (NYHA) II-IV and left bundle branch block (LBBB); an electrical conduction delay within the ventricle that is responsible for the incoordinate mechanical activation of the left ventricle i.e mechanical dyssynchrony. As a result of this electrical delay the left ventricle is commonly activated via electrical activity spreading through the ventricular septum from the right bundle. Consequently the activation of the left myocardial mass, especially of the posterolateral segments, occurs outside the specialised conduction system and is therefore very delayed.

**Methods**

Eleven patients with systolic heart failure (EF 26±6%) and left bundle branch block (LBBB, QRS 175±17 ms) underwent measurements of left ventricular (LV) developed pressure, aortic flow velocity time integral (VTI) (an index of stroke volume) and myocardial oxygen consumption (MVO2) at four pacing states: biventricular pacing with AVD 40ms (BiV-40), AVD 120ms (BiV-120, commonly used nominal AV delay) and at the individualised haemodynamic AVD optimum (BiV-Opt); and intrinsic conduction (LBBB). Heart rate was fixed by atrial pacing.

**Results**

BiV-120, relative to LBBB, increased LV developed pressure (11±2%, $p<0.001$) and aortic VTI (11±3%, $p<0.001$), but also increased MVO2 (11±5%, $p=0.04$).

BiV-Opt, relative to BiV-120, further increased LV developed pressure (2±1%, $p=0.035$) and aortic VTI (3±1%, $p=0.017$). MVO2 trended up by 7±5% ($p=0.22$).

Mechanoenergetics at BiV-40 were no different from LBBB (p=ns).

The 4 states lay on a straight line for Δexternal work (ΔLV developed pressure × Δaortic VTI) against Δ MVO2, with slope 1.80, significantly greater than 1 ($p<0.05$).

**Conclusions**

Acute atriobiventricular pacing at the nominal AV delay increased both external cardiac work done and myocardial oxygen consumption. However, the increase in cardiac work was ~80% greater than the increase in oxygen consumption, signifying an improvement in cardiac efficiency. The incremental effect of optimization was approximately one-third beyond that of nominal AV pacing, along the same favourable efficiency trajectory.

## 3.2 Introduction

Atriobiventricular pacing (cardiac resynchronization therapy, CRT) in heart failure patients with LBBB and EF<35%, has been shown to increase arterial blood pressure and cardiac output and to also increase external ventricular work (Leclercq C. 1998, Auricchio A. 2002, Kass D.A. 1999, Butter C. 2001, van Gelder B.M. 2005) and efficiency (Nelson G.S. 2000). The pioneering small studies of the acute haemodynamic effects of biventricular pacing paved the way for large randomized controlled trials which demonstrated reductions in morbidity and mortality (Cleland J.G. 2005, Young J.B. 2003, Abraham W.T. 2002, Cazeau S. 2001, Bristow M.R. 2004, Moss A.J. 2009, Tang A.S. 2010). Some questions remain unanswered, however.

First, the effect of atriobiventricular pacing on myocardial oxygen consumption ($MVO_2$) *per beat* is not certain. One invasive study (Nelson G.S. 2000) found that $MVO_2$ fell after 2 minutes of pacing, but since this was accompanied by a lower heart rate, it is not clear whether oxygen consumption per beat was altered.

Studies using non-invasive estimation of $MVO_2$ using positron emission tomography (PET) have reported that regional $MVO_2$ changed with CRT with a more favorable redistribution of the pattern of oxygen consumption in the myocardium (Ukkonen H. 2003, Lindner O. 2005). Although global $MVO_2$ was statistically unchanged, some studies have indicated that biventricular pacing of LBBB (Ukkonen H. 2003) or absence of LBBB (Lindner O. 2005) shows a trend of higher $MVO_2$.

Second, it is not known whether the pattern of mechanoenergetic effects of AV delay adjustment resembles that of CRT. Doubt exists because CRT is believed to exert its haemodynamic and clinical benefits predominantly by improving synchrony between ventricular walls and only partly by shortening the AV delay; pure AV delay adjustment may therefore give a different balance of mechanoenergetic effects than CRT overall.

I set out to answer both questions in one experiment by invasively monitoring cardiac output, aortic and left ventricular pressures and myocardial oxygen consumption, in a contemporary cohort of patients undergoing cardiac resynchronization therapy (CRT).

I tested the mechanoenergetic effects of CRT with a commonly programmed nominal AV delay (BiV-120), and compared BiV-120 to LBBB. In the same experiment I measured the mechanoenergetic effects of AV delay adjustment; I compared LBBB to a prespecified 'poor' AV delay (BiV-40) and a non-invasively predetermined individualized haemodynamic optimal AV delay (BiV-Opt).

## 3.3 Methods

### 3.3.1 Study Subjects

Sequential patients about to undergo coronary angiography as a routine part of evaluation prior to CRT implantation were approached and gave informed consent to participate in this study. They were entered into the study if their coronary angiogram showed no current significant coronary artery stenosis requiring revascularisation. Twelve patients gave consent. One patient was found to have a significant coronary stenosis and was therefore not entered into the study. In the remaining 11 patients no significant coronary artery stenosis was found and all met the criteria to undergo the complete study. Four of these remaining eleven patients had prior documented clinical symptoms and diagnosis (two patients by stress testing followed by coronary angiography but with no percutaneous intervention and two patients following non-ST elevation myocardial infarction for which one patient had undergone angioplasty to the left circumflex and the other one to the right coronary artery) of ischemic heart disease. Patient characteristics are displayed in Table 3-1. The study was approved by the local ethics committee.

**Table 3-1. Baseline characteristics of patients**

| Patient | Gender | Age (years) | Cause of Heart Failure | QRS width (ms) | Ejection fraction (%) | LVEDD (cm} | NYHA Class | Drugs b-blockers | ACE/ARB | Diuretic | Digitalis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 52 | DCM | 175 | 20 | 7.3 | III | 1 | 1 | 1 | 0 |
| 2 | M | 73 | IHD | 169 | 34 | 6.0 | III | 1 | 1 | 1 | 0 |
| 3 | M | 60 | IHD | 203 | 28 | 4.8 | III | 0 | 1 | 1 | 0 |
| 4 | M | 78 | DCM | 158 | 30 | 4.3 | IV | 1 | 1 | 0 | 0 |
| 5 | M | 76 | DCM | 145 | 24 | 5.0 | III | 0 | 1 | 1 | 0 |
| 6 | M | 80 | IHD | 166 | 35 | 4.1 | III | 0 | 1 | 1 | 0 |
| 7 | M | 65 | IHD | 194 | 20 | 6.7 | III | 1 | 1 | 1 | 0 |
| 8 | F | 62 | DCM | 192 | 33 | 5.4 | IV | 1 | 1 | 1 | 0 |
| 9 | M | 68 | DCM | 183 | 27 | 6.5 | III | 0 | 1 | 1 | 0 |
| 10 | M | 42 | DCM | 170 | 15 | 6.4 | III | 1 | 1 | 1 | 0 |
| 11 | M | 64 | DCM | 166 | 25 | 8.0 | III | 1 | 1 | 1 | 0 |
| Mean | | 65 | | 175 | 26 | 5.9 | Total | 7 | 11 | 10 | 0 |
| St.dev. | | 11 | | 17 | 6 | 1 | | | | | |

### 3.3.2 Measurements

#### 3.3.2.1 Patient preparation

Temporary biventricular pacing was established *via* the femoral route as follows; one quadripolar electrode catheter (Josephson Curve, Bard Vikings) was positioned in the right atrium and one pentapole electrode catheter (Josephson Curve, Bard Woven) in the right ventricle at the apex.

Temporary LV pacing was established using an AL1 and/or a channel sheath to gain access to the coronary sinus and a ATW wire was positioned in a lateral or posterior-lateral branch for LV pacing (Lane R.E. 2008), Figure 3-1. Left ventricular capture was confirmed with a 12 lead ECG recording.

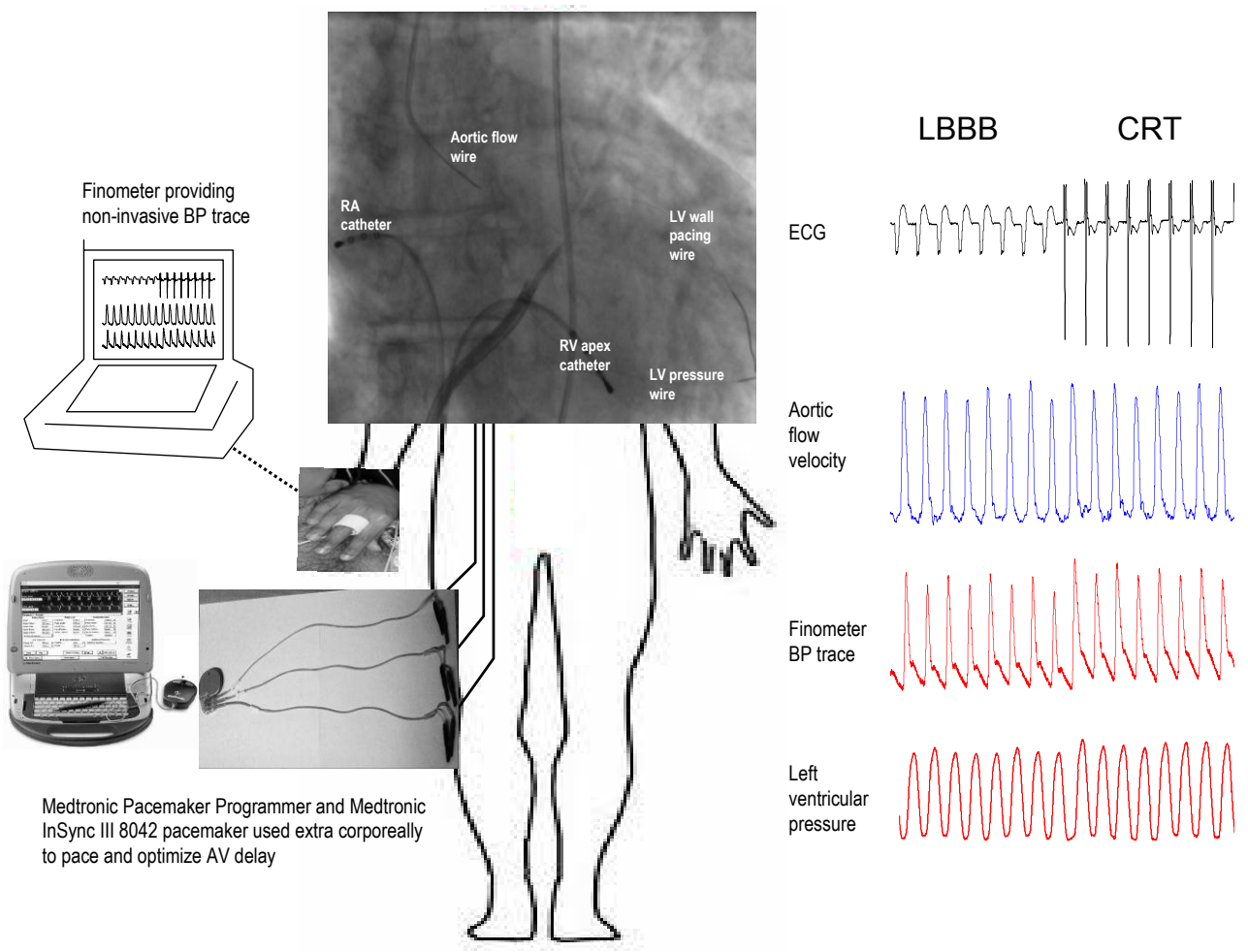


**Figure 3-1. Experimental setup depicting the typical position of the three pacing wires (in RA, RV apex and posterolateral LV).**

The Finometer was used for non-invasive haemodynamic AV delay optimization during stage I. In stage II, invasive measurements of aortic flow velocity and left ventricular pressure measurements were recorded at the 4 pacing states

(AVD 40ms, AVD 120ms, predetermined optimal AVD and LBBB) and their product was used for estimation of external cardiac work.

Stable pacing and sensing for all three pacing wires was confirmed and checked periodically throughout the study. In all patients, heart rate was kept fixed by atrially pacing at 100bpm. A pressure wire (Volcano PrimeWire 7900) was placed in the LV cavity via a diagnostic catheter, which was subsequently withdrawn 4-5cm into the aorta and kept at this position throughout the study, leaving the pressure wire in the LV cavity. A flow wire (Volcano FloWire 1400) was inserted into the same catheter and carefully positioned in the aorta, approximately 4cm from the aortic valve to obtain a stable flow velocity signal.

#### 3.3.2.2 Stage I: Prior establishment of non-invasive haemodynamic AV delay optimum

A non-invasive blood pressure measurement device (Finapres Medical Systems, Amsterdam, Netherlands) was applied to the patient's finger. The RA, RV and LV pacing leads were connected via custom made connectors to a standard CRT pacemaker (Medtronic InSync III 8042).

Non-invasive haemodynamic AV delay optimization was carried out using an alternation algorithm as previously described (Whinnett Z.I. 2006, Whinnett Z.I. 2006, Whinnett Z.I. 2008, Whinnett Z.I. 2008, Whinnett Z.I. 2011). In brief, a series of AV delays were tested and compared against a reference AV delay (120 ms) using several forward and backward transitions, which allowed the relative systolic blood pressure difference between the AV delays to be determined to a high level of precision (Whinnett Z.I. 2006, Pabari P.A. 2010). I tested a range of AV delays for each patient (40, 80, 160, 200, 240, and so forth at 40 ms intervals) until intrinsic conduction was reached. The hemodynamically optimal value was defined for each individual as the AV delay corresponding to the maximum of the parabola fitted to the measured data (Whinnett Z.I. 2006, Whinnett Z.I. 2006).

#### 3.3.2.3 Stage II: Invasive measurements at 4 pacing settings (including non-invasive haemodynamic optimum)

Measurements were made in random order, at 4 pacemaker settings: AVD 40 ms (BiV-40); reference AVD 120 ms (BiV-120, a commonly programmed nominal AVD), individual's non-invasive

haemodynamic optimum and AAI (intrinsic ventricular conduction i.e. LBBB). Note that the optimum AV delay (BiV-Opt) was defined in stage I, i.e. using only non-invasive pressure measurements. Therefore the data obtained in stage II with this pacemaker setting does not simply represent the highest value of any stage I measurement, rather it represents the invasive haemodynamic values arising as a consequence of the pacemaker being programmed to the predefined optimal setting.

Invasive left ventricular pressure and aortic flow were assessed using BiV-120 as the reference state (Whinnett Z.I. 2006). The product of aortic flow velocity integral and left ventricular developed pressure (systolic – diastolic) was used as an index of stroke work within each patient for comparison of pacing conditions.

For the invasive assessment of myocardial oxygen consumption the flow wire was then repositioned, through a diagnostic catheter, in the left coronary artery in a proximal position where a clear Doppler signal could be recorded. The site was the left main stem in 10 patients, but had to be the proximal circumflex artery in 1 patient. The velocity waveform was traced automatically (by the ComboMap console Pressure and Flow system), and this profile of the velocity waveform was digitally acquired by our system for automatic ensemble averaging across beats, to obtain a velocity-time integral for all the four pacing states tested within each patient. Myocardial oxygen consumption was estimated by multiplying arteriovenous oxygen saturation difference, $\Delta AVO_2$, (in the left coronary artery and coronary sinus) by coronary artery flow velocity-time integral.

For each pacing state, quintiplicate pairs of arterial and venous blood samples were withdrawn, for saturation assessment, after at least 90 sec of pacing in that state (Nelson G.S. 2000, Pitt B. 1968, Suga H. 1990). Coronary flow was defined as the velocity-time integral averaged over the 60s period of blood sample withdrawal.

### 3.3.3 Data acquisition

Left ventricular pressure was measured by the sensor-tipped wire. Aortic pressure was measured using a standard fluid-filled catheter which was carefully calibrated before the study measurements, by matching against the pressure wire signal, with the pressure wire and catheter co-located in the aorta.

Haemodynamic and ECG data were acquired using a NIDAQ AI-16E-4 analog-to-digital card (National Instruments, Austin, TX) and Labview (National Instruments, Austin, TX). They were analysed with custom software based on the Matlab platform (MathWorks, Natick, MA).

### 3.3.4 Statistics

Values are presented as mean ± SEM, unless otherwise stated. Analysis of data was performed using the mixed linear model approach. Paired comparisons of continuous variables were made using Student's paired *t* test. A p-value of $<0.05$ was taken as statistically significant. Stata version 11.0 for Windows (StataCorp LP, College Station, Texas) was used for statistical analysis.

## 3.4 Results

The absolute values of PR intervals, optimal AV delays and haemodynamic parameters during LBBB (AAI pacing at 100bpm) are shown in Table 3-2. In addition, the absolute values of the haemodynamic parameters at all tested AV delays are also shown in Table 3-3.

**Table 3-2. AV conduction and haemodynamic parameters at an atrially paced rate (AAI) of 100bpm**

| Patient | PR interval with AAI pacing (ms) | Optimal AV delay (ms) | Coronary flow VTI (cm) | A-V oxygen saturation (%) | Myocardial oxygen cons. index (au) | LV developed pressure (mmHg) | Aortic VTI (cm) | Cardiac Work index (au) |
|---|---|---|---|---|---|---|---|---|
| **1** | 220 | 155 | 12 | 63 | 753 | 83 | 22 | 1859 |
| **2** | 250 | 187 | 41 | 51 | 2092 | 128 | 12 | 1473 |
| **3** | 253 | 176 | 33 | 48 | 1622 | 140 | 22 | 3019 |
| **4** | 215 | 148 | 20 | 39 | 786 | 118 | 8 | 972 |
| **5** | 235 | 186 | 19 | 72 | 1379 | 129 | 14 | 1837 |
| **6** | 350 | 193 | 17 | 67 | 1102 | 85 | 14 | 1207 |
| **7** | 240 | 175 | 18 | 56 | 1036 | 90 | 19 | 1694 |
| **8** | 270 | 211 | 20 | 61 | 1229 | 112 | 14 | 1569 |
| **9** | 205 | 140 | 31 | 67 | 2089 | 133 | 22 | 2911 |
| **10** | 295 | 211 | 12 | 46 | 560 | 114 | 11 | 1237 |
| **11** | 285 | 213 | 24 | 70 | 1684 | 124 | 15 | 1849 |
| Mean | 256 | 181 | 23 | 58 | 1303 | 114 | 16 | 1784 |
| Stand. Dev. | 42 | 26 | 9 | 11 | 523 | 20 | 5 | 652 |
| SEM | 13 | 8 | 3 | 3 | 158 | 6 | 1 | 197 |

**Table 3-3. Raw values of all haemodynamic parameters at 100bpm, at all biventricular paced states**

| Patient | Myocardial Oxygen Consumption (au) | | | LV developed pressure (mmHg) | | | Aortic Velocity time integral (cm) | | | Cardiac work index (au) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AVD-40 | AVD-120 | Opt-AVD | AVD-40 | AVD-120 | Opt-AVD | AVD-40 | AVD-120 | Opt-AVD | AVD-40 | AVD-120 | Opt-AVD |
| **1** | 704 | 758 | 775 | 80 | 87 | 87 | 21.8 | 24.7 | 25.3 | 1737 | 2149 | 2197 |
| **2** | 1736 | 2354 | 2507 | 133 | 141 | 150 | 12.4 | 13.4 | 14.8 | 1649 | 1882 | 2221 |
| **3** | 1835 | 2288 | 2069 | 148 | 157 | 153 | 22.6 | 25.9 | 25.7 | 3333 | 4066 | 3917 |
| **4** | 925 | 998 | 978 | 114 | 134 | 137 | 7.7 | 9.2 | 9.2 | 871 | 1226 | 1255 |
| **5** | 1272 | 1669 | 1656 | 112 | 138 | 139 | 14.5 | 15.8 | 16.6 | 1626 | 2174 | 2313 |
| **6** | 1300 | 1364 | 1461 | 103 | 113 | 114 | 17.9 | 18.9 | 20.0 | 1843 | 2130 | 2276 |
| **7** | 936 | 1037 | 1151 | 87 | 99 | 101 | 16.9 | 19.4 | 19.4 | 1462 | 1916 | 1969 |
| **8** | 1228 | 1347 | 1223 | 100 | 119 | 121 | 12.6 | 13.8 | 14.3 | 1251 | 1642 | 1720 |
| **9** | 1854 | 1903 | 1959 | 144 | 152 | 154 | 23.0 | 24.7 | 24.4 | 3323 | 3754 | 3751 |
| **10** | 655 | 533 | 830 | 101 | 122 | 132 | 10.7 | 11.5 | 12.0 | 1076 | 1397 | 1582 |
| **11** | 1444 | 1668 | 1928 | 110 | 128 | 134 | 14.4 | 15.7 | 16.1 | 1588 | 2003 | 2160 |
| Mean | 1263 | 1447 | 1503 | 112 | 126 | 129 | 15.9 | 17.5 | 18.0 | 1796 | 2213 | 2306 |
| St.Dev | 429 | 594 | 566 | 22 | 21 | 22 | 5.1 | 5.7 | 5.5 | 811 | 896 | 825 |

### 3.4.1 Effect of biventricular pacing on haemodynamics

Left ventricular developed pressure (systolic minus diastolic) rose from LBBB to AV 120ms (Biv-120) by 11±2% ($p<0.001$) and an additional 2±1% increase was observed ($p=0.035$) at the optimal haemodynamic AV delay (BiV-Opt). At AVD 40ms (BiV40), pressure was 13±2% worse than BiV-120 ($p<0.001$) and not statistically different to LBBB ($\Delta$=-2±3%, $p=0.50$).

Aortic velocity time integral (index of stroke volume), measured throughout each individual's study, rose by 11±3% ($p=0.002$) from LBBB to BiV-120, rising a further 4±1% ($p=0.017$) at BiV-Opt. At BiV-40, aortic VTI was 10±1% worse than BiV-120 ($p<0.001$) and no different to LBBB ($\Delta$=1±3%, $p=0.87$). All four pacing states are shown in Figure 3-2.

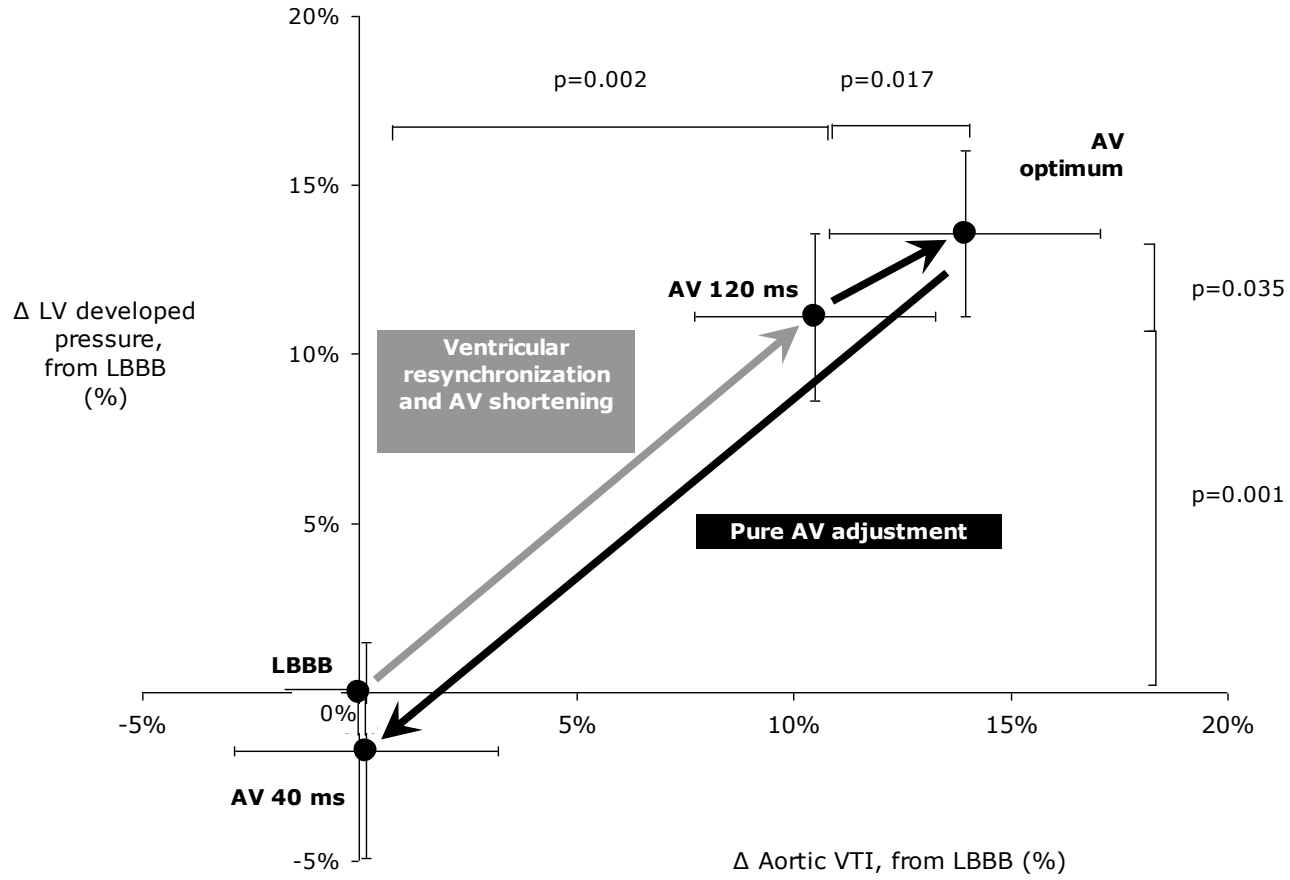


**Figure 3-2 Relationship between changes in LV developed pressure and aortic VTI at three AV delays with LBBB as a reference**

The haemodynamic response measured by LV developed pressure and aortic VTI (stroke volume index) when pacing from LBBB to the 3 biventricular AVDs of 40ms, 120ms and the non-invasively predetermined haemodynamic AV optimum. The optimal AVD produced the highest pressure and aortic VTI, statistically significantly higher than the AVD 120 (nominal setting). The changes in pressure and aortic VTI were in similar proportions at all pacing states, i.e 1:1. Biventricular pacing at a physiologically 'too short' AV delay (40ms) resulted in the same haemodynamic profile as LBBB. Therefore, changing the AV delay of biventricular pacing can affect haemodynamics dramatically; at one extreme optimal AVD provides better haemodynamics than for example AVD 120ms (a commonly programmed AVD when AV optimization is not performed ) and on the other extreme any benefit from ventricular resynchronization is offset.

During atriobiventricular pacing the relationship between Δaortic VTI and ΔLV developed pressure, from LBBB, was characterized by the regression equation, y = 1.140 x - 0.017. The slope, 1.14, was not statistically different to 1 (p=NS); i.e both parameters changed by equal proportions.

Compared with LBBB, external cardiac work (indexed by aortic VTI × LV developed pressure) increased at BiV-120 by 24±6% (p=0.001), and by a further 7±2% (p<0.001) at BiV-Opt; p=0.012 versus AV-120. BiV-40 was not different to LBBB (Δ=-1±6%, p=0.76), Figure 3-3.

### 3.4.2 Myocardial oxygen consumption

The $MVO_2$ increased from LBBB to BiV-120 by 11±5% (p=0.04) and to BiV-Opt by 18±4% (p=0.003); there was no significant difference in the myocardial oxygen consumption between AV-120 and AV-Opt, p=0.22.The $MVO_2$ between BiV-40 and LBBB was not significantly different (Δ=0±3%, p=0.83), Figure 3-3.

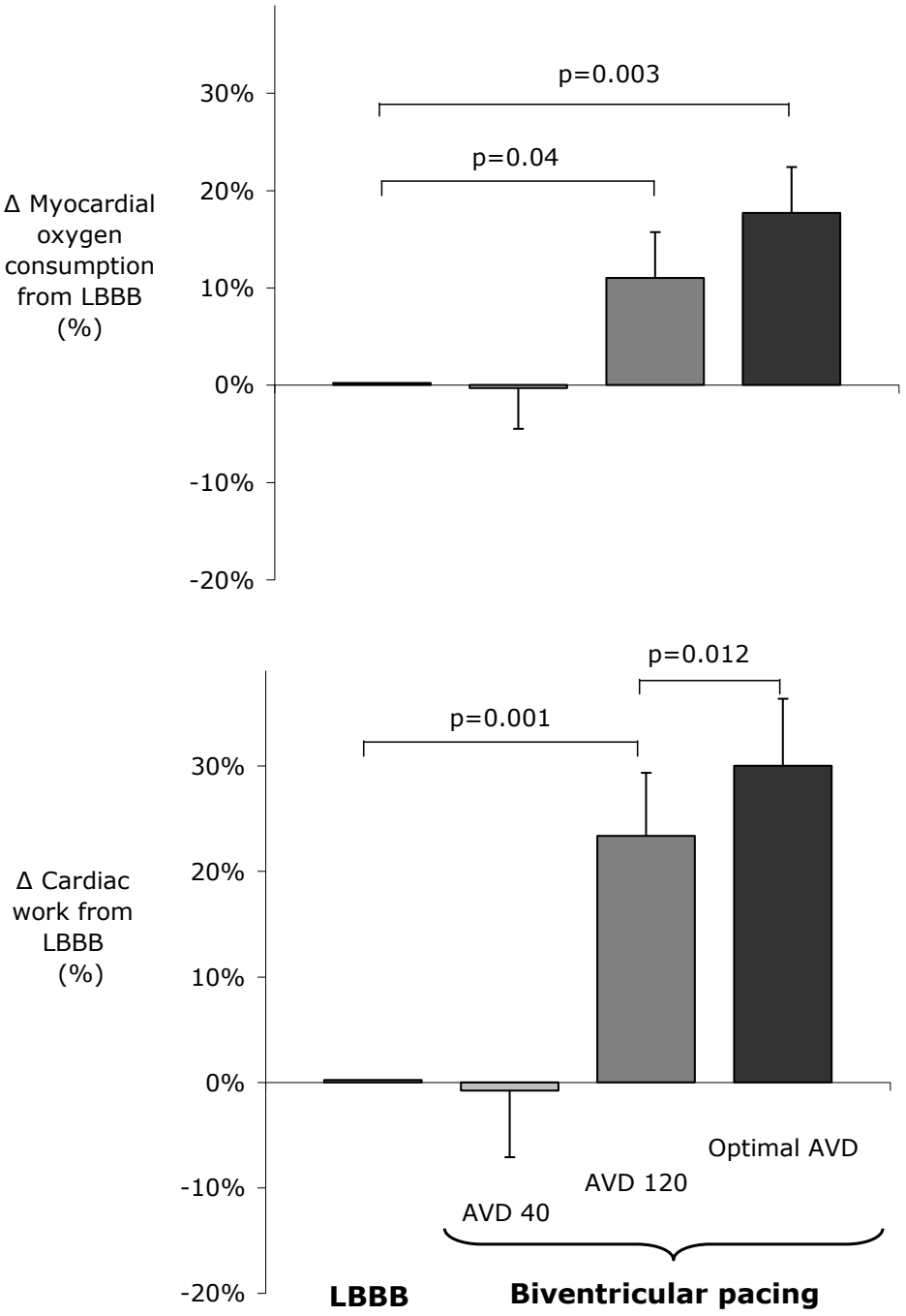


**Figure 3-3. Effect of biventricular pacing with three different AV delays on myocardial oxygen consumption (top figure) and cardiac work (indexed by the product of LV developed pressure and aortic velocity time integral – bottom figure), compared to intrinsic conduction (LBBB).**

Myocardial oxygen consumption increases significantly when paced with an AVD of 120ms and at the optimal AV delay, compared to LBBB. Similarly, but proportionally more, the cardiac work rises at AVD 120ms and optimal AVD; this rise is approximately one-third higher at optimal AV delay than at AVD 120ms. AVD 40ms was not significantly different compared with LBBB.

### 3.4.3 Mechanoenergetic effect of biventricular pacing

The 4 states lay on a straight line, because the (resynchronization) increment from LBBB to BiV-120 had the same direction as the effects of adjustment of AV delay (between BiV-40, BiV-120, BiV-Opt). This common direction had a slope (percentage increment in external cardiac work done per percentage increment in $\Delta MVO_2$) of 1.80±0.003, significantly greater than 1 (p=0.02), Figure 3-4.

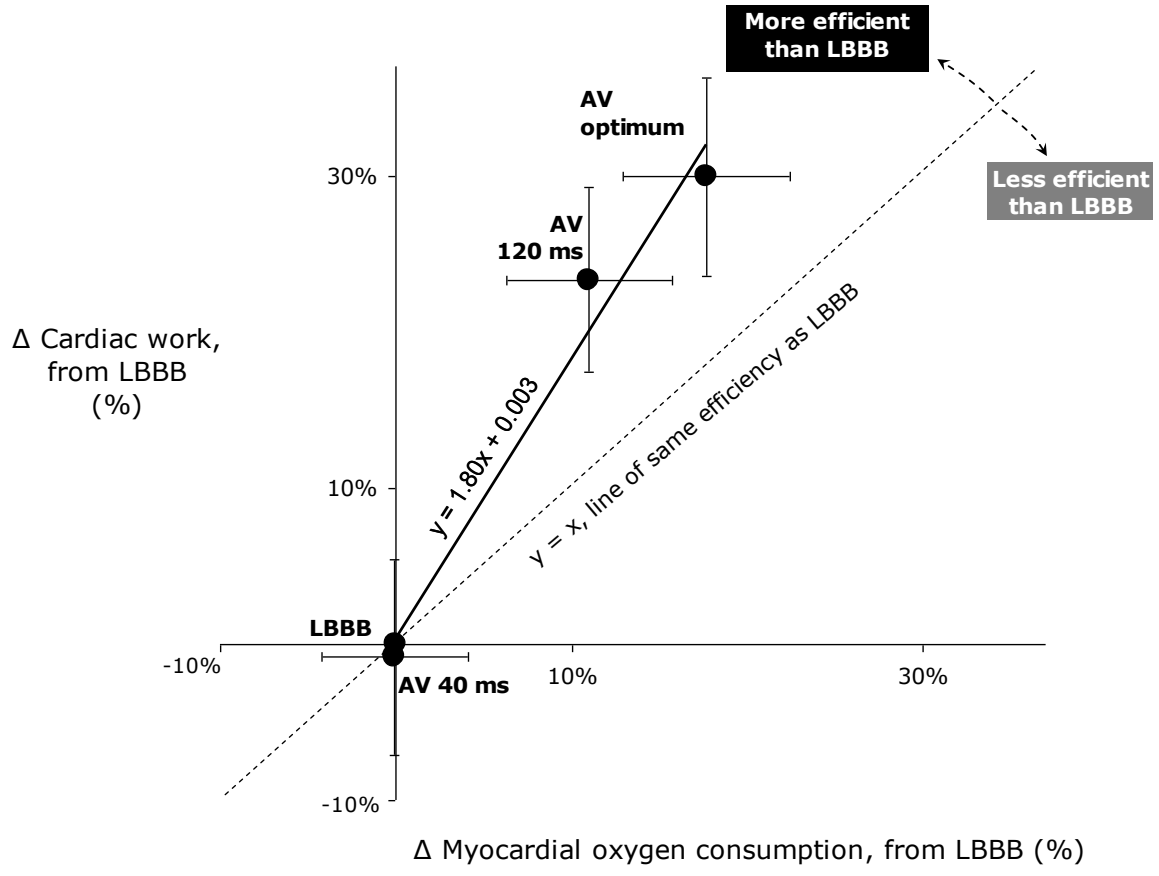


**Figure 3-4. Relationship between the change in cardiac work (indexed by the product of LV developed pressure and aortic velocity time integral) and change in myocardial oxygen consumption with biventricular pacing at each of the three AV delays (40ms, 120ms and optimal AV), from LBBB.**

The slope (Δcardiac work ÷Δmyocardial consumption) of the regression line is 1.80 (significantly higher than 1, p=0.02), implying a more efficient myocardial state with biventricular pacing, at 120ms or optimal AV, than in or Biv-120ms. Of the two higher-efficency states, the AV-Opt generates one-third more 'useful' cardiac work than AV-120, p=0.012.

### 3.4.4 Relationship between coronary flow and mechanoenergetics

Coronary flow was positively correlated to myocardial oxygen consumption ($r=0.88$, $p<0.00001$, Figure 3-5). Similarly, coronary flow also increased with elevations in cardiac work ($r=0.53$, $p<0.001$, Figure 3-5).

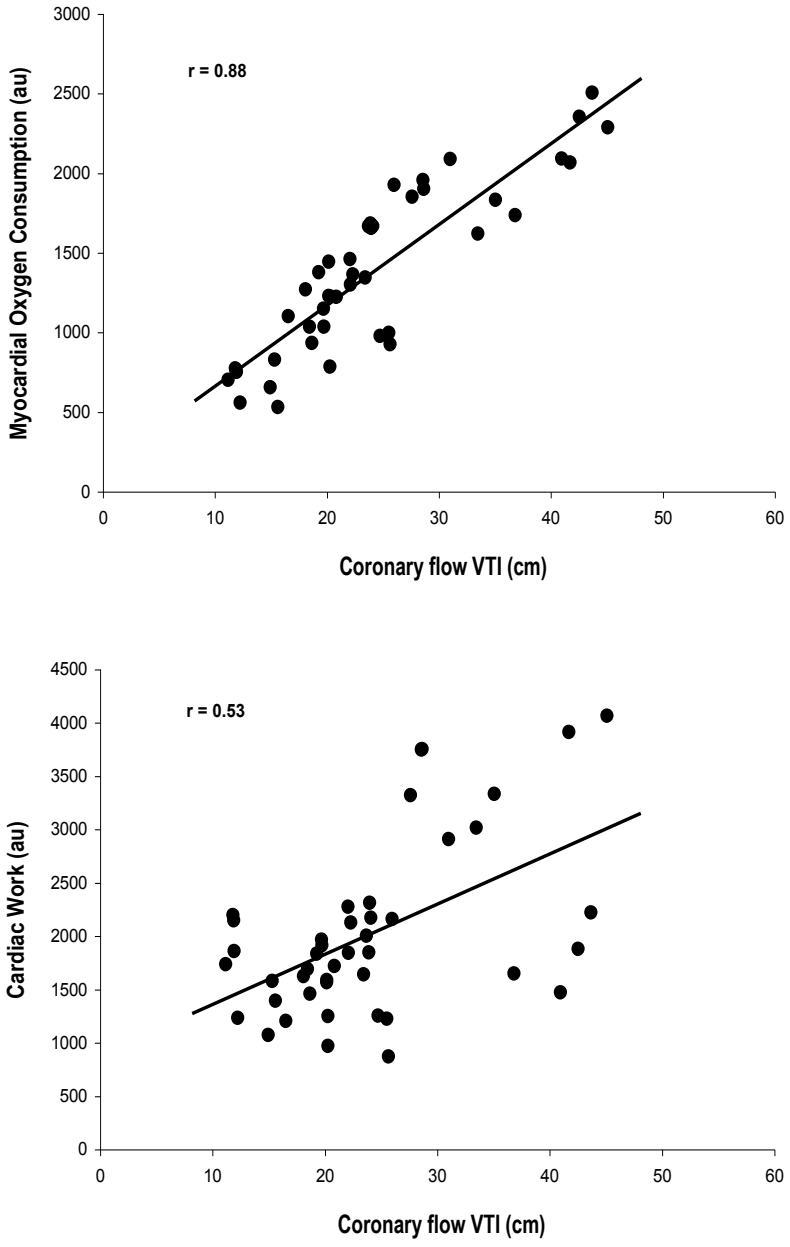


**Figure 3-5. Relationships between coronary flow and myocardial oxygen consumption and cardiac work.**

Coronary flow is significantly positively correlated to both rises in myocardial oxygen consumption and cardiac work.

## 3.5 Discussion

In this study I investigated invasively the cardiac mechanoenergetic profile of biventricular pacing and haemodynamic AVD optimization. Our findings were that, while biventricular pacing at AVD 120 ms (a common nominal setting of CRT devices) increased external cardiac work delivered, it did so at the expense of some increase in myocardial oxygen consumption ($MVO_2$). Fortunately, the proportionate increase in external cardiac work was 80% more than that in oxygen consumption, which indicates that the increment had a higher efficiency than baseline LBBB function.

Second, moving from AVD 120ms to the individual's predetermined AV optimum significantly increased external cardiac work delivered by one-third, with a trend to a further increase in $MVO_2$. The trajectory of this further increment from optimization was similar to that of switching the biventricular pacemaker on at AVD 120ms.

Finally, setting a universally unfavourable AV delay (40ms) put the mechanoenergetic profile of biventricular pacing back to values closely resembling LBBB: the notable feature is that unfavourable AV delay alone was able to "undo" the entire mechanoenergetic benefit of cardiac resynchronization.

### 3.5.1 Impact of biventricular pacing on myocardial oxygen consumption

Our study demonstrates that, when heart rate is kept fixed and therefore not influencing mechanoenergetics, biventricular pacing with a nominal AV delay of 120ms increases the $MVO_2$ *per beat*. In principle, the acute effect of CRT only affects the timing of activation of myocytes and cannot directly manipulate the internal metabolism of sarcomeres or mitochondria (Mills R.W. 2009). Poorer synchrony means wall movement is occurring at times that are more different between sites. As a result, cavity pressure developed is delayed and overall lower. If inward wall movement at each local site is the same, then the total energy consumed by inward movement over the whole (dyssynchronous) chamber must be less. Of course, it is possible that the sum of local inward movements is larger in a dyssynchronous heart, but it has to be larger by more than the degree of fall in pressure developed, before

their mutual product – the leading determinant of metabolic cost – can be higher than the synchronous heart.

Resynchronization of the ventricular walls by biventricular pacing prevents substantial segments of myocardium from escaping with light duties (Prinzen F.W. 1999) (i.e. contracting early, at lower pressure and therefore lower metabolic cost, but at a time where they cause internal shifts of blood within the ventricle rather than usefully ejecting blood). From this viewpoint it is less surprising that CRT might increase the average (and therefore total) oxygen consumption of the myocardium.

Positron emission tomography scanning data, also at fixed heart rate, have shown that biventricular pacing raises oxidative metabolism in the septal myocardium by 15%, with no significant changes in the lateral or anterior walls (Ukkonen H. 2003). It is the septum which has the opportunity to contract early at lower cavity pressures – and therefore at lower metabolic cost – during LBBB. MRI tagging in the canine model has also confirmed that at the site of pacing, early local contraction (in comparison to the rest of the ventricle which therefore results in a lower rise in chamber pressure) dramatically reduces local work done (Prinzen F.W. 1999).

Many interventions that increase work done by the heart do so at the expense of increasing myocardial oxygen consumption (Holubarsch C. 1994, Teboul J.L. 1993). A report that biventricular pacing might be unique, in permitting an increase in work done while reducing oxygen consumption (Nelson G.S. 2000) has therefore been very attractive. The biventricular pacing element of that study was conducted in 5 of 10 invasively studied patients (having set aside a further 1 in whom sufficient systolic pressure response was not obtained). The characteristics of those patients were typical of patients being considered for CRT at that time (2000), namely almost exclusively non-ischaemic dilated cardiomyopathy, long PR interval (mean PR 196.5±13.6 ms), wide QRS (mean QRS 179.1±3.4 ms) and markedly reduced ejection fraction (mean EF 19.7±2.6%). Such patients are – even now – widely considered to be ideal candidates for CRT. Our own study's patients are more typical of current cohorts undergoing CRT implantation, namely a mixture of ischaemic and non-ischaemic cardiomyopathies, Table 1. That study also differed from ours in that it allowed heart rate to change naturally and used a statistical correction to adjust for any

reflex fall in heart rate with biventricular pacing. In contrast our study fixed heart rate at 100 bpm. The previous approach gives the answer to a question which might be argued to be more clinically important: net effect (with reflex heart rate response); in contrast our current approach gives the answer to a more specific mechanistic question: pure direct cardiac effect (without reflex heart rate response). Together with the difference in patient populations, this procedural difference may explain the superficially different results of our two studies.

Although it may be disappointing to find that, in our cohort of 11 patients at fixed heart rate, biventricular pacing did not yield a fall in MVO2, it should be remembered that fall in MVO2 is not essential for an intervention to make the heart more efficient. Nor need it necessarily be expected of an intervention that makes the walls of the left ventricle contract more simultaneously, against a higher cavity pressure, rather than at different times against a lower cavity pressure.

Moreover, it was evident from these data that the rises in cardiac work led to increases in the coronary flow. In addition, the higher the coronary flow that was measured the higher the myocardial consumption became (Figure 3-5). It appears that coronary flow is an important contributor of the changes in the MVO2 and it may be influenced by changes in left ventricular contractility. Therefore I performed a more detailed investigation into identifying the mechanisms determining left coronary flow and also assessed the effects of CRT and AV delay optimization on flow; these are discussed in Chapter 4.

### 3.5.2 Commonalities between biventricular pacing and adjustment of AV delay

In our study, initiation of biventricular pacing raised cardiac work by 24±6% % for an increment in myocardial oxygen consumption of only 11±5%. This means that the incremental change had a trajectory ~180% as efficient as the behaviour of the myocardium in the native LBBB state.

Beyond this establishment of CRT at the nominal AV delay of 120ms, however, further adjustment of AV delay to a prior noninvasively determined haemodynamic optimum, gave further, albeit smaller,

increments in cardiac work of 7±2% (approximately an additional one-third of the effect of AV-120), and a non-significnat increase in myocardial oxygen consumption.

The fact that AV delay optimization produced an effect that appears to be a smaller-scaled but in proportion version of the effect of switching on nominal-setting CRT itself, suggests that they may have considerable overlap in physiological mechanisms, for the following reason. The step from LBBB to AV120 ms is a combination of ventricular resynchronization and shortening of AV delay. The change from AV120 to AV optimum (181+/-26 ms) is likely to be largely due to change in AV delay (rather than further improvement in ventricular synchrony). Since the two trajectories appear to be similar in direction, we reason that either the two processes (ventricular resynchronization and change in AV delay) have coincidentally the same ratio of effects on the various measured variables (cardiac work and $MVO_2$), or the AV delay process is such a dominant contributor to the combination step (LBBB to AV120) that it dominates the trajectory of the effects on the measured variables. Moreover, it is striking that setting the AV delay too short, at 40 ms, effectively annuls all the mechanoenergetic effects of biventricular pacing, back to a haemodynamic state equivalent to LBBB.

These observations have implications for which actions of a biventricular pacemaker are responsible for the ultimate benefits: ventricular resynchronization or AV delay adjustment. Either the contribution of pure ventricular resynchronization is collinear in direction (i.e. in balance between DELTA MVO2 and DELTA WORK DONE) with pure AV adjustment, or ventricular resynchronization makes only a relatively small contribution to the combined effect of CRT.

### 3.5.3 Clinical implications

The impact of AV optimization on the measured parameters in this study was about ¼ the effect of switching on CRT a fixed AV delay of 120ms. This estimate is statistically unbiased because the measurement of the effect was from data separate from those used for identification of the optimal AV delay. Each patient's "optimum" AV delay was determined first, by a rapid protocol of non-invasive blood pressure measurements during alternations of AV delay settings (Whinnett Z.I. 2006), from which

a parabola was plotted and the peak identified, so that that setting could be used in the later invasive experiment. Thus, the finding that invasive pressure is higher at the optimum cannot be attributed to selection of the highest amongst random variation (Pabari P.A. 2010), since had this occurred the subsequent invasive pressure and aortic velocity time integral measurements would not on average have been any higher than the AV 120 values.

The effect of optimization had the same balance of haemodynamic effects (and same inclination to improved efficiency) as nominal-programmed CRT itself, although smaller (one-third that of nominal CRT), and so I should expect the same balance of morbidity-mortality benefits but an endpoint trial to verify this would need to be much larger (×9) than the landmark trials that have so clearly established the clinical benefits of CRT. A smaller effect size does not mean lower cost-effectiveness, since optimization can be much cheaper (with much less adverse consequences) than the implant procedure, especially if a reproducible and valid fully-automatic method becomes available within the CRT device as seems inevitable.

A second clinical implication is that optimization that selects the wrong AV delay does net harm to haemodynamics. Although extreme mis-selection (AV 40ms) is required to systematically abolish the haemodynamic effect of CRT across the whole population, milder mis-selection (i.e. getting only close to the true optimum) may still prevent the full potential haemodynamic benefit of optimized CRT.

### 3.5.4 Study limitations

Our study was an invasive study and the number of subjects was not large. However, it was sufficient to address the physiological question being considered. Patients were heterogeneous in terms of aetiology and drug therapy but I believe they are representative of contemporary cohorts undergoing CRT.

All participants were paced at a rate of 100bpm during the study. This prevented reflex reduction in heart rate which is a feature of CRT but had the advantage that it allowed the direct mechanoenergetic

consequences of resynchronization and AV optimization to be studied uncomplicated by changes in heart rate.

In this study, I found that programming the AV delay to a very short setting, for example 40ms, it completely removed the effect of biventricular pacing, with acute haemodynamics falling to baseline LBBB levels. This may be considered as an unfair comparison of AV 40 to LBBB, due to the extreme atrio-ventricular dissociation that such a short AV delay can cause. A more representative comparison of the relative effect of AV optimization and resynchronization at this short AV delay would have been the comparison between biventricular pacing and RV pacing. However, the aim of testing such a short AV delay was not to show equivalence to LBBB, but it was merely an attempt to demonstrate that despite achieving resynchronization, when AV delay is programmed to a setting too far away from the optimal AV, any gains in haemodynamics achieved by AV optimization and resynchronization, together, can be completely lost just by extreme AV dissociation. Equally, less short AV delays causing less atrioventricular dissociation would cause a lesser loss of haemodynamics. This is an important consideration when using unreliable optimization methods which can select an 'optimum' setting far away from the true clinical optimum and therefore systematically hinder the beneficial effect of CRT.

In our study, the AV optimum was selected by non-invasive measurement of BP, prior to invasive measurements. This avoided bias and minimised the duration of the invasive study.

I have not attempted, and do not intend, to assess improvement in mortality from optimization. The data showed that the mechanoenergetic effect of optimization (away from AVD 120) is about one-quarter of that elicited by implantation of the device. Therefore the most likely impact on survival would be ~¼ the 29% benefit seen in CARE-HF, i.e ~7%. However an optimization endpoint trial adequately powered to confirm this would need to be $4^2$=16 times the size of an implantation endpoint trial.

Finally, whether every patient should be optimized or only those that are considered non responders cannot be answered by this study. However, if a reproducible optimization method is available that is cheap and not uncomfortable for the patient, then (given the average ~25% advantage over nominal settings) why not offer it to all? In contrast, if reproducible optimization is only available at great expense

and patient inconvenience, then it may be pragmatic to only recommend it to patients who are looking for more symptomatic response than they first received.

## 3.6 Conclusions

Biventricular pacing, in patients in whom heart rate was kept constant, increased useful cardiac energy output by 70% more than the increase in myocardial oxygen consumption, i.e. the increment had an improved efficiency. Optimization increased both in the same favourable proportions by one-quarter as much as biventricular pacing itself. The trajectories of effect on haemodynamic measurements of AV optimization and of institution of nominal-AV biventricular pacing were very similar, to the extent that mis-selection of AV could completely abolish the haemodynamic effects of biventricular pacing, rendering the patient back to a mechanoenergetic status equivalent to intrinsic LBBB. This suggests that improvement of AV delay may be an important contributor to the haemodynamic (and therefore clinical) effects of CRT. In this study, AV optimization appears to extend this improvement 25% further.

# 4 Improvement in coronary blood flow with acute biventricular pacing is predominantly due to an increase in a diastolic backward-travelling decompression (suction) wave

## 4.1 Abstract

**Background**

Normal coronary blood flow is principally determined by a backward–travelling decompression (suction) wave in diastole. This wave may be attenuated in chronic heart failure, reducing blood flow, as regional relaxation and contraction overlap in timing. I hypothesized that biventricular pacing by restoring left ventricular (LV) synchronization and improving LV relaxation might increase this decompression wave, improving coronary flow.

**Method and Results**

Ten CHF patients (9 male; age 65±12; EF 26±7%) with left bundle branch block (LBBB, QRS duration 174±18 ms) were atrio-biventricularly paced at 100bpm. LV pressure was measured and wave intensity calculated from invasive coronary flow velocity and pressure, with native conduction (LBBB) and during biventricular pacing at atrioventricular (AV) delays of 40ms (BiV-40), 120ms (BiV-120), and separately pre-identified haemodynamically-optimal AV delay (BiV-Opt).

Compared against LBBB, BiV-Opt enhanced coronary flow by 15±4% ($p=0.003$), LV $dP/dt_{max}$ by 19±4% ($p<0.001$) and $_{neg}dP/dt_{max}$ by 16±3% ($p<0.001$). The cumulative intensity of the diastolic backward decompression (suction) wave increased by 36±8% ($p=0.011$). The majority of the increase in coronary flow occurred in diastole (64±8%, $p=0.03$). The systolic compression waves also increased, forward by 33±11% ($p=0.043$) and backward by 33±10% ($p=0.014$).

BiV-120 generated a smaller LV $dP/dt_{max}$ (by 23±12%, p=0.034) and $_{neg}dP/dt_{max}$ (by 23±10%, p=0.039) increase than BiV-OPT, against LBBB as reference; BiV-Opt and BiV-120 were not statistically different in coronary flow or waves. BiV-40 was no different from LBBB.

**Conclusions**

When biventricular pacing improves left ventricular contractility, it increases coronary blood flow, predominantly by increasing the dominant diastolic backward decompression (suction) wave.

## 4.2 Introduction

Although atrio-biventricular pacing (cardiac resynchronization therapy, CRT) has been shown to improve haemodynamics acutely (Leclercq C. 1998, Auricchio A. 2002, Kass D.A. 1999, Butter C. 2001, van Gelder B.M. 2005, Nelson G.S. 2000), surprisingly, its effects on coronary blood flow have been understudied.

It is plausible that dyssynchrony which causes the LV wall segments to contract at different times, and therefore reduce the LV pressure developed per myocardial segment and the amount of work done per segment. By resynchronising, all segments contract at higher stress and more work is overall done which would lead to a total increase in cardiac work and this will increase the metabolic demands leading to higher myocardial blood flow (Figure 4-1).

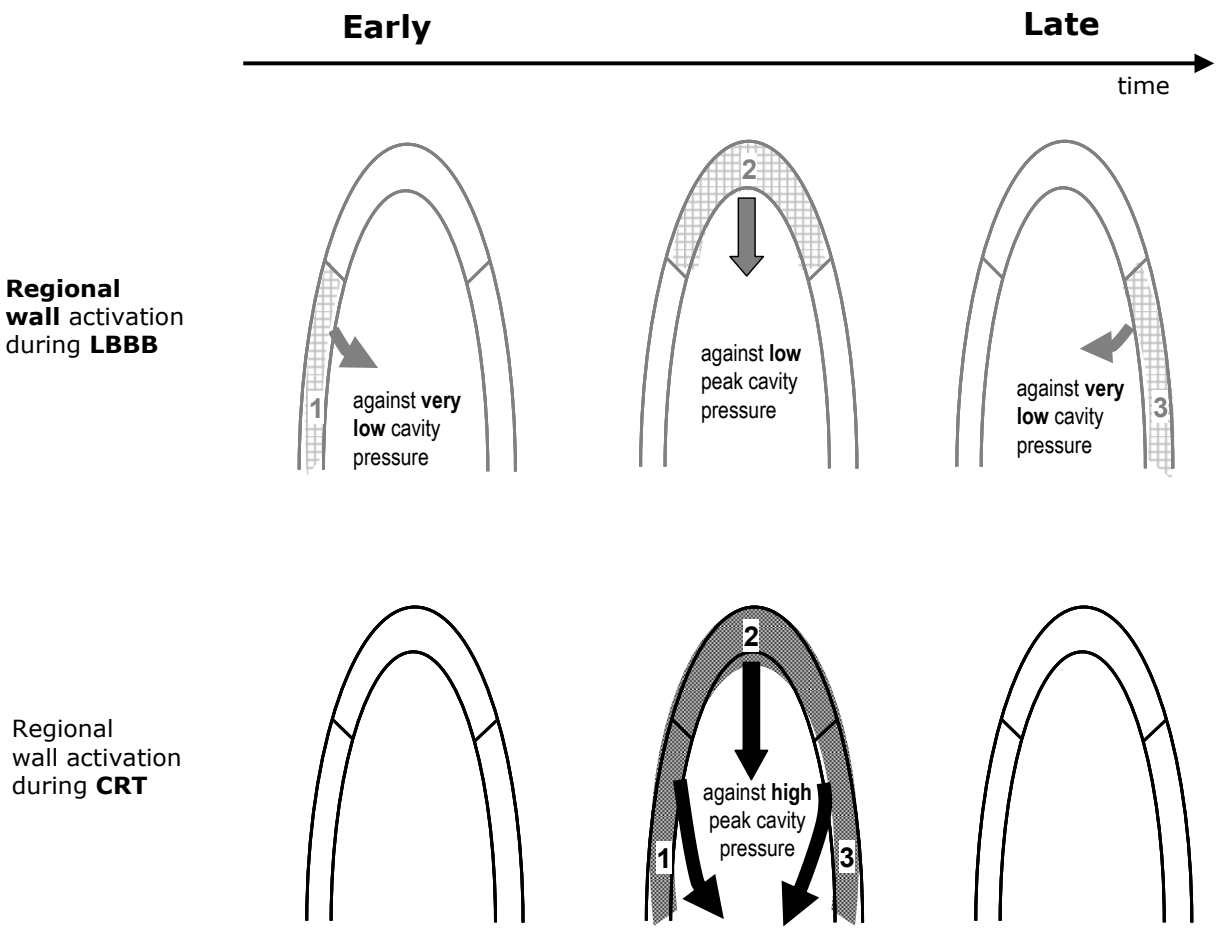


**Figure 4-1. A conceptualized diagram illustrating the pressure difference between LBBB and resynchronization during contraction for each of three myocardial wall segments**

During LBBB, wall segment 1 contracts first and 3 contracts last. Both of these segments contract at times of very low 'off peak' LV pressures; with only segment 2 contracting against peak LV pressure, which is itself low. When these three wall segments are resynchronized, they contract simultaneously, each working to generate higher LV pressure (long black arrows) than they did during LBBB. With each segment contracting against a higher pressure, there may be greater demand for myocardial blood flow.

One study (Nelson G.S. 2000) reported that acute resynchronization pacing in patients with dilated cardiomyopathy and LBBB resulted in a non-significant trend to fall in mean coronary blood flow measured by intra-coronary Doppler. Another study showed no change in global myocardial blood flow measured by $^{11}$C-acetate positron emission tomography (PET) in patients with ischemic or non-ischemic cardiomyopathy at 4 months following implantation, although there was evidence of redistribution of coronary blood flow to the septal wall (Lindner O. 2005, Lindner O. 2005). No study has reported the instantaneous phasic changes in coronary blood flow over the cardiac cycle and additionally, since the

intracoronary pressure was not measured, it was not possible to establish the hemodynamic mechanisms of any changes in flow.

The coronary bed is unique amongst systemic arteries, as flow occurs predominantly during diastole. The reason for this is that the intramural coronary arteries are compressed during systole and during diastole when this compression is released pressure falls faster at the microcirculatory end of the vessel, than at the aortic end. The difference in pressure gradient in diastole causes a suction wave which travels from the distal to the proximal end of the coronary arterial tree accelerating coronary artery blood flow.

Using modern haemodynamic monitoring equipment, it is possible to directly measure the waves associated with the differential pressure changes at each end of the vessel. This allows a detailed quantification of the interaction between the myocardium, coronary artery and the aorta in determining blood flow along the coronary artery. Formal identification and quantification of these waves is called wave intensity analysis (Davies J.E. 2006, Parker K.H. 1990, Jones C.J. 1992, Sun Y.H. 2000).

In the human coronary arteries, the most important waves responsible for accelerating blow flow are the backward decompression wave during ventricular relaxation (diastole) and the forward compression wave during left ventricular (LV) contraction (systole). These waves have been found to have abnormal patterns in conditions such as LV hypertrophy (Davies J.E. 2006), coronary artery disease (Hadjiloizou N. 2008) and in aortic stenosis (Davies J.E. 2011).

Dyssynchrony is often conceptualized as failure of the contraction to be synchronized across different segments of the left ventricle, but equally might be viewed as failure of relaxation to be synchronized. Since it is the act of relaxation that generates the backward decompression wave which is responsible for the majority of coronary flow, dyssynchrony could be attenuating the backward decompression wave and thereby reducing coronary flow. Vigor of contraction can be quantified using the maximal systolic rate of rise of LV pressure ($dP/dt_{max}$) and that of relaxation using the maximal diastolic rate of fall of LV pressure ($_{neg}dP/dt_{max}$).

To test the hypothesis that cardiac resynchronization, and alteration of AV delay, can affect the backward decompression wave and thereby coronary flow, I measured invasively the effects of biventricular pacing on intracoronary haemodynamics and used wave intensity analysis to establish the origin of any changes.

## 4.3 Methods

### 4.3.1 Study Subjects

Twelve sequential heart failure patients in sinus rhythm with no significant valve disease scheduled for coronary angiography as a prelude to CRT implantation were recruited for this study. Patients only entered the measurement phase of the study if they were found to have visually unobstructed coronary arteries. One patient was found to have a significant coronary stenosis and was therefore excluded. In one patient it was not possible to position the flow wire in the left main stem in a position that provided a consistent stable velocity trace. Therefore 10 patients underwent this study. Patient characteristics are displayed in Table 4-1.

**Table 4-1**. **Baseline characteristics**.

| | n, mean and SD (%) |
|---|---|
| Male | 9 (90%) |
| Age (years) | 65.5 SD 12 |
| Cause of Heart Failure | |
| IHD | 3 |
| DCM | 7 |
| QRS width (ms) | 173 SD 17 |
| Ejection Fraction (%) | 27 SD 6 |
| LVEDD (cm) | 5.8 SD 1 |
| NYHA Class | |
| III | 8 |
| IV | 2 |
| Drugs | |
| β-blockers | 6 (60%) |
| ACE-I/ARB | 10 (100%) |
| Diuretic | 9 (90%) |
| α-blockers | 2 (20%) |
| Digitalis | 0 |
| Calcium antagonist | 2 (20%) |

All patients gave prior written informed consent for this study which was approved by the local ethics committee.

### 4.3.2 Measurements

#### 4.3.2.1 Patient preparation

Temporary biventricular pacing was achieved by placement, via the femoral route, of one quadripolar electrode catheter (Josephson Curve, Bard Vikings) in the right atrium (RA), one pentapole electrode catheter (Josephson Curve, Bard Woven) in the right ventricular apex and, through an AL1 and/or a channel sheath positioned in the coronary sinus, an ATW wire was placed posterolaterally for LV pacing.

The stability of the pacing wires was periodically confirmed during the study to ensure consistent atrio-biventricular pacing. The RA, right ventricle (RV) and LV pacing leads were connected via custom-made connectors to a standard CRT pacemaker (Medtronic InSync III 8042). All patients were studied at a controlled atrial rate of 100bpm.

#### 4.3.2.2 Atrioventricular (AV) delay optimization

Optimization of the AV delay was carried out using a non-invasive beat-to-beat blood pressure measurement device (Finapres Medical Systems, Amsterdam, Netherlands) applied to the patient's finger. An algorithm of alternations, as previously described (Whinnett Z.I. 2006, Whinnett Z.I. 2006, Whinnett Z.I. 2008, Whinnett Z.I. 2008, Whinnett Z.I. 2011) was used to identify the optimal AV delay. This algorithm involves a series of tested AV delays each separately compared against a reference AV delay (120 ms) using several forward and backward transitions. This permits the relative systolic blood pressure difference between the tested AV delay and reference AV to be determined to high precision (Whinnett Z.I. 2006, Pabari P.A. 2011). The AV delays tested for each patient ranged from 40, 80, 160, 200, 240 ms, and so forth until intrinsic AV conduction was reached with evidence of LBBB. The AV delay (identified by parabolic interpolation) corresponding to the maximum change in blood pressure from AV 120 ms was considered to be the optimal delay (Whinnett Z.I. 2006, Whinnett Z.I. 2006).

#### 4.3.2.3 Invasive coronary measurements at 4 pacing states

Left main coronary artery pressure and flow velocity were recorded by a sensor-tipped solid state pressure wire (Volcano PrimeWire 7900) and a sensor-tipped solid state flow wire (Volcano FloWire

1400), both positioned through a Judkins left (JL4) diagnostic catheter. The diagnostic fluid-filled catheter measured the aortic systolic pressure. Wave intensity analysis could then be applied, Figure 4-2.

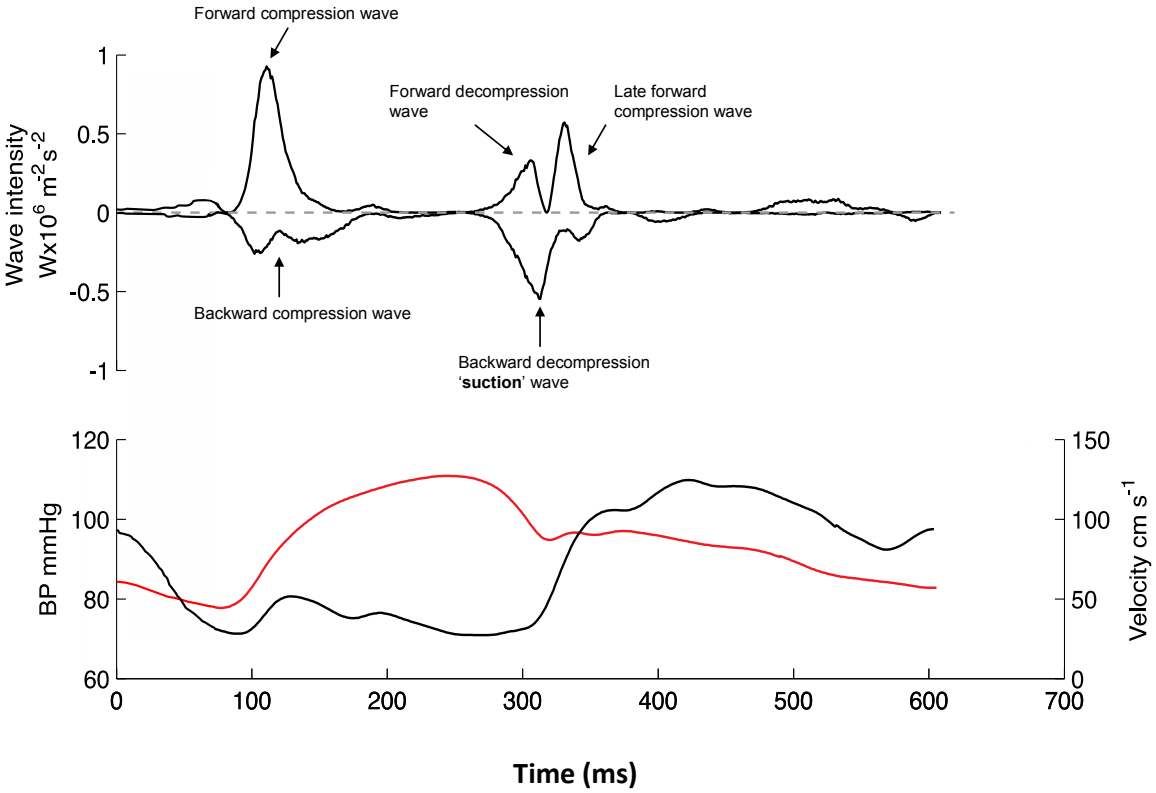


**Figure 4-2 Wave intensity analysis of proximal left coronary artery in a heart failure patient**
This is an example patient included in this study, paced at a constant heart rate of 100bpm at the optimal AV delay. Shown on the top diagram are the main waves isolated by wave intensity analysis. The most dominant waves are the forward compression wave in systole and the backward decompression or suction wave in diastole. In the bottom panel the pressure (red) and flow velocity (black) in the proximal left coronary artery are shown, throughout the cardiac cycle.

Recordings were made for up to 2 minutes (Nelson G.S. 2000, Pitt B. 1968, Suga H. 1990) at 4 pacemaker settings: AV delay 40 ms (BiV-40); reference AV delay 120 ms (BiV-120, manufacturer's nominal AV delay), individual's non-invasive haemodynamic optimum (BiV-Opt) and at LBBB (intrinsic ventricular conduction during atrial (AAI) pacing). The four settings were tested in random order determined by a computer random number generator.

### 4.3.3 Data acquisition and analysis

Haemodynamic and ECG data were acquired using a NIDAQ AI-16E-4 analog-to-digital card (National Instruments, Austin, TX) and Labview (National Instruments, Austin, TX). They were analysed with

custom software written in Matlab (MathWorks, Natick, MA). The aortic pressure and coronary pressure and flow velocity data were filtered and ensemble averaged, and wave intensity analysis performed as previously described (Davies J.E. 2006). The LV $dP/dt_{max}$, $_{neg}dP/dt_{max}$, coronary flow velocity time integral, coronary pressure and analysis of wave intensity magnitudes was performed in Matlab (MathWorks, Natick, MA) using automated algorithms. Velocity time integral was defined in the following way where t represents time during the cardiac cycle from $t_{start}$ to $t_{end}$, $v_t$ the instantaneous flow velocity at time $t$, and $\delta t$ the interval between successive measurements which was 1 ms:

$$\text{Velocity time integral} = \sum_{t_{start}}^{t_{end}} v_t \cdot \delta t$$

### 4.3.4 Statistics

Estimates of the mean are presented with their standard error of the mean as mean ± SEM. Descriptions of the spectrum of baseline patient characteristics are given as mean and standard deviation (SD) explicitly. There are 10 patients and therefore the uncertainty of the mean can be calculated from standard deviation as follows: SEM=SD/√10, or vice versa mutatis mutandis.

Paired comparisons of continuous variables were made using a Student's paired *t* test. A repeated measures ANOVA was used for multiple comparisons. A p-value of <0.05 was taken as statistically significant. Statview 5.0 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

## 4.4 Results

The baseline haemodynamic data of all patients studied are shown in Table 4-2.

**Table 4-2. Haemodynamic data of all the patients during intrinsic ventricular conduction (LBBB) when atrially paced at 100 bpm**

| Haemodynamic parameter | Mean±SEM |
|---|---|
| Systolic blood pressure (mmHg) | 125.1±4.9 |
| LV $dP/dt_{max}$ (mmHg/s) | 1044±78 |
| LV $_{neg}dP/dt_{max}$ (mmHg/s) | 959±78 |
| Total coronary flow VTI (cm) | 21.7±2.9 |
| Systolic coronary flow VTI (cm) | 4.8±0.9 |
| Diastolic coronary flow VTI (cm) | 16.9±2.9 |

### 4.4.1 Increase in coronary flow with biventricular pacing at a fixed heart rate

Coronary flow velocity time integral (VTI) increased significantly with biventricular pacing by 17±4% (p=0.009) at Biv-120 and by 15±4% (p=0.003) at BiV-Opt, with respect to LBBB (Figure 4-2). Coronary flow VTI was not increased by biventricular pacing at the very short AV delay of BiV-40 (5±5%, p=0.6) compared against LBBB (Figure 4-3).

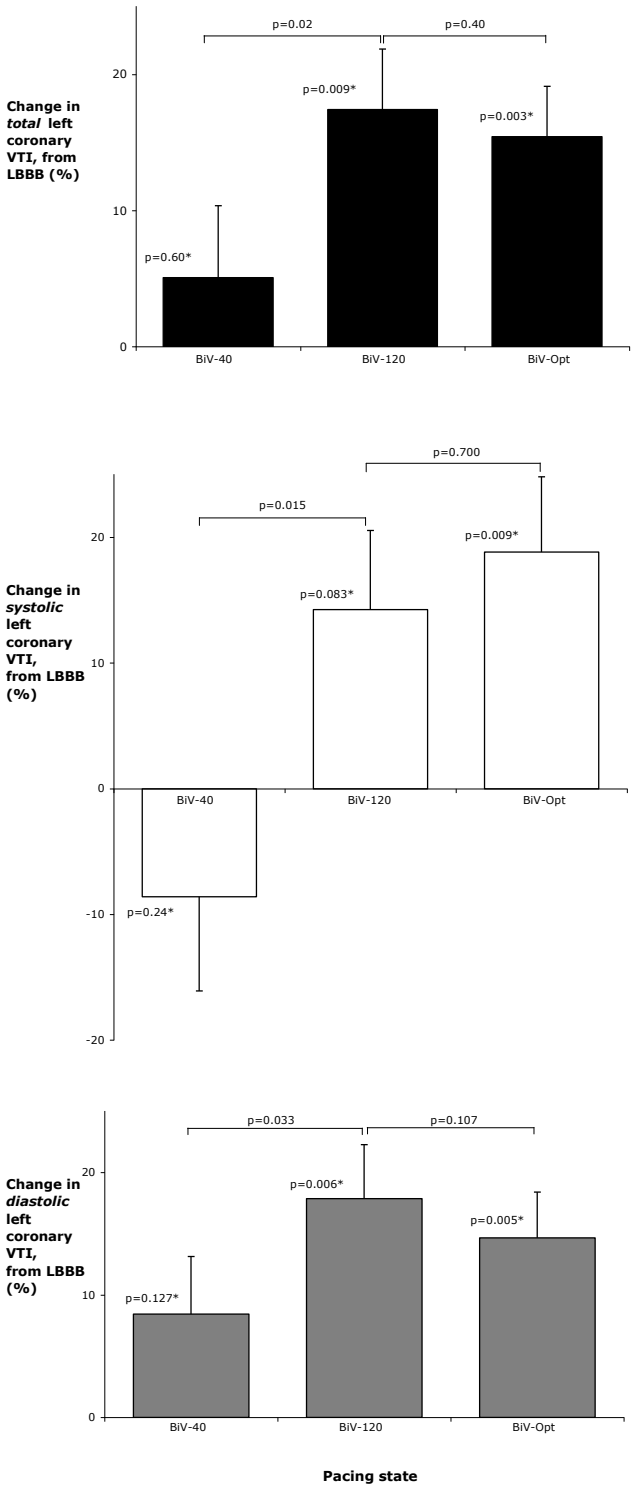


**Figure 4-3. Changes in total, systolic and diastolic left coronary flow VTI from LBBB to three tested AV delays at a fixed heart rate. Data are mean ± SEM; p values were calculated using a paired Student's t-test.**

The total coronary flow VTI was significantly increased at BiV-Opt and BiV-120 when compared to LBBB. There was no difference in total flow VTI between BiV-40 and LBBB. P-values with an asterisk represent the comparison between LBBB and that AV setting.

Of the increase in flow VTI from LBBB to CRT, the diastolic increase contributed the most: 74±6% (p=0.01) at BiV-120; and by 64±8% (p=0.03) at BiV-Opt. Changes in systolic and diastolic flow VTI showed the same pattern of flow across the three AV delays. In all pacing states the ratio of diastolic to systolic flow VTI was unchanged, ~4:1 (repeated measures ANOVA, p=0.54).

### 4.4.2 Increase in ventricular contractility with biventricular pacing at a fixed heart rate

Biventricular pacing increased LV $dP/dt_{max}$ by 16±4% (p<0.001) at Biv-120, and by 19±4% (p<0.001) at BiV-Opt, with LBBB as reference. LV $_{neg}dP/dt_{max}$ was enhanced by 13±3% (p=0.003) at BiV-120 and by 16±3% (p<0.001) at Biv-Opt.

BiV-40 was not significantly different from LBBB in terms of LV $dP/dt_{max}$ (3±4%, p=0.83), nor of LV $_{neg}dP/dt_{max}$ (5±3%, p=0.25), as shown in Figure 4-3. BiV-Opt showed a small but statistically significant greater LV $dP/dt_{max}$ (by 23±13%, p=0.034) and LV $_{neg}dP/dt_{max}$ (by 20±9%, p=0.039) than BiV-120 (Figure 4-4).

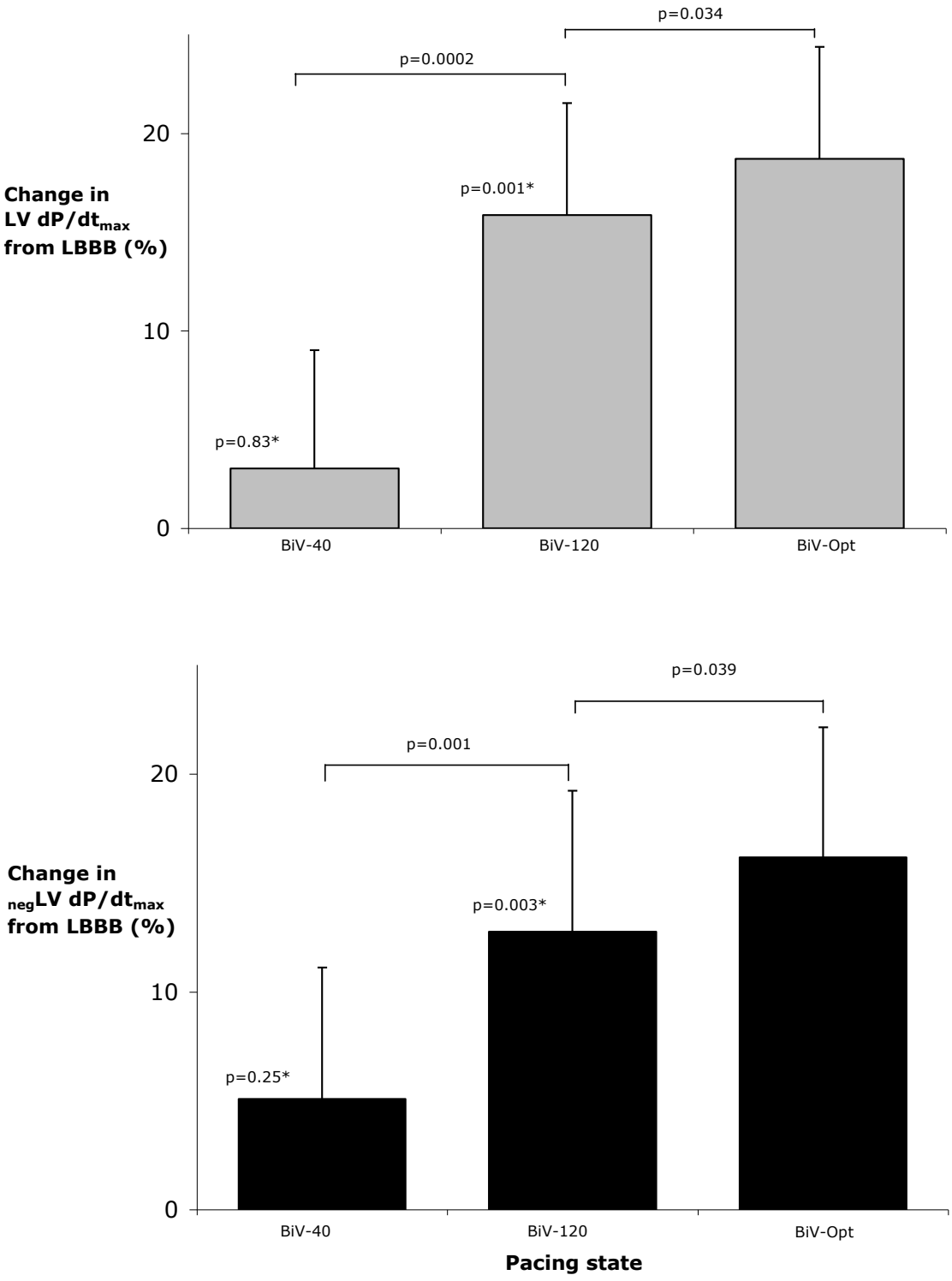


**Figure 4-4. Changes in LV $dP/dt_{max}$ and LV $_{neg}dP/dt_{max}$ at three AV delays from LBBB. Data are mean ± SEM, p values were calculated using a paired Student's t-test.**

Both the LV dP/dt max and LV dP/dt min enhanced from LBBB to BiV-120 and by slightly, but statistically significantly, more at BiV-Opt. There was no significant difference between LBBB and BiV-40. P-values with an asterisk represent the comparison between LBBB and that AV setting.

Across all 4 pacing states, LV $dP/dt_{max}$ and $_{neg}dP/dt_{max}$ correlated well, ($r^2$=0.81, p<0.00001).

### 4.4.3 Increase in intracoronary waves with biventricular pacing at a fixed heart rate

The wave intensity of the major intracoronary waves throughout the cardiac cycle for the 4 pacing states is shown in Table 4-3.

**Table 4-3. Cumulative wave intensity of major left coronary artery waves and comparison of these between all four pacing states. Data are presented as mean ± SEM**

| | Wave Intensity (AUC) x $10^3$ $W \cdot m^{-2} \cdot s^{-1}$ | LBBB | Biv-40 | BiV-120 | BiV-Opt | P-value (BiV-Opt Vs LBBB) | P-value (Biv-40 Vs LBBB) |
|---|---|---|---|---|---|---|---|
| | **Systole** | | | | | | |
| 1 | Forward compression | 9.1±1.9 | 8.6±1.9 | 11.4±2.3 | 12.1±2.5 | **0.04** | 0.51 |
| 2 | Backward compression | 7.5±1.5 | 7.2±1.7 | 9.0±1.6 | 9.9±1.9 | **0.01** | 0.75 |
| | *Net wave contribution to forward flow (1 minus 2)* | 1.6±1.4 | *1.4±1.0* | *2.4±1.3* | *2.3±1.7* | | |
| | **Diastole** | | | | | | |
| 3 | Forward decompression | 2.1±0.5 | 3.2±0.7 | 3.5±0.8 | 3.3±0.6 | 0.15 | 0.20 |
| 4 | Late forward compression | 3.2±0.8 | 2.4±0.9 | 2.7±0.6 | 2.8±0.9 | 0.76 | 0.42 |
| 5 | Backward decompression (suction) | 7.8±1.4 | 7.6±1.3 | 10.1±2.0 | 10.4±2.1 | **0.01** | 0.71 |
| | *Net wave contribution to forward flow (5 plus 4 minus 3)* | *8.8±1.9* | *6.7±1.8* | *9.3±2.4* | *9.9±2.1* | | |
| | | | | | | P-value | |
| | *Proportion of diastolic contribution to total net wave contribution to forward flow* | *85* ±5% | *83* ±4% | *80* ±6% | *81* ±5% | ***0.62*** | |

The systolic forward compression wave, increased by 30±11% (p=0.047) at BiV-120 and by 33±11% (p=0.043) at BiV-Opt, against LBBB as a reference, Figure 4-4. The opposing systolic total backward compression wave increased by almost identical amounts 30±15% (p=0.119) and by 33±10% (p=0.014) at BiV-Opt.

The dominant wave in diastole, backward decompression wave, was increased by 35±10% (p=0.028) at BiV-120 and by 36±8% (p=0.011) at Biv-Opt, at a time in the cardiac cycle when there were no opposing waves (Figure 4-5). None of these three waves were statistically significantly different between BiV-120 and BiV-Opt, although the numerical values for Biv-Opt were 7±11% higher for forward

compression wave, 9±8% higher for backward compression wave and 3±6% higher for backward decompression wave, relative to Biv-120 ($p=0.25$, $p=0.23$, $p=0.71$, respectively).

At BiV-40 the forward compression, backward compression and backward decompression waves were not different to LBBB (0±11%, $p=0.512$, 3±17%, $p=0.745$ and 10±13%, $p=0.707$, respectively).

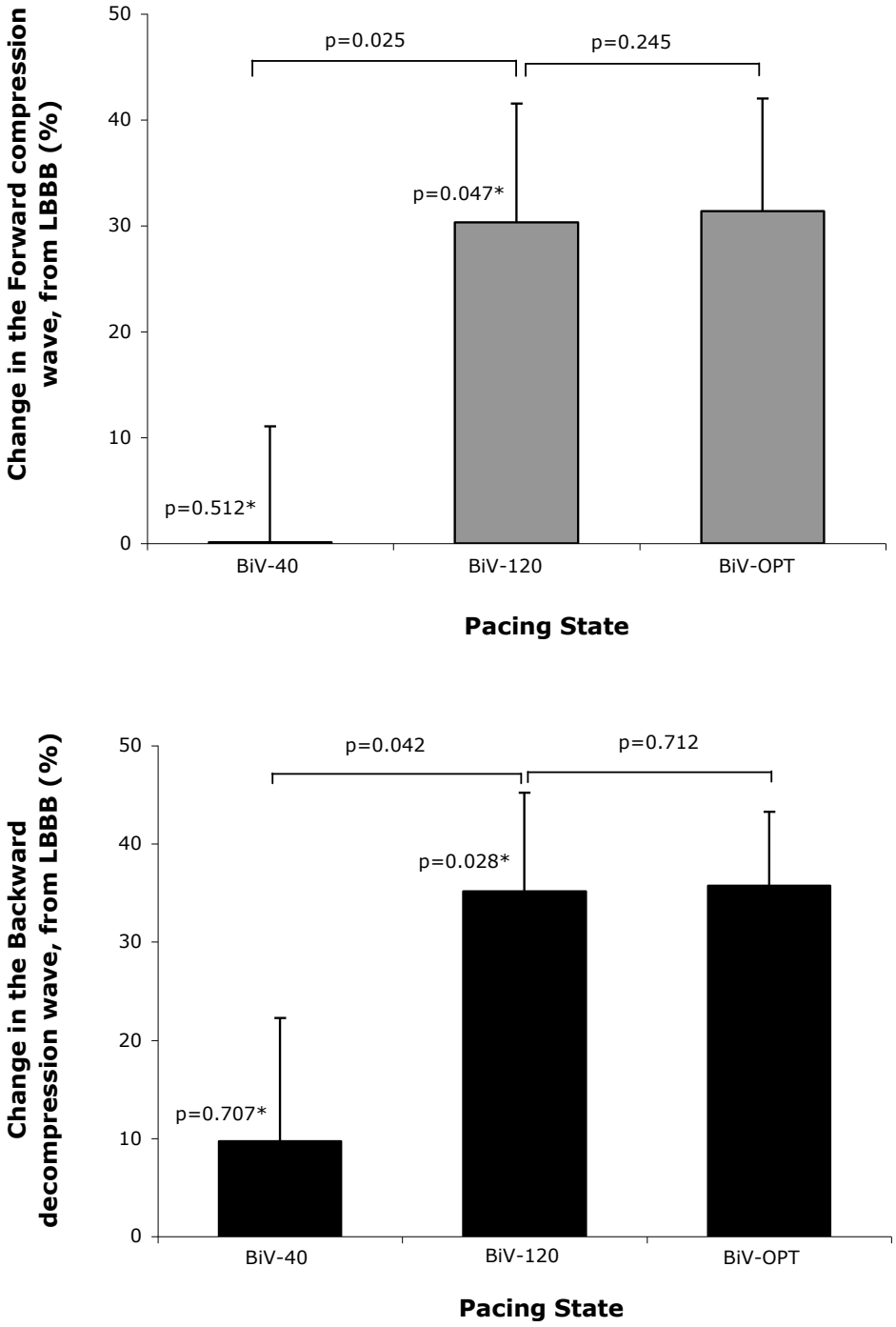


**Figure 4-5. Changes in the predominant systolic (forward compression) and diastolic (backward decompression) waves at the three AV delays with LBBB as the reference**

Both the forward compression and backward decompression waves are significantly increased at BiV-Opt when compared to LBBB. At BiV-120 the waves were not different to BiV-Opt. The intensities of the waves at BiV-40 were not statistically different to LBBB. P-values with an asterisk represent the comparison between LBBB and that AV setting.

There were significant correlations between the systolic waves (forward and backward compression) and LV $dP/dt_{max}$: $R^2$=0.25, p=0.0009 and $R^2$=0.39, p=0.00002, respectively. There was also a correlation between the backward decompression wave and LV $_{neg}dP/dt_{max}$ ($R^2$=0.23, p=0.0017) as shown in Figure 4-6.

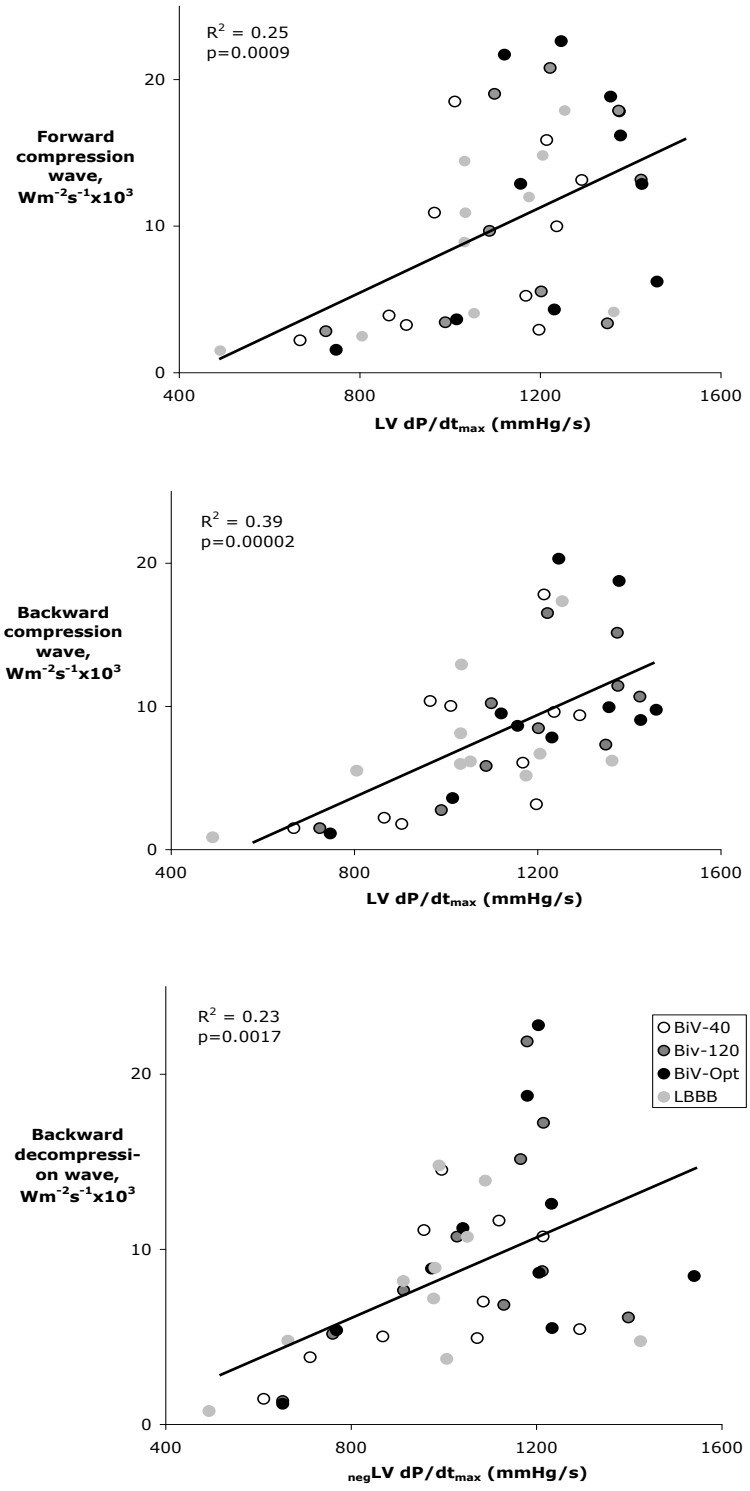


**Figure 4-6. Impact of LV $dP/dt_{max}$ and LV $_{neg}dP/dt_{max}$ on their temporally corresponding coronary waves.**

In each part of the cardiac cycle, the peak rate of intraventricular pressure change (LV $dP/dt_{max}$ for systole, and LV $_{neg}dP/dt_{max}$ for diastole) correlated with the corresponding waves, consistent with myocardial compression and decompression of the coronary microcirculation generating the waves.

## 4.5 Discussion

In this invasive study of patients with systolic heart failure, I found that in patients with heart failure and LBBB, resynchronization by biventricular pacing increases the flow in the left main coronary artery through enhancement of ventricular relaxation which increases the diastolic backward-travelling decompression (suction) wave.

### 4.5.1 Impact of biventricular pacing on left coronary artery flow

Our study has demonstrated that the total left coronary artery flow increased during biventricular pacing at AV 120 and optimal AV, when compared with LBBB. This finding may be explained by at least the change in the pattern of ventricular contraction and relaxation during pacing.

The impact of LBBB and resynchronization on myocardial metabolism (Mills R.W. 2009) and consequently demand for blood flow is likely to be mediated by the change in the pattern of contraction and relaxation during the cardiac cycle. The dyssynchrony of LBBB causes LV wall segments to contract at different times, reducing the rate of active stress generation and limiting the rise in pressure developed. For example, because septal and posterolateral wall segments do not contract simultaneously, the contraction of each segment is not against the full pressure developed by the others, and so the work needing to be done by the segment is smaller. Resynchronization improves simultaneity of contraction of ventricular wall segments (Prinzen F.W. 1999) and thereby increases both LV pressure and stroke volume. The external work done per individual wall segment is therefore likely to be higher, which may explain the raised metabolic demands on blood supply, as indicated in Figure 4-1.

MRI tagging in the canine model has shown that at the site of pacing, early local contraction (in comparison to the rest of the ventricle which therefore results in a lower rise in chamber pressure) dramatically reduced local external work done (Prinzen F.W. 1999) with a corresponding increase in local external work performed in more remote regions. Local mechanical work correlates positively with changes in myocardial oxygen demand (Delhaas T. 1994) and may explain the finding of the reduction of myocardial perfusion in LBBB (McGowan R.L. 1976, Ono S. 1992) which is magnified with increasing

heart rates (Beppu S. 1997, Helmer G.A. 1996). In the absence of a change in myocardial mechanical efficiency, the increase in external work done with biventricular pacing, would therefore be expected to increase myocardial blood flow, as was found in our study.

The only previous study in humans that examined left coronary flow and left ventricular mechanoenergetics reported that biventricular pacing, compared with LBBB, caused an increase in work and (when matched for heart rate) had no significant effect on oxygen consumption (Nelson G.S. 2000) or average coronary flow. However, that study differed from ours in design, permitting reflex-driven variation in heart rate, while ours fixed atrial rate at 100 bpm.

At both AV 120 and optimal AV the biventricular pacemaker is resynchronizing ventricular contraction (and thereby also resynchronising ventricular relaxation). The difference between them is principally in the relative timing of atrium and ventricle. At AV 120 the interval between atrial and ventricular activation is set at a constant value for all patients, whereas at optimal AV, each patient has an individually-programmed AV delay calculated beforehand to be likely to deliver the most effective cardiac function as assessed by the largest increment in peripherally measured systolic pressure. Our study showed that resynchronization by biventricular pacing had a much larger effect than any difference between AV 120 and optimal AV, but that selecting a very poor AV delay was able to counteract the increased flow of resynchronization.

I cannot be certain whether there was a subtle undetected difference in coronary flow between AV 120 and optimal AV. It is plausible that there may be a difference between AV 120 and optimal AV but too small to be identified. This may be a result of the signal-to-noise ratio of the measurements of flow not being adequate enough for picking up a very small difference. More measurements of coronary flow and more patients recruited would have helped detecting a possible small difference. This would have prolonged an already long (3- 4 hours) very invasive and complex study, exposing the patients to further risk. Importantly, the fact that a very poor AV delay (AV 40) was able to significantly reduce the coronary flow compared to that measure at AV 120/optimal AV, suggests that AV delay cannot be irrelevant.

### 4.5.2 Characterization of the biphasic coronary flow profile during biventricular pacing: dominance of a diastolic increase in flow

In this study I found that both the systolic and diastolic components of coronary flow increased when biventricular pacing was introduced at an AV delay which improved left ventricular $dP/dt_{max}$ and $_{neg}dP/dt_{max}$; these improvements were observed at AV 120 and at the individual's optimal AV delay. Proportionally, the systolic and diastolic flow appeared to be elevated by the same magnitude, 14-19% and 15-18%, respectively.

However, the increased diastolic flow contributed the most to the total increase in flow and as a result its relative contribution was between 64 -74%.

### 4.5.3 Driving forces behind changes in coronary flow during biventricular pacing

Optimal (and near optimal, BiV-120) biventricular pacing improves electrical synchronization and ventricular filling, which improve ventricular contractility and relaxation as demonstrated by the effects on the left ventricular pressure's first derivatives in Figure 4-3. This raises myocardial oxygen demand leading to an increased myocardial blood supply, but the mechanisms underlying this increase in blood supply have yet to be identified.

### 4.5.4 Mechanisms of coronary flow rise during biventricular pacing

In this study I found that both the backward compression wave and forward compression waves increased in magnitude when the ventricle was biventricularly paced at both optimal AV delay and near optimal, BiV-120 (Figure 4-5). This finding is reassuring from a mechanistic perspective, and demonstrates the inter-relationship between increasing ventricular contractile performance with biventricular pacing (measured by the increase in $dP/dt_{max}$ and $_{neg}dP/dt_{max}$) and the magnitude of these waves. Biventricular pacing intensifies not only contraction but also relaxation, and therefore enhances

not only the compression waves but also the backward decompression wave which is dominantly responsible for increasing coronary flow.

Although similar findings have been demonstrated by increasing heart rate with pacing in animals studies, our study appears to be the first in humans to identify such a clear link between increasing ventricular contractility and relaxation and improved coronary haemodynamics manifest by the backward decompression wave (Figure 4-7).

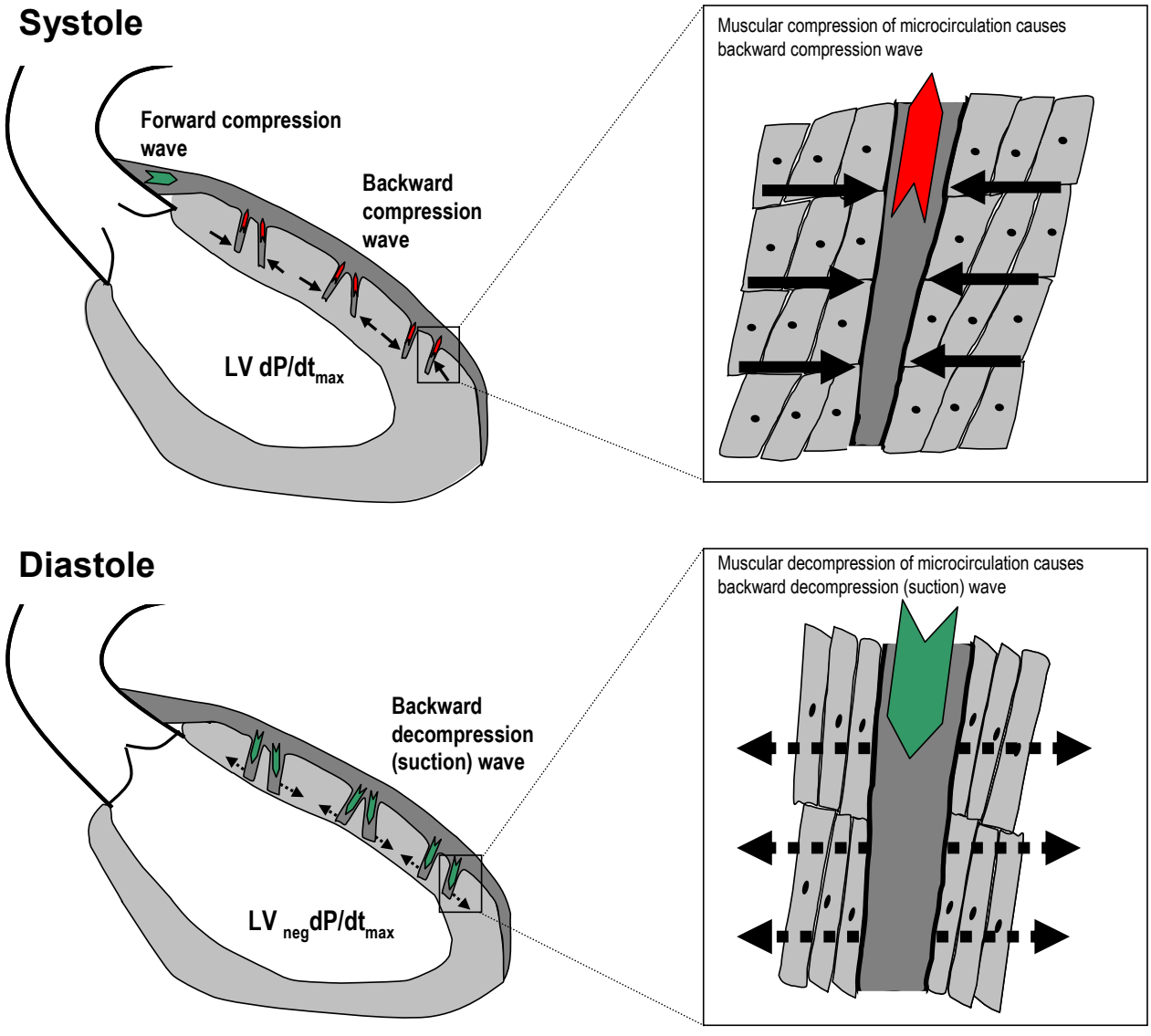


**Figure 4-7. A schematic presentation of the action of the main waves on the direction of blood flow, during the cardiac cycle**

During systole the two main waves, the forward compression and backward compression waves, act in opposing directions and as a result the systolic net wave contribution to forward coronary flow is small. In diastole the backward decompression "suction" wave is largely unopposed and therefore the net wave contribution to forward flow is considerably larger than during systole.

Under normal pressure load conditions, the coronary microcirculation is subject to transmission of the pressure loads from the LV cavity. In this way, a simplified analogy would be to consider the microcirculation behaving somewhat like a sponge. During systole the coronary microcirculation is squeezed, displacing a volume of blood, measured as a backward-travelling compression wave. During diastole, as microcirculation compression is relieved, a suction wave is generated in proportion to the increase in microcirculatory volume. The greater the degree of compression during systole, the greater the capacity for decompression during diastole. In this way blood flow within the coronary arteries can be closely regulated by compression and decompression in addition to vasodilatory mechanisms.

Conditions which alter this normal relaxation pattern such as left ventricular hypertrophy (Davies J.E. 2006), or those which lead to excessive LV pressure loading such as those in severe aortic stenosis can disrupt the normal relationship between LV contraction-relaxation and detrimentally reduce alter coronary haemodynamics (Krams R. 1989, Davies J.E. 2011).

In systole, although the forward compression wave has very similar magnitude to the diastolic backward decompression wave, because there is an almost equal and opposite opposing systolic wave, the systolic net effect on forward coronary flow is, as a result, significantly less (Table 4-2). This contrasts with diastole, when the backward decompression wave is unopposed for much of its duration, leading to a large increase in coronary blood flow.

### 4.5.5 Insight from very suboptimal AV delay during biventricular pacing

The effect of varying the AV delay during biventricular pacing, on coronary and ventricular physiology has never been studied to this detail. The effects of optimal AV (and near-optimal AV delay of 120ms) have been discussed above.

A very undesirable AV delay of 40 ms, despite still being a biventricularly paced state, did not improve any of the haemodynamic parameters (ventricular pressure derivatives, coronary flow and wave intensity) above the LBBB state. This indicates that despite ventricular resynchronization which itself

improves ventricular haemodynamics, programming AV delay to a value which compromises ventricular filling so severely, can offset the expected beneficial effects of CRT on ventricular contractility and coronary waves. This does not imply that AV 40 is equivalent to LBBB, because mechanistically they are very different but what it implies is that AV delay is an important determinant of the improved haemodynamics of CRT. This an important consideration when using inadequately validated or poor methods of optimization, because identification of an AV 'optimum', using non-reproducible methods, could be so far away from the true optimum which could then significantly compromise the overall benefit gained by CRT.

Our interpretation of these findings is that left ventricular contractility regulates its own coronary flow, via mechanisms readily visible in the coronary waves. Improved contractility depends, however, on two factors: co-ordination of ventricular contraction and adequacy of preload (which undesirable AV delay can impair), Figure 4-8.

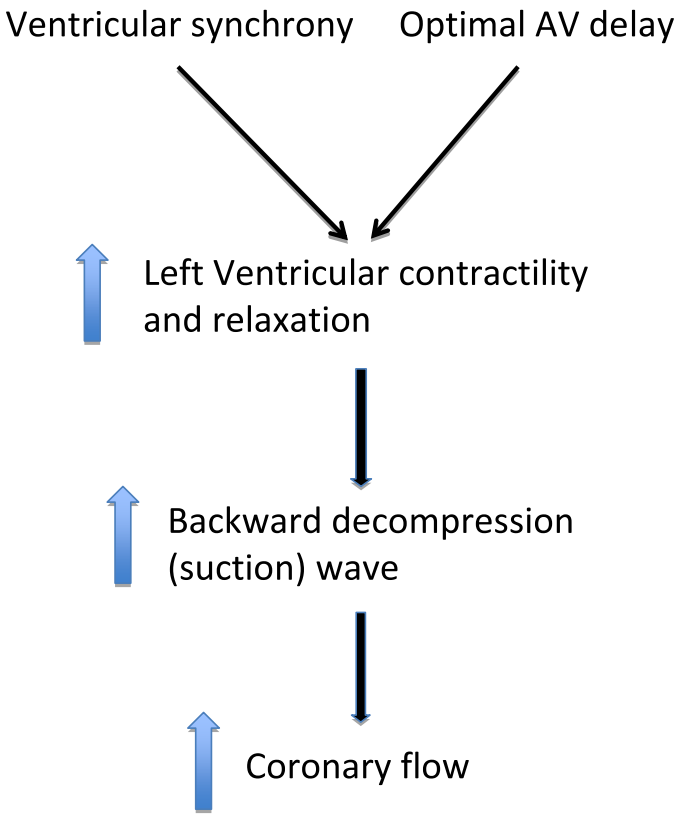


**Figure 4-8. Relationship between ventricular contractility and relaxation and coronary flow during acute biventricular pacing**

Left ventricular contraction and relaxation improves during acute biventricular pacing as a result of ventricular resynchronization and AV optimization. This improvement causes an increase in the diastolic backward decompression "suction" wave with an increase in coronary flow.

### 4.5.6 Clinical implications

Resynchronization and optimization of CRT increases the ability of the heart to develop pressure (which is of use in predicting outcomes (Suzuki H. 2010, Bogaard M.D. 2011, Duckett S.G. 2011) and also increases coronary blood flow. The increase in coronary blood flow is principally through an increase in microcirculatory suction in diastole.

The patients I studied all had currently unobstructed arteries. In other patients with ongoing significant obstruction from coronary stenosis and /or microcirculatory disease, there may be less opportunity for coronary flow to increase to match increasing demand with biventricular pacing. This might tend to attenuate clinical benefits of CRT in CHF patients with ongoing ischaemia.

### 4.5.7 Study limitations

The ten patients I studied are a small number to make definitive conclusions for all patients, although they were not selected for any particular clinical characteristics and are representative of a contemporary cohort of patients without obstructive coronary disease undergoing CRT. This experimental protocol is complex and demanding for patients and not necessary or suitable for routine clinical practice. Although it was able to explore phenomena in the acute ventricular and coronary physiological consequences of biventricular pacing and AV delay optimization, it was not designed to cover wider questions such as differential effects of age and gender on coronary physiology during acute biventricular pacing. In addition, variability between heart failure aetiologies with differing degrees of myocardial microcirculatory impairment may alter the magnitude of response to biventricular pacing.

I did not allow natural variations of heart rate during the experiment. However, the choice to fix the atrial rate permitted us to assess the direct effect of biventricular pacing on important aspects of ventricular physiology and its consequences on coronary haemodynamics, by avoiding confounding by reflex heart rate regulation.

I cannot be certain whether there is a contribution from microvascular resistance to our findings, or how large it was, because I did not give adenosine to make microcirculatory resistance minimal and constant. Instead, I can only conclude that biventricular pacing at AV 120 or AV optimum, which increases indices of myocardial systolic and diastolic function, also increases coronary flow velocity and wave intensity. Secondly, in patients with macrovascular coronary stenoses, the early diastolic suction wave in a diseased vessel is heavily influenced by the state of anastomoses with adjacent territories. I did not evaluate the patients for anastomoses because I recruited patients without obstructive macrovascular disease. There may have been unrecognised impact of anastomoses. Our design, which measured flow at the left main stem, rather than in a distal coronary branch, may have minimised such impact.

Left ventricular pressure first derivatives can be criticised as measuring an effect of contractility which is loading-dependent, rather than measuring a conceptual ideal of loading-independent contractility.

However, in the case of biventricular pacing which improves ventricular synchrony and ventricular preload, $dp/dt_{max}$ and $_{neg}dP/dt_{max}$ are credible markers of the combined effect.

The baseline value for LV $dP/dt_{max}$ was higher than one would expect it to be in this patient cohort with significant LV dysfunction. Historically, in many acute cardiac resynchronization studies, the value for this haemodynmic variable was reported to be under 1000 mmHg/s. In my study, the average value of the repeated measurements of this variable, during atrial pacing at 100bpm, was just above 1000mmHg/s. Although pacing at a fixed high atrial rate may have had some influence in the measured values, the other more obvious explanation may be that on average the patients recruited, even though they fulfilled contemporary indications for resynchronization, had a less diseased myocardium than historical CRT studies. It is worth noting that other studies in patients with heart failure and EF <35%, for example Cotton JM. 2011, have also reported LV $dP/dt_{max}$ and LV $_{neg}dP/dt_{max}$ values above the 1000 mmHg/s mark.

## 4.6 Conclusions

Biventricular pacing at an AV delay which increases ventricular contractility and relaxation also improves the myocardial blood supply. Wave intensity analysis indicates that the mechanism for the improved coronary blood flow is principally an increase in the intensity of diastolic backward decompression (suction) wave. For resynchronization with nominal AV delay, and with additional AV optimization, increases in ventricular performance, haemodynamics, coronary waves and coronary flow appear to go hand in hand.

# 5 Fully automatable noninvasive plethysmographic optimization of cardiac resynchronization therapy: a miniaturizable and implantable technology

## 5.1 Abstract

**Background**

Non-invasive haemodynamic optimization of cardiac resynchronization therapy (CRT) using Finometer continuous blood pressure monitoring is highly reproducible, but uses expensive, non-implantable equipment. In this study I explored whether a simple photoplethysmogram signal might be used instead.

**Methods**

In 20 patients (age 65±12) with CRT I automatically optimized AV delay, using a multiple-transitions protocol, at 2 atrially paced heart rates; just above sinus rate ('slow ApVp', 77±11 bpm) and 100 bpm ('fast ApVp'), and repeated it to assess reproducibility.

**Results**

In all 20/20 patients, an optimum AV delay was identified on each occasion. At 100bpm, the simple photoplethysmogram had a wider scatter between repeat optimizations than did the Finometer: standard deviation of difference (SDD) 22 ms versus 14 ms, respectively, $p<0.05$. The simple photoplethysmogram improved in reproducibility when the slope instead of the peak of its signal was used to define optimal AV delay and was as reproducible as Finometer (SDD 14ms versus 14ms, p=NS).

At the slow heart rate, the reproducibility of the photoplethysmogram declined from 14 to 22 ms ($p<0.05$) and that of the Finometer from 14 to 26 ms ($p<0.05$).

Increasing the number of replicates averaged improved reproducibility: for example, SDD of simple photoplethysmogram optimization (using peak) falls from 62 ms with 2 replicates to 22 ms with 8 replicates ($p<0.05$). At 100 bpm, the protocol of 8 replicates takes 12 minutes.

**Conclusions**

Simple photoplethysmographic AV optimization can be processed fully automatically in approximately 12 minutes and the optimum can be obtained with good test-retest reproducibility.

## 5.2 Introduction

Reliable adjustment of the atrioventricular delay (AV) for an individual patient may improve acute haemodynamics more (Kass D.A. 1999, Auricchio A. 1999, Sawhney N.S. 2004, Whinnett Z.I. 2006) than just the observed heamodynamic improvement of CRT at default settings (Yu Y. 2003, Butter C.D. 2001, Breithardt O. 2002, Auricchio A. 2002, Van Gelder B.M. 2004, Nelson G.S. 2000, Kass D.A. 1999, Blanc J.J. 1997).

Non-invasive blood pressure monitoring has been shown to be able to achieve reproducible haemodynamic optimization of AV delay (Whinnett Z.I. 2006). However, the Finometer technology is expensive and not universally available in the typical clinical setting where CRT optimization is carried out. Moreover, the technology does not lend itself to miniaturization for implantation with the pacemaker, which would be the ideal for any optimization technique.

Alternative haemodynamic technologies which do not have the disadvantages of the Finometer, but match its efficiency in identifying the haemodynamic optimal AV delay, would be attractive if available. There are many haemodynamic monitoring technologies available, covering a range of degrees of invasiveness, complexity and cost. At the very simplest end of the spectrum is the photoplethysmographic signal, familiar in routine clinical practice in vascular laboratories from devices such as Biopac PPG100C Photoplethysmogram and Hokanson EC6 Plethysmograph and from its display on a pulse oximeter. This technique might be readily introduced into the CRT optimization laboratory, by using either signals from one of a number of commercially available devices, or by connecting one of the widely used available and cheap finger probes available for pulse oximeters into custom systems for use in local laboratories.

In this study I evaluated the potential to use the photoplethysmographic signal to identify the optimal AV delay and compare its efficiency to that of Finometer. A pulse oximeter probe is a convenient means of making photoplethysmographic measurements. It has the advantage of being a simple technology, considerably cheaper than the Finometer technology and potentially miniaturizable for implantation (Turcott R.G. 2008).

In order to test how well this approach might work using equipment very familiar to us as general cardiologists, I used a pulse oximeter from our ward. Unlike the Finometer signal, however, the raw pulse oximeter signal is not a direct proxy for pressure. First, the signal from an unmodified oximeter typically has built-in electronic filters that remove baseline trends over a few beats because these are not relevant to assessing oxygen saturation – yet these trends contain the information that I seek during optimization. Second, the pulse oximeter signal contains information about blood volume changes in small blood vessels, including capillaries and venules and hence is sensitive to respiration and body movement. Accordingly, I arranged for the patient to lie still and fitted a switch to allow the built-in electronic filters to be switched off (such a switch is often available in the devices used in vascular laboratories, but is not usually available in the devices familiarly present on cardiology wards).

In the study I first looked at how the two technologies performed as competing approaches to haemodynamic optimization of AV delay. I evaluated the relative reproducibility of optimization by each technology, head to head.

Second, I assessed the impact of alternative signal processing. I tested the option of using the peak of systolic upslope (maximum of first derivative), rather than simply the peak systolic value, to identify the optimal AV delay in each patient.

Third, I explored the effect of elevation of heart rate and of averaging multiple replicates of measurements on the reproducibility of optima derived by the two technologies and evaluated the impact on the time that would be consumed by a haemodynamic optimization session.

Finally, in a subset of patients who agreed to undergo a prolonged echocardiographic protocol, I compared the performance of the 2 haemodynamic technologies to the performance of 2 quantitative echocardiographic optimization processes: mitral valve and left ventricular outflow tract velocity-time integral measurements.

## 5.3 Methods

### 5.3.1 Subjects

Twenty ambulatory patients with biventricular pacemakers or biventricular defibrillators implanted for clinical indications were enrolled in this study.

At the time of study 3 patients were in NYHA class I, 11 were in NYHA II and 6 were in NYHA III. 11 patients were male, age range 46-81 years (mean 65 years). Cause of heart failure was ischemic in 8, idiopathic dilated in 10 and hypertensive in 2. Mean systolic blood pressure by sphygmomanometer was 105 ± 12 mmHg. Mean left ventricular ejection fraction of the patients at the time of the study was 33 ± 8 %. 16 patients were taking angiotensin-converting enzyme inhibitors, 6 angiotensin-II receptor antagonists, 18 beta-blockers, 7 spironolactone, 12 a diuretic (loop or thiazide) and 6 digoxin. Patients gave informed consent for this study which was approved by the local ethical committee.

### 5.3.2 Measurements

#### 5.3.2.1 Simple photoplethysmogram

I recorded the transcutaneous photoplethysmogram signal using a modified finger probe pulse oximeter (Ohmeda Biox 3700e). The pulse oximeter waveform is a non-invasive index of tissue blood volume change (Challoner A.V.J. 1979). Based on transmission mode photoplethysmography, it uses a light-emitting diode to illuminate the underlying tissue, and measures the light intensity on the other side of the tissue. Increased volume of blood per unit cross-sectional area decreases the light intensity measured by the photodetector.

The pulse oximeter had to be modified slightly for use in this study. Standard clinical pulse oximeters have circuitry to re-scale the detected signal continuously because of the wide dynamic range of pulse oximetry signal between patients. The continuous rescaling keeps the electrical signal in a range suitable for amplification and display on a screen without going off top or bottom. However, for the purpose of optimization, it is important for the scale to be able to be held constant while the AV setting is changed, so that the impact of the change in AV delay is not confounded by changes in scale.

On the other hand, the procedure is very much simplified if auto-rescaling is available because there is still the problem of wide between-patient differences in average light absorption. Rescaling is needed for the individual patient before the pacemaker setting adjustment begins.

Each patient needs only one brief period of auto-scaling of the signal while lying comfortably until the pulsatile signal is obtained, which may take 5-10 seconds, as would be the case if the device was being used to measure oxygen saturation. At that stage, a switch is operated, which turns off the auto-scaling. The auto-scaling remains off for the rest of the session.

Other commercial simple photoplethysmography devices used in clinical vascular laboratories and in cardiovascular research environments for the purpose of tracking fluctuations in haemodynamics, have the ability to turn on and off auto-rescaling at will.

#### 5.3.2.2 Beat to beat continuous non-invasive blood pressure monitoring

I used a Finometer (Finapres Medical Systems, Amsterdam, Netherlands) to record beat-to-beat non-invasive blood pressure. This technique, developed by Peňáz (Peňáz J. 1973) and Wesseling (Wesseling K.H. 1995), uses a rapid servo system with a finger cuff actuator, allowing it to adjust the pressure in a finger cuff to keep a reference photoplethysmogram signal flat throughout systole and diastole. Achieving this constant blood volume within the finger means the extramural pressure being applied must be matching the intramural pressure, and therefore the time course of the pressure that the cuff has had to apply can be treated as the intrarterial pressure waveform. This process, volume-clamp photoplethysmography, is well validated for measuring instantaneous changes in blood pressure (Smith N.T. 1985, Van Egmond J. 1985, Petersen M.E. 1995, Jellema W.T. 1996, Imholz B.P.M. 1998).

An ECG signal was recorded using Hewlett-Packard 78351A monitor. Analog signals were taken via a National instruments DAQ-Card AI-16E-4 (National Instruments, Austin, TX) and Labview (National Instruments, Austin, TX). They were analysed off line with custom software based on the Matlab platform (MathWorks, Natick, MA) (Davies L.C 1999).

#### 5.3.2.3 Protocol of haemodynamic AV optimization

I carried out AV optimization using the protocol of multiple replicate transitions between a fixed reference AV delay (AV 120 ms) and a number of pre-specified tested AV delays (potentially 40, 80, 140, 160, 200, 240, 280, 320 ms but limited to the AV settings which give ventricular pacing rather than intrinsic ventricular conduction).

For each tested AV delay, I calculated the relative change in the haemodynamic signal when AV delay was transitioned from the reference (AV 120 ms) delay to the tested delay. I defined this difference as the average measurement (such as systolic BP) for the 10 beats after the transition minus the 10 beats before it.

I made 8 replicate measurements of this difference (Figure 5-1): 4 with 'forward' transitions as described above and 4 with 'backward' transitions in which case the sign of the change in signal was reversed.

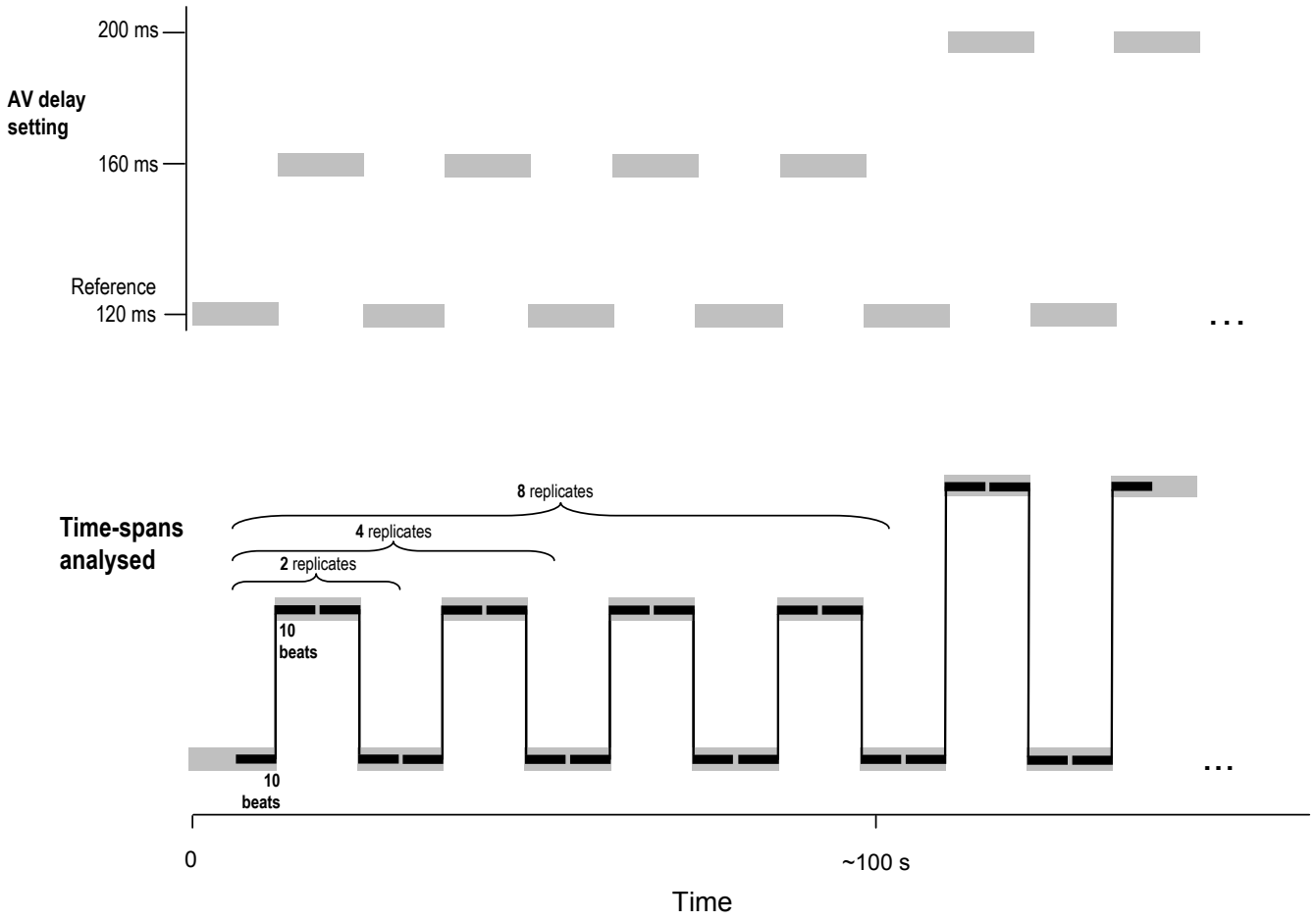


**Figure 5-1. Multiple replicate transitions performed during our optimization protocol at 100bpm.**

Multiple transitions performed between the reference AV delay (120 ms) and a tested AV delay (160) followed by another tested AV delay (200ms) are shown in the top panel. The bottom panel shows the 10 beats before and after a transition which are sampled in order to calculate the relative mean haemodynamic change when the AV setting is transitioned. It also shows how I generate 2, 4 and 8 replicates of haemodynamic data between the fixed reference AV delay and a tested AV delay. This process is repeated for each tested AV delay.

The photoplethysmogram and the Finometer blood pressure waveforms were recorded simultaneously during the AV transitions. One sensor was placed on the index finger of one hand, and the other on the index finger of the other hand.

I AV optimised separately at two heart rates: an atrially paced rate just above the individual patient's resting sinus rate (averaging 77bpm), which I called 'slow ApVp', and at an atrially paced rate of 100bpm, which I called 'fast ApVp'. To assess reproducibility, the entire process was again repeated on the same day in all 20 patients, at each heart rate.

From the Finometer data, each beat was assessed by the peak systolic blood pressure (SBP) and the steepest systolic upslope of blood pressure. From the simple photoplethysmogram data, similarly the peak value and the steepest systolic upslope were evaluated.

All processing was calculated off line not because it was complex or time consuming but because the optimization process depended on the relative levels of the measurements at all the tested settings, which was only determinable after all settings had been tested, but there was no clinically relevant delay introduced by this. Processing the data took less than 30 seconds (of which calculating the slope of the Finometer and simple plethysmogram took less than 1 second).

For each individual patient, the haemodynamic value for each tested AV delay (relative to the reference AV delay, 120 ms) was plotted and a quadratic curve was fitted. The peak of the resulting curve was taken as the optimal AV delay (Figure 5-2). This was carried out separately for Finometer data and simple photoplethysmogram data.

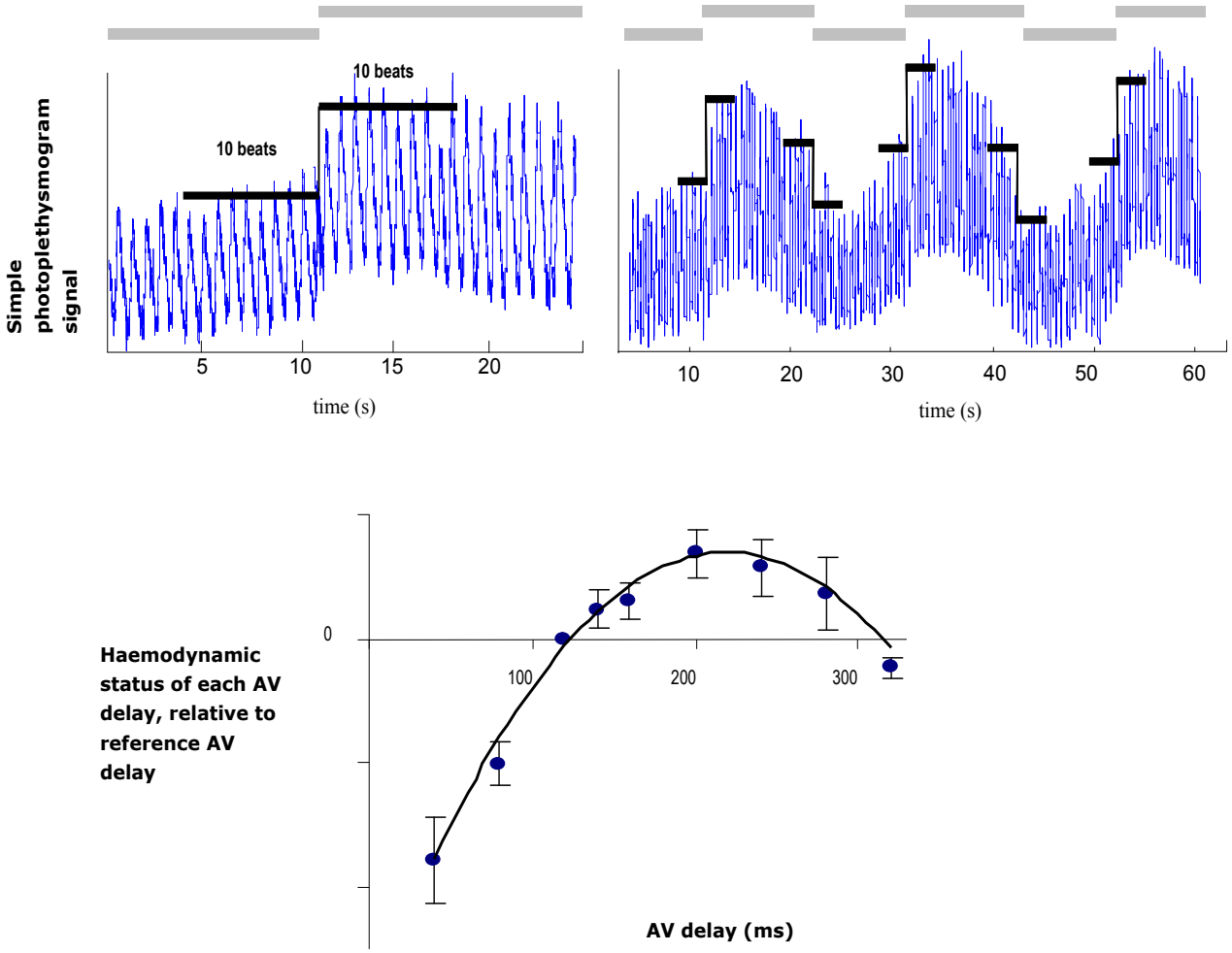


**Figure 5-2. Identification of the optimal AV delay in an example patient using the peak of the waveform (photoplethysmogram) from the pulse oximeter. The optimization is composed of a series of individual transitions between the reference AV delay (120 ms) and a tested AV delay.**

Example of a single transition is shown in top left panel; the mean of ten beats (shaded area) before and after the transition is used to calculate the relative difference (arbitrary units). Multiple replicate transitions between the reference and the tested AV delay are shown in the top right panel. All the tested AV delays and their relative change (arbitrary units) to the reference AV delay are shown in the bottom panel. The peak of the inverted parabola corresponds to the optimal AV delay.

All steps of the acquisition and analysis, including calculation of the optimum, occurred fully automatically from the data, using custom software (which is available to researchers from the authors). The only manual step required was the changing of pacemaker settings for which manufactures have not yet made commercially available automatable access: for the purposes of this study a human operator changed the settings at the times indicated by the algorithm.

#### 5.3.2.4 Protocol of echocardiographic optimization

12 of the 20 patients agreed to undergo the echocardiographic optimization study. This was conducted using left ventricular outflow tract (LVOT) and mitral valve velocity-time integrals (VTIs), at the slow heart rate. For each of the echocardiographic methods and at each AV setting I acquired and averaged the VTI of ≥ 4 beats, excluding ectopic beats. In addition, I assessed within-session test-retest reproducibility in all 12 patients.

Images were obtained using a ProSound SSD-5500SV system (Aloka, Tokyo, Japan), with the operator blinded to the AV delays which were randomly programmed by a second operator. These were acquired with the patient positioned in the dorsal decubitus or left lateral decubitus position, at passive end expiration. Medcon software (McKesson, San Francisco, USA) was used for offline analysis. Optimization by either echocardiographic method took approximately 25 minutes.

### 5.3.3 Statistics

I used the Bland-Altman statistics to compare between one optimization session and another, and to compare one haemodynamic technology with the other. Correlations were quantified by Pearson's product-moment correlation coefficient. Paired comparisons of Normally-distributed continuous variables were made using Student's paired *t* test. Paired comparisons of non-Normally-distributed continuous variables were made using Wilcoxon's matched-pairs signed rank test. A p-value of $<0.05$ was taken as statistically significant. Statview 5.0 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

## 5.4 Results

### 5.4.1 Comparison of reproducibility of optimal AV delay between simple photoplethysmogram and Finometer

A patient example of optimization and reproducibility of the optimal AV setting (for eight replicates averaged), carried out on the same day at fast ApVp for all 20 patients, are shown in Figure 5-3 (A and B, respectively). The standard deviation of difference (SDD) was 22 ms for simple photoplethysmogram; for Finometer it was significantly better at 14 ms ($p<0.05$).

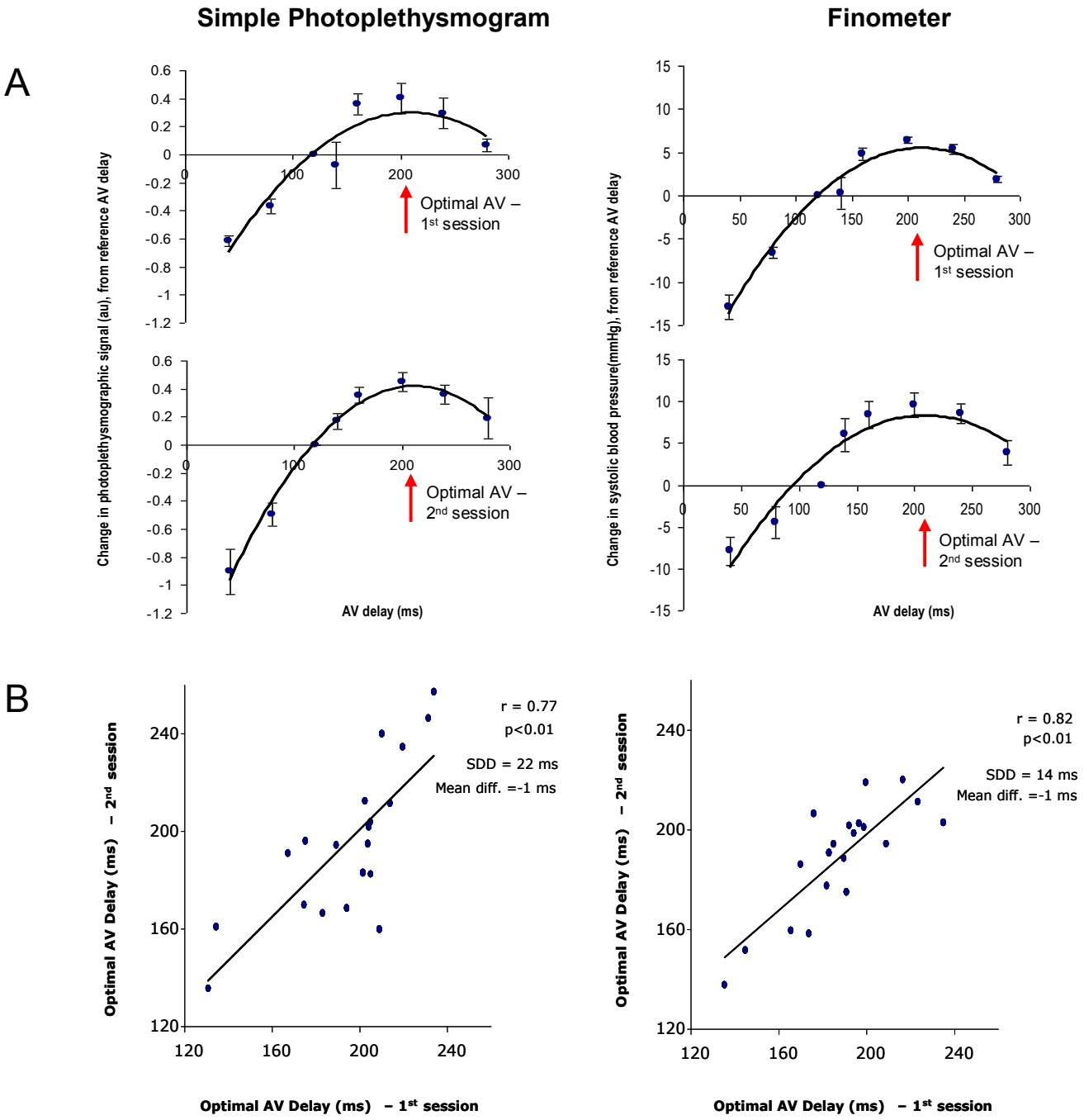


**Figure 5-3. Reproducibility of the optimal AV delay, when using the peak of the waveform.**

Each patient had two optimization sessions on the same day (an example patient is shown in panel A). In panel B, in the left diagram, the optimization from the first session is plotted against the one from the second session (for all 20 patients), with both optimal AV delays calculated using the photoplethysmogram signal from the pulse oximeter. In the right figure, the same plot is made using the optima derived from the Finometer data.

### 5.4.2 Effect of signal processing (peak versus slope of waveform) on reproducibility of haemodynamic optimization

The reproducibility of optimal AV delay identified by simple photoplethysmogram improved when, instead of the peak, the slope (maximum of 1st derivative) of the waveform during the cardiac cycle was used. The SDD improved significantly from 22 ms to 14 ms ($p<0.05$) for the photoplethysmogram, while it did not change significantly for the Finometer (Table 5-1).

**Table 5-1. Impact of signal processing on reproducibility of AV delay; comparison between simple photoplethysmogram and Finometer**

The reproducibility (standard deviation of difference, SDD) of the simple photoplethysmogram significantly improves when the maximum slope (maximum of 1st derivative) of the waveform is used to define the optimal AV delay. The reproducibility of the Finometer, however, remains unchanged by this alternative signal processing.

| Technology | Reproducibility (standard deviation of difference, ms) | | |
|---|---|---|---|
| | Using peak | Using slope | p-value (peak versus slope) |
| Photoplethysmogram | 22 | 14 | p<0.05 |
| Finometer | 14 | 17 | n/s |

The individual reproducibility of each of the 20 patients is shown in Figure 5-4, for optimization using the slope of the waveform from the photoplethysmogram. It shows that individuals had very different optima, but each individual's optimal AV delay was reproducible between one optimization and the next.

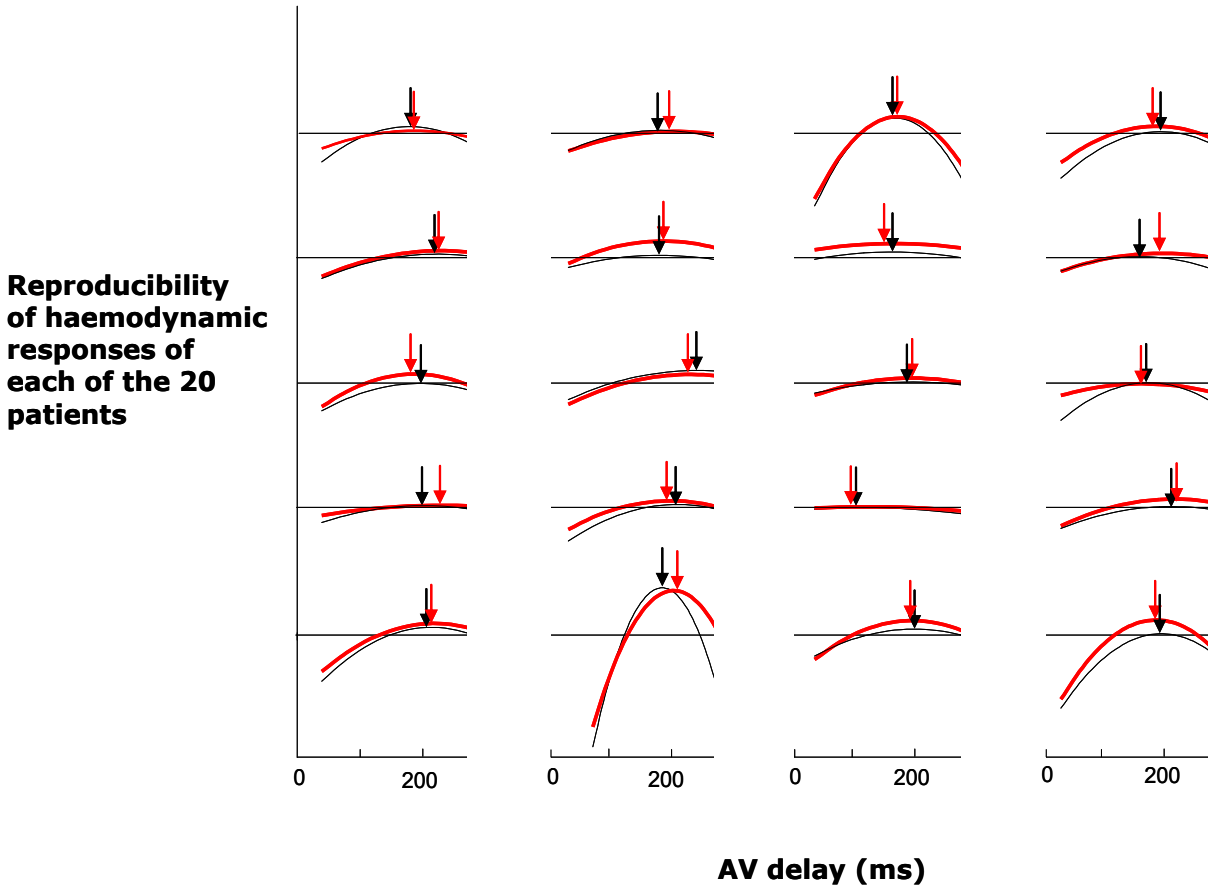


**Figure 5-4. Individual parabolic optimization curves, when using the slope of the photplethysmogram signal from the pulse oximeter, for each of 20 patients on two separate sessions.**

Each pair of curves shows the optimization pattern of a single patient (black=1st optimization, red=2nd optimization. Arrows show the peaks of the fitted parabolas, which are taken as the optima. It can be seen that different patients have different degrees of curvature of their haemodynamic response and different optimal AV delays, but the optima are consistent between optimization sessions.

### 5.4.3 Effect of number of replicates analysed on reproducibility of haemodynamic optimum

The reproducibility (standard deviation of the difference of optimum, SDD), using the peak of the waveform from the photoplethysmogram, improved progressively for 2, 4, and 8 replicates: from 62ms to 34ms ($p<0.05$) to 22ms ($p<0.05$), respectively, as shown in Figure 5-5. The same effect was seen when using the slope of the waveform. The same effects were seen with the Finometer data (Figure 5-5).

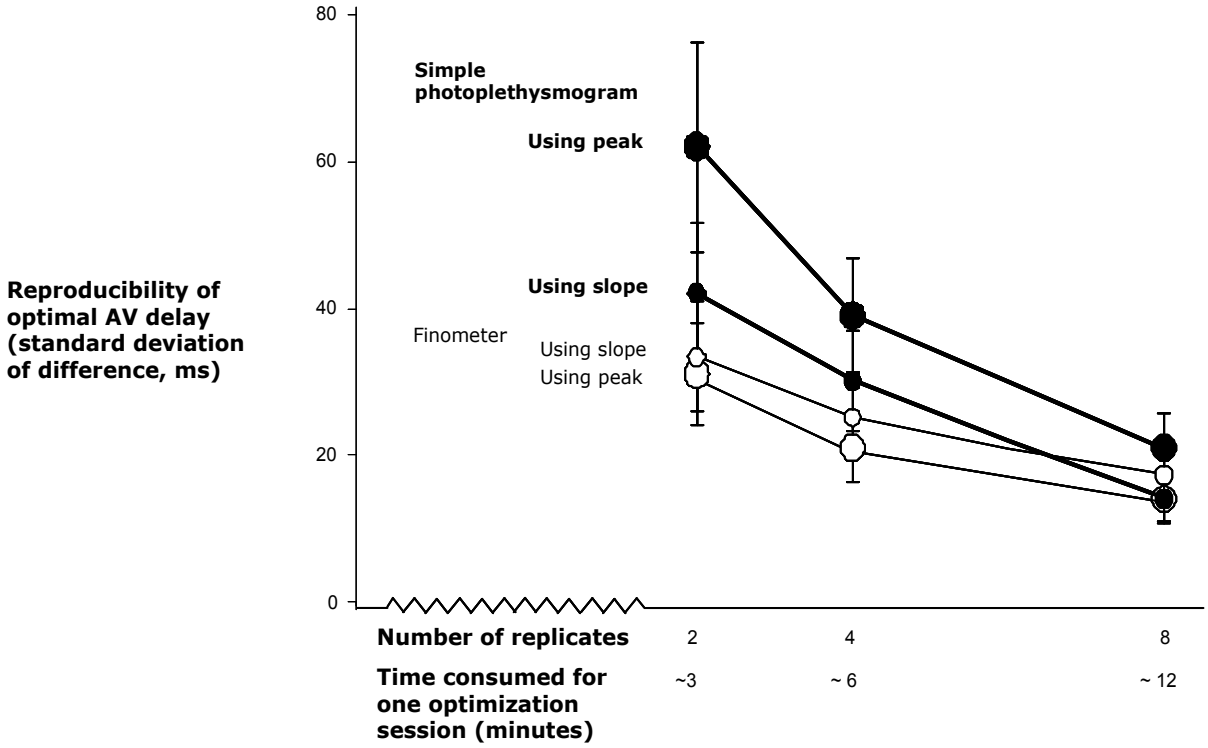


**Figure 5-5. Impact of number of replicates averaged on the reproducibility and time consumed by optimization.**

Reproducibiility improves as the number of replicates averaged is increased. This improvement for both technologies and for both types of signals is achieved at the expense of increased time consumed by acquisition of haemodynamic data. In each case, the reproducibility for the 8-replicate process is significantly better than the 2-replicate process ($p<0.05$ for each pairwise comparison).

The agreement of the optimal AV delay between the two technologies similarly improved as the number of replicates was increased from 2 to 8: SDD fell from 49ms to 20ms ($p<0.05$), respectively.

### 5.4.4 Effect of heart rate on reproducibility of haemodynamic optimization

By comparison to the reproducibility at fast ApVp, reproducibility at slow ApVp was significantly worse. The SDD of optima using the simple photoplethysmogram slope deteriorated from 14 to 22 ms at slow heart rate ($p<0.05$), and using the Finometer peak it deteriorated from 14 to 26 ms at slow heart rate ($p<0.05$).

### 5.4.5 Comparison of photoplethysmography with echocardiographic optimization

In the 12 patients who underwent both haemodynamic and echocardiographic optimization, the reproducibilities (expressed as SDD) of optimal AV delay were: for Finometer 21ms, for the simple photoplethysmogram 17 ms, for LVOT VTI 43 ms and for mitral valve VTI 40 ms. Although the echocardiographic methods had such wide reproducibility scatter that they could not be considered a gold standard for comparison, for the record, photoplethysmogram optimization had a better agreement with Finometer optimization (SDD 24ms) than did either LVOT VTI (74ms, $p<0.05$) or mitral valve VTI (55ms, $p<0.05$). As might be expected from their individual poor reproducibility, the agreement between the two echocardiographic methods was poor (SDD=70ms).

## 5.5 Discussion

In this study I have found that a simple photoplethysmogram can be used for optimization of cardiac resynchronization devices in just the same way as a Finometer. If the peak of the photoplethysmographic waveform is used, the optimum has a slightly lower reproducibility, which can be resolved by using the steepness of the upslope rather than the peak of the photolethysmogram waveform.

I have also shown a potentially uncomfortable trade off between time taken to perform an AV optimization (through the use of average of multiple replicates) and the reproducibility of the optimum.

Elevating heart rate improves the reproducibility of haemodynamic optimization for both technologies, and in parallel the agreement between the two technologies also improves. This also speeds up the optimization process.

### 5.5.1 Simple photoplethysmogram versus Finometer

A variety of technologies are available which can be used for haemodynamic optimization of CRT devices. They cover a spectrum of cost, bulk and technical complexity. In this study I have chosen two technologies which are simple to use.

The Finometer has been extensively used but is a large device which works on a principle that is not convertible to a completely implanted device which would be the most attractive arrangement for a haemodynamic optimization feature of an implanted pacemaker. A simple photoplethysmographic circuit, in contrast, is light, inexpensive, free of all moving parts, and completely implantable as has been shown in animal studies (Turcott R.G. 2008).

Proprietary plethysmogram devices using specially-designed hardware, firmware and software have already been introduced into research studies of pacemaker optimization (Butter C. 2004).

Our study shows that it is feasible to use the photoplethysmographic signal from a standard clinically-available pulse oximeter in a routine outpatient clinical setting for a 12-minute optimization, i.e. that no special proprietary processing is necessary. In all 20 of the 20 patients, the pulse oximeter shows an

inverted parabola of haemodynamic changes (Figure 5-4). Within patients, this peak is reproducible in successive optimizations; between patients there are large differences.

Optimization by photoplethysmography mirrors the findings of optimization by Finometer. Although the correspondence between Finometer and simple photoplethysmogram is not perfect, it should be remembered that the correspondence cannot be any closer than the reproducibility of each technology individually.

Haemodynamic optimization by Finometer and optimization by photoplethysmography are likely to be driven by the same underlying physiological principle. Discrepancy between them, being not substantially larger than the discrepancy between each technology and itself, is not grounds to reject one or the other.

### 5.5.2 Processing of the simple photoplethysmogram to maximize information value

Using the peak of the simple photoplethysmogram signal does not produce as good reproducibility, of optimal AV delays, as the peak of the Finometer signal does. However, by using the maximum steepness of the slope, instead of the peak, the reproducibility of the photoplethysmogram improves and matches that of the Finometer. Using the steepness of the slope of the Finometer waveform does not make its reproducibility of Finometer optimization any better. I speculate that these findings are related to the different ways these technologies operate.

The Finometer, a volume clamp photoplethysmographic technology, uses a rapid servo system with a finger cuff actuator, allowing it to adjust the pressure in a finger cuff to keep a photoplethysmogram signal flat throughout systole and diastole, which means effectively a constant blood volume within the finger. The extramural pressure required to achieve this is in principle equal to the intrarterial pressure and therefore the waveform of the extramural pressure applied by the finger cuff reflects the pressure waveform of the digital artery. The extramural pressure keeps the veins and venules largely collapsed because they have much lower intramural pressures than arteries. Therefore they have very little

influence on the waveform displayed by the Finometer, which is therefore almost exclusively of arterial origin.

The plethysmogram, in contrast, picks up not only the arterial pulsations but also the slow fluctuations of venous volume, such as those arising from respiration (Fung Y.C. 1966, Meyer J.U. 1988, Secker C. 1997, Kim J.M. 1986). The photoplethysmogram is therefore much more influenced by the relatively slow fluctuations in venous volume (for example with respiration) than is the Finometer signal.

The additional source of noise (respiratory venous fluctuations) makes the photoplethysmogram have a lower signal-to-noise ratio for detection of arterial pressure changes during changing of AV settings, and so gives poorer reproducibility of optimization than the Finometer.

Using the first derivative (slope) of the signal attenuates far more dramatically the slow fluctuations (i.e. noise, such as the venous respiratory trends) than fast fluctuations (i.e. arterial volume pulsations), (Figure 5-6). This relatively enriches the useful information in the simple photoplethysmogram allowing it to become comparable with the Finometer.

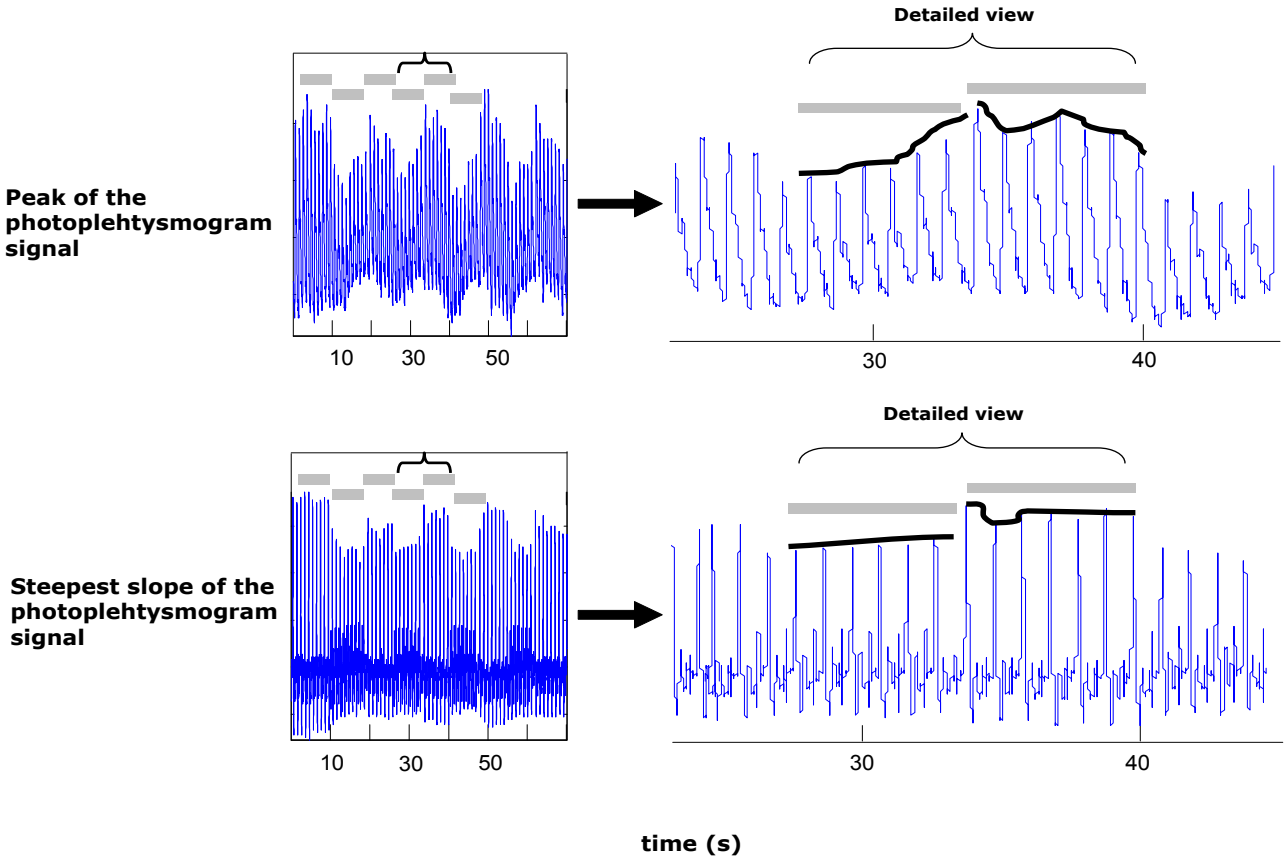


**Figure 5-6. Differences in the beat-to-beat variability between the peak and the steepest slope of the photoplethysmogram signal.**

A recording of the beat-to-beat changes of the peak of the pulse oximeter photoplethysmographic signal through a series of transition periods (marked by the shaded areas) between the reference AV delay and a tested AV delay are shown in the top left panel. Beats before and after a transition, are displayed in detail in the top right panel. The same recording is shown for the slope of the photoplethysmographic signal (bottom left and right panels). The beat-to-beat variability of the peak of the photoplethysmographic signal seems to be larger (black lines in top right panel) than the variability of its slope (flatter black lines in bottom right panel).

### 5.5.3 Trade-off between time and increasing number replicates to improve reproducibility

This study shows that attempting to minimise the time consumed in an optimization process by limiting it to just a few measurements causes optimization to be poorly reproducible. Increasing the number of replicates of measurement progressively improves the precision of the optimum.

There is no established convention on how many replicate measurements should be made at each setting during an optimization. At which stage reproducibility becomes adequate, is a matter for the individual

centre to decide, but it is sensible to establish this from an informed position of knowing the trade-off between time and reproducibility for that institution's preferred optimization method.

Certainly there is no need to know the optimal AV delay more precisely than the pacemaker allows AV delay to be programmed. However, it may not even be justified to spend the time needed to reach that level of precision if this would take many hours in an optimization clinic.

However, if a technology has a reproducibility which is so poor that its confidence interval in an individual spans over the entire range of plausible optimal AV delays, then it may be a rational alternative to set the an arbitrary fixed (or even random) AV delay to save time and expense of ineffectual optimization.

An automated optimization protocol of multiple transitions using an inexpensive simple photoplethysmographic device, could efficiently optimise cardiac resynchronization devices in a few minutes, without heavy demands on skilled operators.

### 5.5.4 Curvature of the parabola

The curvature of the parabolas fitted tended to vary between individuals. From the quadratic equation $ax^2+bx+c$, the 'a' value describes the degree of the curvature. As the parabolas fitted were inverted in all patients the 'a' value was negative in all. The more negative the value the more curved the parabola is. Although this study was not designed to look at the curvature of the parabola between different groups of patients, there was a trend of a larger parabolic curvature in the non-ischaemic patients than in the ischaemic patients; a= -0.00102258 versus -0.000694679 (p=0.078), respectively. This observation should be evaluated in a larger, prospective, adequately powered study designed to evaluate the effect of AV optimization parabolic curvature, taking into consideration a number of variables; ischaemics versus non-ischaemics, the extent of myocardial scar, the severity of heart failure by ejection fraction, and timing of optimization from the initial implantation date of the CRT device.

### 5.5.5 Comparison to Echocardiographic optimization

The reproducibility of the simple photoplethysmogram optimization was more than twice as precise as the echocardiographic method, for less than half the time required for optimization. Reproducibility scatter (SDD) of averaged values falls with the square root of the number of replicates made. Thus to use greater averaging of replicates to make echocardiography match simple photoplethymography would have needed at least as 4× as much as time as currently consumed. Since the echocardiographic protocol already took twice as long, it would take 8 times as long as the haemodynamic methods to achieve equal precision.

I do not a make a claim that the simple photoplethysmogram or Finometer is a gold standard for optimization. Such a claim would need to be based on a series of properties which should be tested in sequence:

1) Reproducibility, i.e data from separate optimization sessions analysed with mutual blinding, give the same optimum.
2) Consistency amongst several independently-acquired classes of measurement, e.g data acquired using separate equipment yields essentially the same optimum on blinded analysis. (This criterion can only be tested between classes of measurements that are individually reproducible)
3) Physiological impact, i.e ability of optimization using a measurement to consistently raise the level of some (other) variables measured independently.

When *quantitative* haemodynamic optimization (such as measuring change in blood pressure) allows large numbers of replicate measurements to be conducted and averaged, therefore quenching noise, it scores relatively well on reproducibility.

Unfortunately, the large RCT data of, for example, SMART AV delay used a *qualitative* measurement (visual selection of preferred transmitral Doppler pattern) for which reproducibility and consistency do not appear to have been formally assessed.

Therefore, although I do not believe I can recommend a definitive gold standard for CRT optimization, I can at least recommend workers assess reproducibility and consistency of optimization methods they are considering: having eliminated the irreproducible methods, if all the remaining methods agree with each other (within the limits of their own reproducibility) then any of them may be taken as a reasonable standard.

### 5.5.6 Clinical Implications

Finometer non-invasive blood pressure technology produces more reproducible optimization than simple photoplethysmogram waveform peaks, and has the advantage of being calibrated in mmHg. However, this technology is not widely available in most clinical environments. Moreover, because it depends on volume-clamping by a cuff surrounding a finger, it cannot be developed into an implantable technology.

Simple phoplethysmographic circuitry on the other hand, while being potentially implantable, has a slightly poorer reproducibility if the peak of the signal is used, because the simple photoplethysmogram volume signal is more susceptible to venous noise rather than the Finometer pressure signal. However, with no greater effort of acquisition, the steepest slope (rather than the peak of the signal) can be used, which improves its reproducibility to match that of the Finometer. If it was desired to have a fully implantable system, then this first derivative of the simple photoplethysmogram signal, which gives information of the same value as the Finometer, makes it a potentially attractive solution for inbuilt pacemaker-based optimization, as has already been demonstrated to be feasible in animals (Turcott R.G. 2008).

### 5.5.7 Study limitations

This study compared the ability of two haemodynamic monitoring technologies to reproducibly identify an optimum AV, and also contrasted them to echocardiographic optimization. It was not designed to test the clinical benefit of haemodynamic optimization, nor to characterise differences between notional

responders versus non responders. The reproducibility was assessed only over the very short term (same day) because when differences are found in longer-term reproducibility, these might be due to changes in underlying patient status and therefore cannot be confidently attributed to non-reproducibility of the optimization process.

The sampling rates of the photoplethysmographic signal were different (30 Hz for the simple plethysmograph and 200Hz for the Finometer) between the two technologies. The lower sampling rate may introduce more inaccuracies in the measurement of a haemodynamic parameter and therefore affect the reproducibility of optimization. However, at the heart rate the study was conducted, the smaller sampling rate of the simple plethysmograph most likely played only a small part in the observed reproducibility. This can be explained by the finding that post processing of the simple plethysmographic signal and measurement of the slope rather than the peak (which as discussed above greatly reduced the noise introduced by respiration), improved the reproducibility of optimization to a level that was not significantly different to that of the Finometer.

There is no comparison with invasive haemodynamic measures because I wanted to conduct it in the environment where clinical optimization is usually carried out i.e ambulatory patients. However, the Finometer has been extensively validated for detecting changes in BP using invasive pressure measurements. In addition, the arterial pressure is known to mirror closely the behaviour of intracardiac pressure generation as it was demonstrated in the initial acute studies of CRT. Also, I cannot say for certain that invasive cardiac output changes will mirror pressure changes but since changes in cardiac output are surely the mechanism by which changes in intracardiac pressure generation are conveyed to changes in (extracardiac) arterial pressure it seems unlikely that there is any other relationship than higher cardiac output being closely tied to greater intracardiac and arterial pressure (invasive and non-invasive).

No special steps were taken to deal with any ectopic beats that arose within the recordings of the 2 haemodynamic technologies in this study. No beats were excluded. This approach makes it straightforward to develop into an autonomous process that could be handled by the pacemaker device itself.

Our process of calculation of the slope of the simple photoplethysmogram was done off-line, after the data were acquired, and took less than 1 second, in total. In a truly autonomous optimization system, this might be done simultaneously by circuitry or software within the simple photoplethysmographic device itself: it is possible that such an arrangement may have different characteristics to what I found. Nevertheless, I believe our study provides a proof of concept to what can be achieved easily: it may represent a lower limit on the spectrum of possibilities.

During the study all patients were atrially paced, either just above resting rate (slow ApVp) or at 100 bpm (fast ApVp). This is different from the conditions used in some previous studies on optimization, which have used resting rate (Whinnett Z.I. 2006). The approach I take, of progressively identifying steps that improve the reproducibility of optimization, is most effective when reproducibility is already fairly good, which is the case for higher rates. As the science of optimization develops, it should be possible in principle to apply this knowledge to make the best of any situation, even the sinus resting state, in which reproducibility is relatively poor (Whinnett Z.I. 2006).

## 5.6 Conclusions

Haemodynamic optimization is just as feasible using a simple photoplethysmogram as it is with full Finometer technology. Although the Finometer has the advantage of a well established track record of validity for measuring changes in blood pressure, it is relatively expensive and could not realistically be developed into an implantable technology to accompany the pacing device.

To use the photoplethysmogram effectively for haemodynamic optimization requires the facility to pause any auto-rescaling of the signal (while pacemaker settings are changed) and ideally to use the slope rather than simply the peak value of the signal obtained.

Regardless of the choice of monitoring technology, it is necessary to perform multiple replicate measurements, without which the reproducibility of the optimum may be poor. Elevating the heart rate also improves the reproducibility of haemodynamic optimization.

I speculate that a wide variety of haemodynamic monitoring technologies may behave in parallel fashion with the only important functional difference likely to be their relative susceptibility to signal and noise. Cost, bulk and implantability would be the other relevant aspects when choosing between alternative technologies.

A photoplethysmographic signal from a pulse oximeter in routine use in cardiology departments, reliably provides reproducible haemodynamic optimization in 12 minutes.

# 6 Should current modalities of VV optimization be trusted? An assessment of the internal validity of echocardiographic, electrocardiographic and haemodynamic modalities of optimization

## 6.1 Abstract

**Background**

In atrial fibrillation (AF), VV optimization of biventricular pacemakers can be examined in isolation. I used this approach to evaluate the internal validity of three VV optimization methods.

**Methods and Results**

Twenty patients (16 men, age 75±7) in AF were optimized, at two paced heart rates, by LVOT VTI (flow), non-invasive arterial pressure, and ECG (minimizing QRS duration). Each optimization method was evaluated by: singularity (unique peak of function), reproducibility of optimum, and biological plausibility of the distribution of optima.

The reproducibility (standard deviation of the difference, SDD) of the optimal VV delay is 10ms for pressure, versus 8ms (p=ns) for QRS and 34ms ($p<0.01$) for flow. Singularity of optimum is 85% for pressure, 63% for ECG and 45% for flow ($Chi^2=10.9$, $p<0.005$)

The distribution of pressure optima is biologically plausible, with 80% LV pre-excited (p=0.007). The distributions of ECG (55% LV pre-excitation) and flow (45% LV pre-excitation) optima are no better than random (p=NS). The pressure-derived optimal VV delay is unaffected by the paced rate: SDD between slow and fast heart rate is 9ms, no different from the reproducibility SDD, (p= NS). A subset of patients who underwent repeat optimization at 1.1±0.2 years, using pressure, showed no change in VV optimum.

**Conclusions**

Using non-invasive arterial pressure, VV delay optimization is achievable with high precision, satisfying all 3 criteria of internal validity, and the optimum is unaffected by heart rate.

Neither QRS minimization nor LVOT VTI satisfy all validity criteria and are therefore weaker candidate modalities for VV optimization.

## 6.2 Introduction

Ventricular resynchronization improves the contractility of the left ventricle by stimulating a more simultaneous contraction of the left ventricular wall segments. This allows higher rising and falling rates of left ventricular pressure, ensures less isovolumic contraction and relaxation times with, as a result, more ventricular filling time leading to larger stroke volume.

Therefore maximization of resynchronization by the process VV delay optimization should maximise this physiological benefit and one would assume that this would lead to better long term outcomes. However, although a few small studies have suggested that optimization of the VV delay may provide benefits beyond AV optimization alone (Bordachar P. 2004, Sogaard P. 2002, Auricchio A. 1999) clinical trials such as the Decrease-HF (Rao R.K. 2007), Rhythm II ICD (Boriani G. 2006) and Insync III (Leon A.R. 2005) have failed to show any benefit of VV optimization over the standard setting of VV 0ms. This may have been the result of three main of issues.

First, the effect of changing the VV delay is less than that of changing the AV delay, (Whinnett Z.I. 2006) making it difficult to separate the genuine effect (signal) of changing a setting, from random variability (noise). Because the effect of VV optimization may be 5-10 times smaller than that of CRT implantation, an endpoint study would have to be 25-100 times larger than, for example, CARE-HF. So these studies were very likely underpowered to show any effect of VV optimization.

Second, these trials were conducted in patients with sinus rhythm. Changing the VV delay in patients with sinus rhythm inevitably affects the AV delay on one side of the heart or the other, so it is impossible to know for certain if any effects seen come from the AV or VV changes, or both (Boogard M.D. 2010). Third, the methods of VV optimization used in these trials included electrical based formulae and echocardiographic measurements without stating their test-retest repeatability. Failure of good reproducibility and therefore near random selection of 'optimal settings' would have been a significant contributor to the outcomes of these trials.

For these reasons, whilst the benefits of AV optimization are well established the benefits of VV optimization are less well understood.

In atrial fibrillation however, there is no AV delay to confound VV optimization (Figure 6-1). Therefore, in these patients, the impact of a VV delay change is a direct consequence of that change in the VV delay alone. In this study, I recruited patients in AF as a model for 'pure' VV optimization.

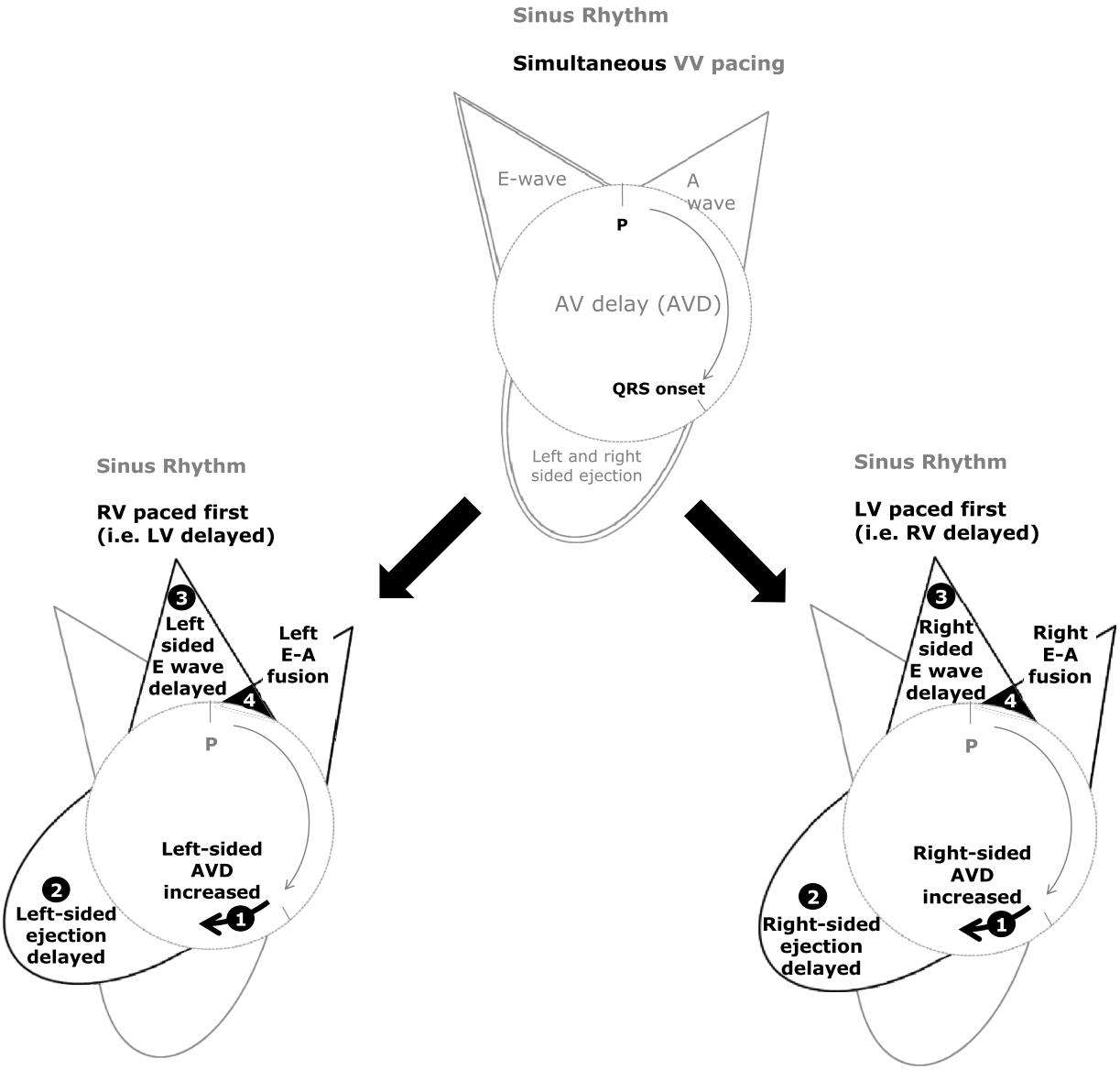


**Figure 6-1. In sinus rhythm, changing the VV delay forces either the left-sided or right-sided AV delay to change.**

Each circle shows 1 cardiac cycle in sinus rhythm, with electrical activity shown on the inside and mechanical activity on the outside. The E-wave is passive ventricular filling and the A-wave is active ventricular filling. For example, in a Medtronic pacemaker, selecting RV pre-excitation instead of simultaneous, while keeping programmed AV delay constant, increases the actual effective AV delay to left-sided pacing, because the programmed AV delay is to the "first lead to be activated" in this manufacturer's convention. The E-wave, which can only occur after the ventricle finishes

ejecting, therefore occurs later (in relation to the A wave) on the left side than it did before the VV delay change. Conversely, selecting LV pre-excitation has the mirror image effect on the right side of the heart. Other manufactures have different conventions for labelling the delays, but the constraint remains: the VV delay cannot be changed without changing the mechanical AV delay on one side of the heart or the other. All apparent VV optimizations in sinus rhythm therefore include an occult element of AV optimization.

As it is not yet realistic to look for differences in clinical outcomes between different markers of optimization, the only way to compare these is to evaluate the relative performance of each method, head to head, in an identical patient group, in order to verify that its behaviour is fit for purpose. Any marker of optimality used to select a pacemaker setting requires three essential features:

1) *Singularity*; there should be only one region of optimality, with progressively poorer function as settings are changed away from this region. If the optimal region is at one extreme of settings, then it is possible that there is one rather than 2 regions of optimality, but it is not possible for there to be 2 regions of optimality separated by a region of non-optimality.
2) *Reproducibility*; if the optimization process is repeated immediately with a new operator blinded to the previously found optimal setting, the newly found optimum should be very similar.
3) *Plausibility*; the distribution of optimum settings should not contradict established physiological principles. For example, frequently finding VV optima with large RV pre-excitation would be in contrast to the principle of resynchronization, i.e. pacing the LV wall simultaneously or even earlier than the RV.

In this study, I tested three different optimization markers that might be used (Tamborero D. 2009, Bertini M. 2008, Turcott R.G. 2010) to identify a VV delay optimum in the AF cohort, in which there was no possibility of VV delay alteration causing confounding changes in the AV delay. The markers tested were ECG (QRS duration minimization), LVOT VTI maximization (flow) and non-invasive arterial BP (pressure).

## 6.3 Methods

### 6.3.1 Patients

Twenty patients (16 men, mean age 75±7 years) in atrial fibrillation, with a CRT device were enrolled in the study. Average NYHA class was 2.4±0.5. The underlying cause of heart failure was ischemic heart disease in 10, dilated cardiomyopathy in 8 and valvular disease in 2 patients.

The study was approved by the Imperial College Healthcare NHS Trust ethics committee, and all patients provided written informed consent.

### 6.3.2 Study Design

Patients were assessed using transthoracic echocardiography, finger photoplethysmography (Finometer) and electrocardiography. Measurements were taken at six VV delays (-40ms, -20ms, 0ms, 20ms, 40ms and 60ms, where a negative VV delay indicates right ventricular pre-excitation). All patients were assessed at 2 heart rates, first at a slow paced rate just above the rate of intrinsic conduction (always ensuring 100% biventricular pacing), and then at a faster paced rate (mean of 27±7 bpm above this). Reproducibility data were obtained by repeating optimization for all patients at both heart rates on the same day. Five patients had already been optimized (by Finometer) at a mean of 1.1±0.2 years previously.

### 6.3.3 Echocardiography

Echocardiographic images were obtained using a ProSound SSD-5500SV system (Aloka, Tokyo, Japan). All images were obtained by the same operator, blinded to the VV delays which were randomly programmed by a second operator. Images were taken with the patient positioned in the dorsal decubitus or left lateral decubitus position, at passive end expiration. Images of 6 consecutive beats were taken for each VV delay (excluding ventricular ectopics and the beat after the ectopic) and at both heart rates.

Optimization was repeated approximately 30 minutes later for reproducibility assessment. The images were saved for offline analysis using Medcon software (McKesson, San Francisco, CA, USA).

Pulsed wave Doppler was used to assess left ventricular outflow tract (LVOT) and mitral valve (MV) flow. The myocardial performance index (MPI) (Tei C. 1995) was calculated by measuring the time from cessation to the start of mitral flow (A) and left ventricular ejection time (ET). MPI = (A - ET) / ET.

The following parameters were measured: LVOT velocity time interval (VTI), MV VTI, time from QRS onset to LVOT VTI onset (LV pre-ejection time), time from MV VTI onset to QRS onset, LVOT and MV VTI wave durations. The optimum VV delay was defined as the setting that produced the highest LVOT VTI or MV VTI. For the time from QRS onset to LVOT flow and time from MV VTI flow to QRS onset, the optimum VV delay was defined as the setting that produced the lowest value.

### 6.3.4 Finger Photoplethysmography

Beat-to-beat systolic blood pressure was recorded using a Finometer device (Finapres Medical Systems, Amsterdam, Netherlands). Optimization of the VV delay was performed using a protocol described in previous work (Whinnett Z.I. 2006). Transitions between a tested VV delay and a fixed reference VV delay (of 0ms) were performed. Eight transition replicates were recorded for each tested VV delay. Each replicate was composed of the 10 beats before and 10 beats after each transition. Analysis was performed using software based on the Matlab platform (MathWorks, Natick, MA, USA). By comparing the mean systolic blood pressure of the 10 beats before the VV delay change to the 10 beats after, the software calculates the relative change in systolic blood pressure (SBP) between each tested VV delay and the reference VV delay. The optimum VV delay was defined as the setting that produced the highest relative SBP value.

### 6.3.5 Electrocardiography

12 lead ECG traces were obtained using a MAC 1200 ST system (GE Healthcare, Chalfont St Giles, UK) at each VV delay and at both heart rates for all patients. In this system, the QRS width is calculated using synchronously sampled and time aligned data across 12 leads, measuring the time from first deflection of the median QRS complex in any lead to the latest deflection in any lead. The average from 2 repeated recordings was used. Recordings which had ventricular ectopics were excluded and the 12 lead ECG repeated. This process was performed twice to assess reproducibility. The VV delay that produced the shortest QRS width was taken as the optimum.

### 6.3.6 Statistical Analysis

A parabola was used for all parameters as previous work has determined that haemodynamic function during CRT optimization follows this consistent shape (Whinnett Z.I. 2006).

The reproducibility and the agreement of different optimization methods were assessed by using Bland-Altman plots and the standard deviation of the difference (SDD) between the optimal VV delays. Paired comparisons of normally-distributed continuous variables were made using Student's paired *t* test. Paired comparisons of non-normally-distributed continuous variables were made using Wilcoxon's matched-pairs signed rank test. A p-value of $<0.05$ was taken as statistically significant. Statview 5.0 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

***Singularity of optimum***

Physiologically meaningful pressure and flow optimization curves are orientated with one maximum region and decreasing values on each side. For QRS minimization, it is one minimum with rising values on each side. The curves were obtained by standard least-squares curve fitting (Microsoft Excel; Microsoft Corporation, Redmond, WA), and the orientation determined from the sign of the quadratic term. By chance alone, of randomly orientated curves half would be expected to be orientated in the

physiologically correct direction. Therefore the raw percentage ($x$) of plausibly orientated curves needs be transformed to $2(x\text{-}50)$ to obtain the proportion in excess of chance. On this scale, Ø represents the average expectation by chance alone, and 100 represents perfect orientation.

## 6.4 Results

20 patients were included in this study; their characteristics are shown in Table 6-1.

**Table 6-1. Baseline patient characteristics**

| Demographics | Mean and SD or n(%) |
|---|---|
| Age | 75 SD 7 |
| Age range | 58 - 91 |
| Male | 16 (80%) |
| Aetiology | |
| Ischaemic | 10 (50%) |
| Dilated | 8 (40%) |
| Valvular | 2 (10%) |
| NYHA class | |
| II | 13 (65%) |
| III | 7 (35%) |
| LVEF (%) | 31 SD 13 |
| QRS | 155 SD 20 |
| Medications | |
| ACEi/ARB | 19 (95%) |
| β-blocker | 17 (85%) |
| Diuretic | 17 (85%) |
| Spironolactone | 8 (40%) |
| Digoxin | 12 (60%) |

### *6.4.1 Criterion 1: Singularity – One optimum region, and worse to one or both sides*

I present complete VV optimization curves for all subjects. All 20 patients' optimization curves for LVOT VTI maximization are shown in Figure 6-2. Their curves for pressure maximization are shown in Figure 6-3. Their curves for QRS minimization are shown in Figure 6-4.

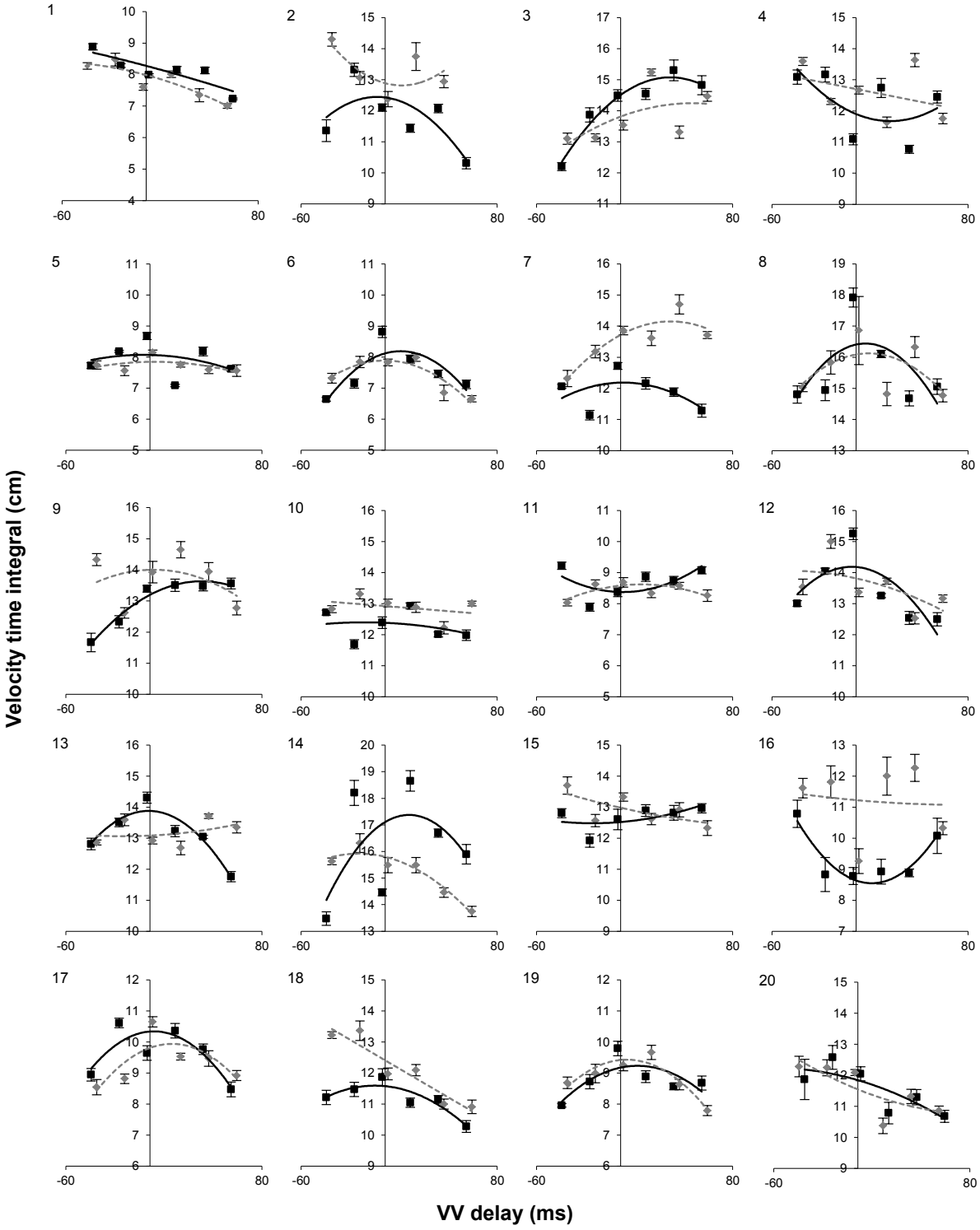


**Figure 6-2. Raw data points and optimization parabolas for LVOT VTI measurements at the fast heart rate.**

First (black) and second (grey) sessions of optimization on the same day, using LVOT VTI at each VV delay (RV 40 to LV 60), for all 20 patients. A parabola was fitted in all optimization sessions and the peak of the parabola was considered to represent the optimal VV delay (optimum=largest VTI).

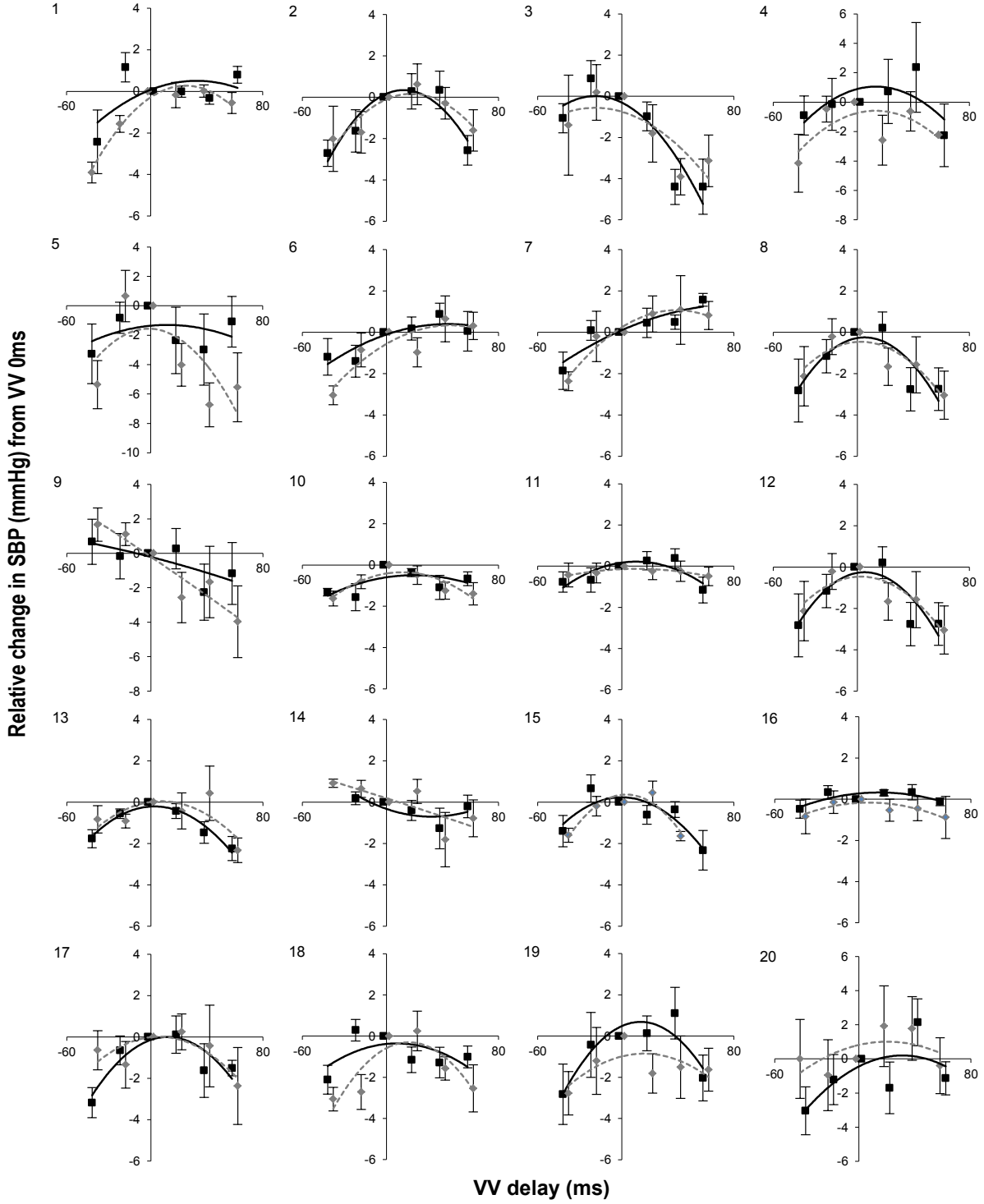


**Figure 6-3. Raw data points and optimization parabolas for non-invasive beat-to-beat systolic blood pressure (SBP) at the fast heart rate.**

First (black) and second (grey) sessions of optimization on the same day, using non-invasive SBP at each VV delay (RV 40 to LV 60) for all 20 patients. A parabola was fitted in all optimization sessions and the peak of the parabola was considered to represent the optimal VV delay (optimum=highest relative SBP).

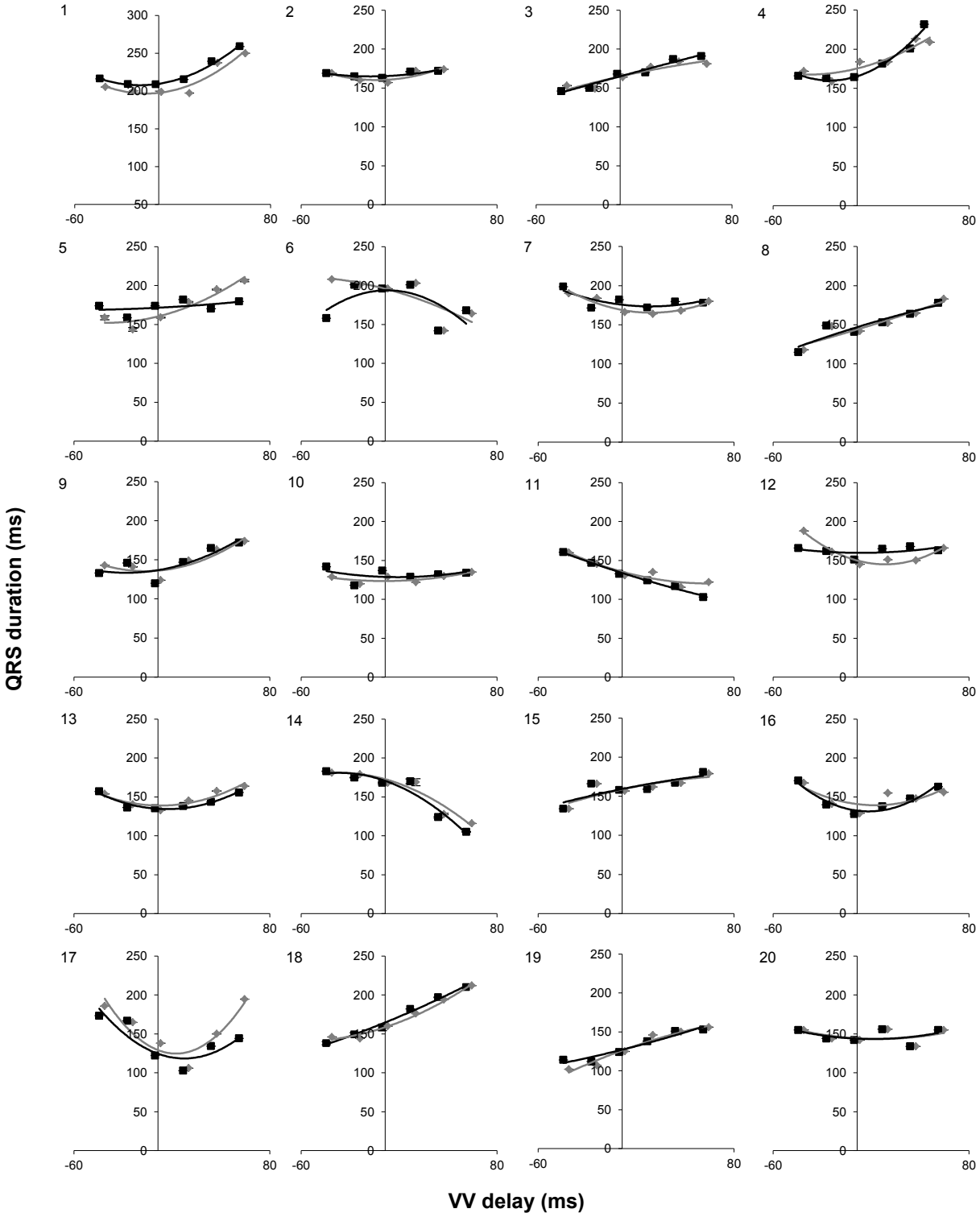


**Figure 6-4. Raw data points and optimization parabolas for QRS width measurements at the fast heart rate.**

First (black) and second (grey) sessions of optimization on the same day, using 12-lead ECG QRS width, at each VV delay (RV 40 to LV 60) for all 20 patients. A parabola was fitted in all optimization sessions and the trough of the parabola was considered to represent the optimal VV delay (optimum=narrowest QRS).

By random chance alone, 50% of the quadratic curves fitted would be expected to be in the physiologically meaningful orientation. Therefore, only instances in excess of 50% were evidence of the physiological validity of a measure, as shown in Table 6-2. The extent of singularity was significantly different between modalities (Chi2=10.9, p<0.005).

**Table 6-2. Comparison of optima singularity between modalities**

Optimization by pressure provided a high degree of optima singularity (expressed in % above chance alone). QRS optimization had a reasonable degree of singularity, but flow optimization was the least convincing. The difference in degrees of singularity between modalities was significant (p<0.005).

| Optimization method | Number of optimizations, out of 40, having a single optimal region | | Number out of 80 | Degree of singularity, beyond expectation of chance |
|---|---|---|---|---|
| | Slow rate | Fast rate | Overall | |
| Pressure | 36 | 38 | 74 | 85% |
| Flow | 30 | 28 | 58 | 45% |
| QRS | 35 | 30 | 65 | 63% |
| | | | $Chi^2$ : | 10.9 |
| Difference between modalities: | | | p-value : | <0.005 |

For optima derived by pressure, the percentage of curves that had the expected physiological orientation (function decaying away from a peak) beyond that expected by chance alone was 80% at the slow and 90% at the fast heart rate. For LVOT VTI, the extent of singularity was only 50% and 40%, respectively, for slow and fast heart rates. For QRS minimization the extent of singularity (which meant a narrow QRS at an optimum VV delay, and wider a QRS away from it) was 75% and 50% at slow and fast heart rates respectively. Percentages in excess of chance for other variables are shown in Figure 6-5.

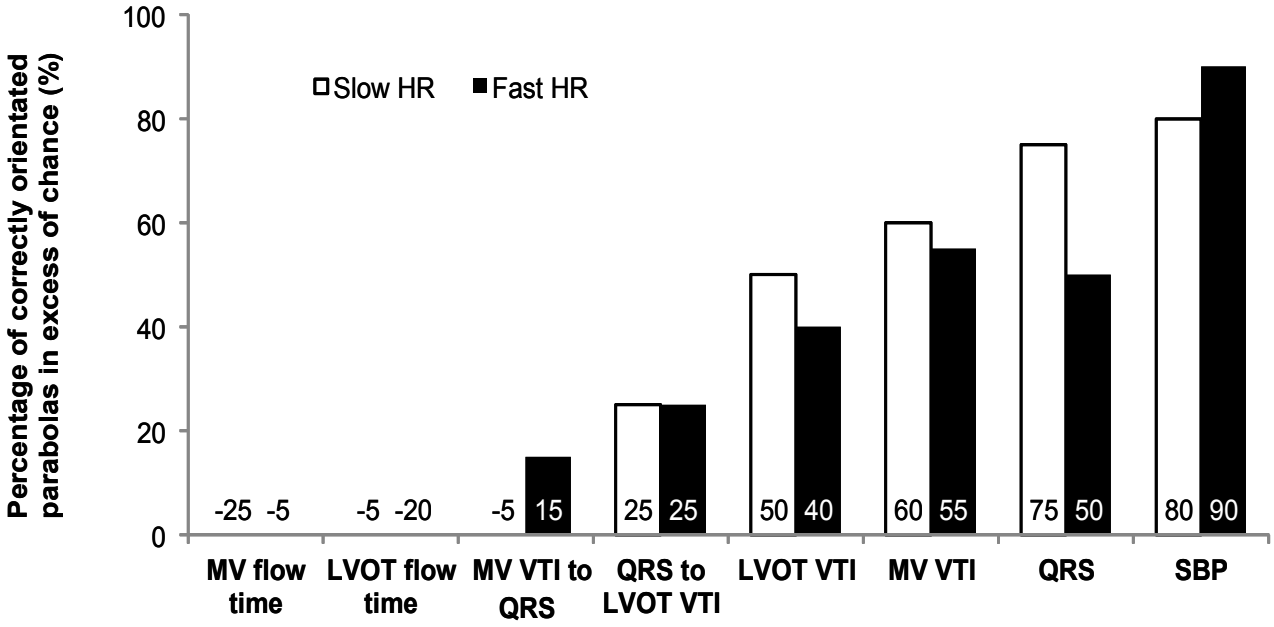


**Figure 6-5. Singularity – the percentage of correctly orientated parabolas, in excess of that expected by chance alone.**

By random chance alone, 50% of the parabolic curves fitted would be expected to be in the physiologically meaningful orientation. Therefore the raw percentage ($x$) of correctly orientated curves needs be transformed to $2(x\text{-}50)$ to obtain the proportion in excess of chance. On this scale, Ø represents the average expectation by chance alone, and 100 represents perfect orientation. SBP had a significantly higher percentage of correctly orientated optimization curves than LVOT VTI and QRS, at both the slow and fast heart rates.

### *6.4.2 Criterion 2: Reproducibility – the same optimum when retested*

The reproducibility of an optimization method was quantified by the standard deviation of the difference (SDD) between successive determinations of the optimal VV delay, with both optimizations conducted within one hour. This is shown for all measures at the slow heart rate in Table 6-3 for and at the fast heart rate in Table 6-4.

### Table 6-3. Agreement of optima between modalities at the slow heart rate

Values on the principal diagonal of the table indicate reproducibility of the optimum using the same modality twice; other values indicate the agreement between modalities. All agreements are quantified as the as standard deviation of difference (SDD, ms) between the two optima obtained, in the 20 subjects.

| | LVOT VTI | QRS to LVOT VTI | LVOT ejection time | MV VTI | MV VTI to QRS | MV ejection time | MPI | QRS | SBP |
|---|---|---|---|---|---|---|---|---|---|
| Echocardiography | | | | | | | | | |
| LVOT VTI | **34.0** | 41.1 | 64.7 | 34.3 | 43.6 | 56.9 | 31.4 | 44.8 | 37.0 |
| QRS to LVOT VTI | 41.1 | **39.2** | 62.6 | 43.1 | 51.6 | 49.5 | 35.8 | 23.8 | 36.1 |
| LVOT ejection time | 64.7 | 62.6 | **58.1** | 57.9 | 67.9 | 51.5 | 67.5 | 60.6 | 61.7 |
| MV VTI | 34.3 | 43.1 | 57.9 | **46.8** | 46.4 | 59.2 | 38.7 | 42.0 | 44.6 |
| MV VTI to QRS | 43.6 | 51.6 | 67.9 | 46.4 | **39.8** | 52.9 | 51.4 | 49.0 | 47.2 |
| MV ejection time | 56.9 | 49.5 | 51.5 | 59.2 | 52.9 | **42.2** | 62.8 | 57.7 | 53.0 |
| MPI | 31.4 | 35.8 | 67.5 | 38.7 | 51.4 | 62.8 | **55.8** | 39.0 | 33.2 |
| Electrocardiography | | | | | | | | | |
| QRS width | 44.8 | 23.8 | 60.6 | 42.0 | 49.0 | 57.7 | 39.0 | **8.0** | 33.3 |
| Finometer | | | | | | | | | |
| SBP | 37.0 | 36.1 | 61.7 | 44.6 | 47.2 | 53.0 | 33.2 | 33.3 | **10.2** |

LVOT indicates left ventricular outflow tract; MV, mitral valve; VTI, velocity time integral; MPI, myocardial performance index; SBP, acute change in systolic blood pressure.

### Table 6-4. Agreement of optima between modalities at the fast heart rate

Values on the principal diagonal of the table indicate reproducibility of the optimum using the same modality twice; other values indicate the agreement between modalities. All agreements are quantified as the as standard deviation of difference (SDD, ms) between the two optima obtained, in the 20 subjects.

| | LVOT VTI | QRS to LVOT VTI | LVOT ejection time | MV VTI | MV VTI to QRS | MV ejection time | MPI | QRS | SBP |
|---|---|---|---|---|---|---|---|---|---|
| Echocardiography | | | | | | | | | |
| LVOT VTI | **35.4** | 46.9 | 43.1 | 49.7 | 51.9 | 52.1 | 47.8 | 41.4 | 45.3 |
| QRS to LVOT VTI | 46.9 | **27.7** | 46.6 | 47.3 | 69.5 | 59.4 | 47.8 | 43.6 | 53.2 |
| LVOT ejection time | 43.1 | 46.6 | **39.2** | 58.7 | 68.7 | 54.1 | 56.2 | 48.4 | 54.6 |
| MV VTI | 49.7 | 47.3 | 58.7 | **38.7** | 56.6 | 64.6 | 46.1 | 33.1 | 38.0 |
| MV VTI to QRS | 51.9 | 69.5 | 68.7 | 56.6 | **31.7** | 58.2 | 57.6 | 51.1 | 40.6 |
| MV ejection time | 52.1 | 59.4 | 54.1 | 64.6 | 58.2 | **54.5** | 69.2 | 59.9 | 52.7 |
| MPI | 47.8 | 47.8 | 56.2 | 46.1 | 57.6 | 69.2 | **45.2** | 48.6 | 42.9 |
| Electrocardiography | | | | | | | | | |
| QRS width | 41.4 | 43.6 | 48.4 | 33.1 | 51.1 | 59.9 | 48.6 | **6.0** | 43.9 |
| Finometer | | | | | | | | | |
| SBP | 45.3 | 53.2 | 54.6 | 38.0 | 40.6 | 52.7 | 42.9 | 43.9 | **9.4** |

LVOT indicates left ventricular outflow tract; MV, mitral valve; VTI, velocity time integral; MPI, myocardial performance index; SBP, acute change in systolic blood pressure.

Optimization by LVOT VTI showed a wide scatter between successive optima (SDD 35.4ms). This meant that 95% of repeat optimizations gave results within ±69ms of the previous optimization. Other

echo markers also performed poorly if considered as potential methods of optimization. The most reproducible methods of optimization were SBP maximization (SDD 9.4ms) and QRS minimization (SDD 6ms). Bland-Altman plots for the three key modalities being studied (flow, pressure and QRS) are shown in Figure 6-6.

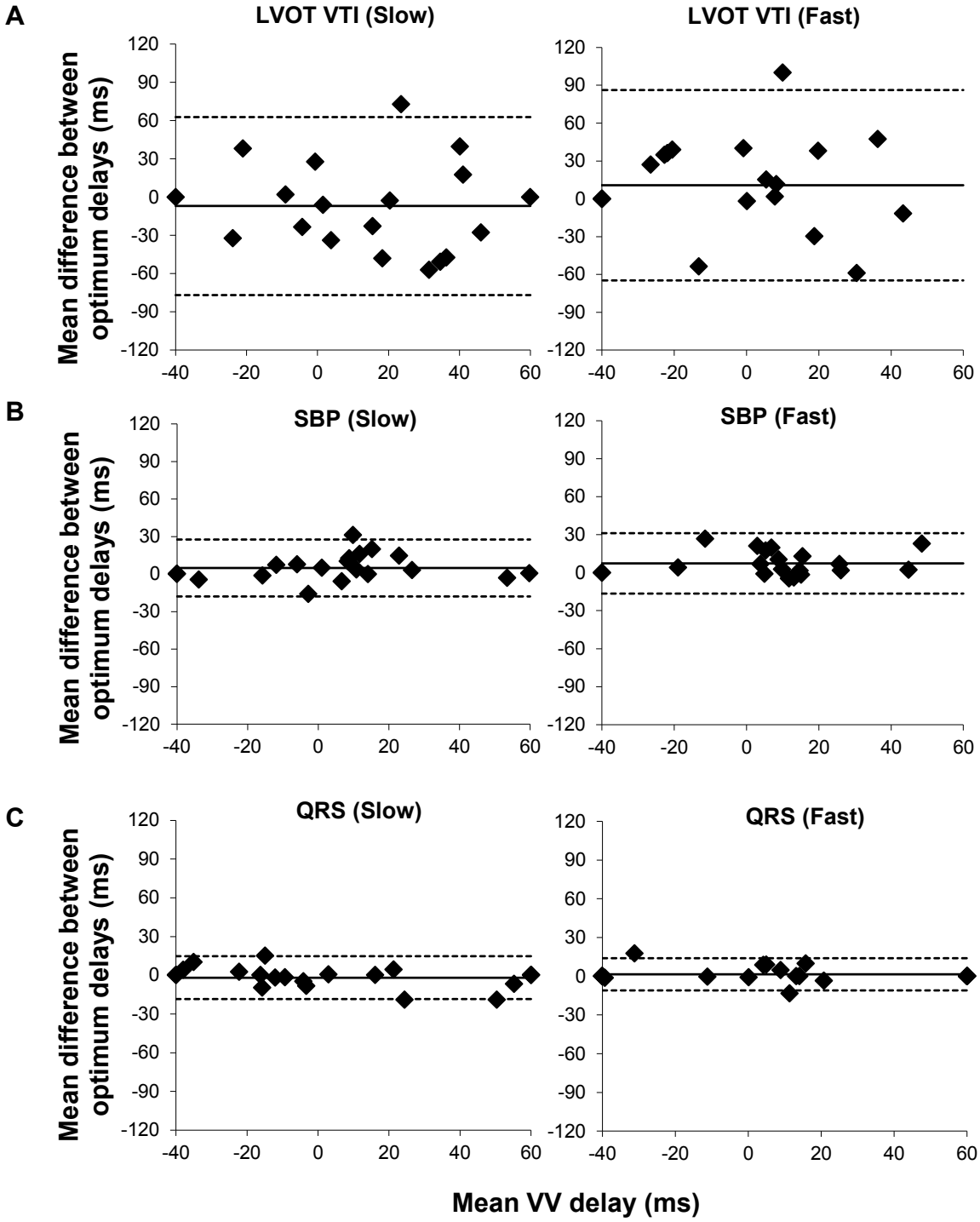


**Figure 6-6. Reproducibility - Bland-Altman plots for LVOT VTI, QRS width and SBP derived optimum settings, at the slow and fast heart rates.**

The reproducibility (standard deviation of the difference – SDD in ms) of LVOT VTI (A) is equally poor at the slow (34ms) and fast (35ms) heart rates. SBP reproducibility (**B**) was better than LVOT VTI at slow (10ms, $p<0.01$) and fast heart rates (9ms, $p<0.01$). The reproducibility of the QRS width (**C**) was also better at slow (8ms, $p<0.01$) and fast (6ms, $p<0.01$) rates.

### 6.4.3 Criterion 3: Plausibility of the distribution of optima

The distribution of optimal VV delays at the fast heart rate, of all 3 optimization methods is shown in Figure 6-7. By pressure, the optimum was often near a 0ms VV delay: 75% were within 20ms of zero. A significant majority (80%, p=0.007) of pressure optima had a degree of LV pre-excitation.

In contrast, the flow and QRS optima tended to be further away from zero: only 60% and 50%, respectively were within 20ms of zero. Moreover, the proportion of optima by these modalities that had a degree of LV pre-excitation was not significantly different from chance (45% for flow and 55% for QRS, p=NS in each case).

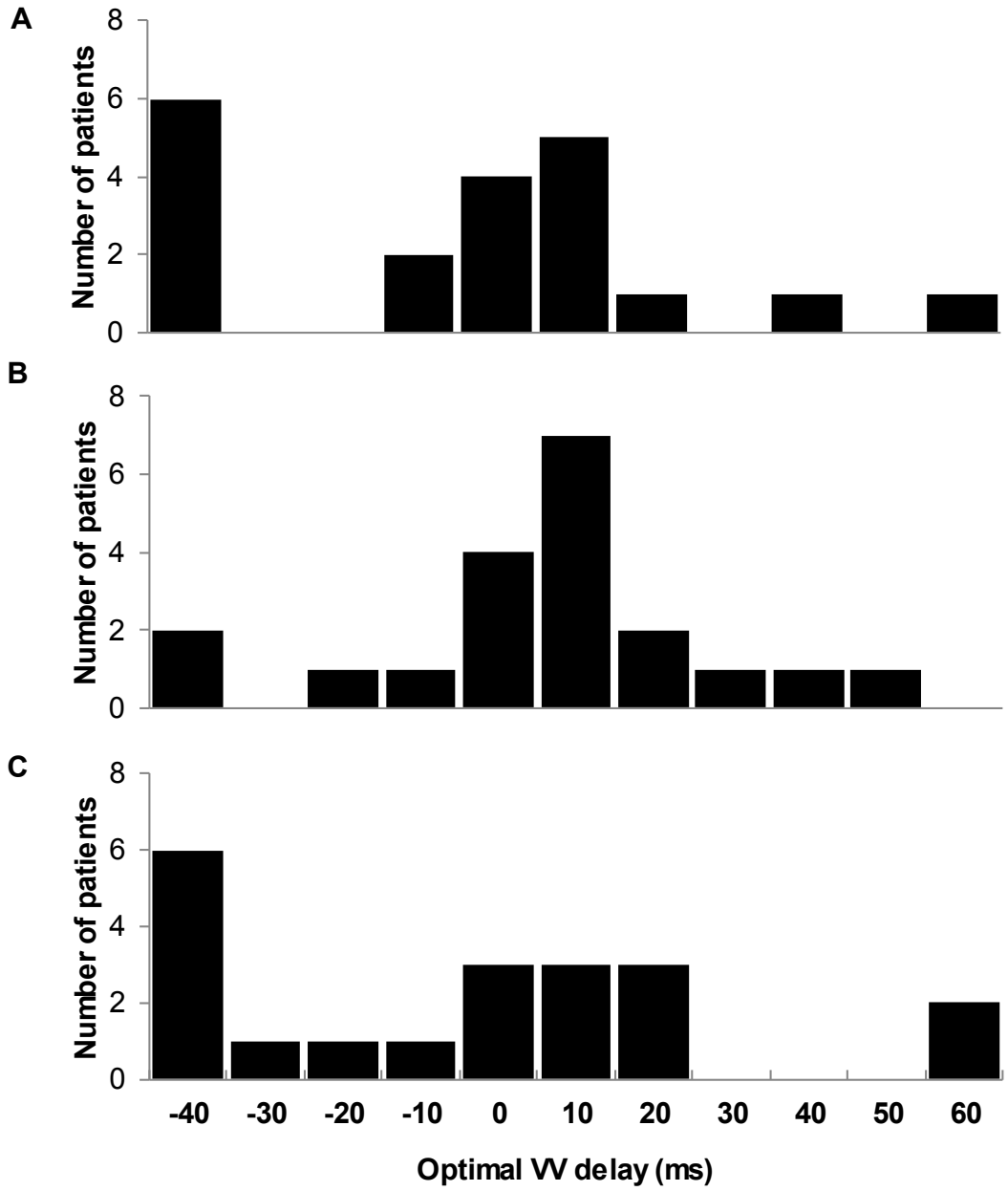


**Figure 6-7. Biological Plausibility – the distribution of LVOT VTI, Finometer SBP and QRS determined optimum VV delays at the fast heart rate.**

LVOT VTI (A) and QRS (C) optima distributions contain a high proportion of optima with significant (-40ms) RV pre-excitation. In contrast, the SBP (B) optima distribution is more central, around VV 0ms, and most optima are LV pre-excited.

### 6.4.4 Agreement of the optimal VV delay between LVOT VTI, QRS width and beat-to-beat systolic blood pressure

Incidentally available was agreement between modalities, also displayed in Tables 6-3 and 6-4. Agreement between methods was poor, typically with a SDD of the order of 40 ms, meaning that if a method gave an optimum of X, the other method would be expected to give an optimum between X-80 ms to X+80ms, a very wide range indeed. In interpreting this number we should be mindful that no irreproducible method will ever agree with any other method (whether or not the other method is reproducible). Thus, it could be argued that the only scientifically valuable numbers on the table are the principal diagonal (which show the degree of reproducibility of each modality) and the twin values of "43.9" in the bottom right corner, which shows the only between-modality test in two modalities (QRS minimization and SBP maximization) that show good reproducibility.

### 6.4.5 The effect of heart rate on the optimal VV delay

It is not possible to determine whether the optimal VV delay changes between heart rates unless the reproducibility of the optimum is known, because irreproducibility would otherwise be erroneously interpreted as evidence of change in optimum between rates. If the true optimum changed from one state to another, in ways that differed between patients, the scatter (SDD) of the observed changes from one state to another would be wider than the scatter when one state is compared with another optimization in the same state.

Of the 3 key modalities tested (VTI, pressure, QRS) only pressure showed adequate singularity, reproducibility and plausibility of the obtained optima, to be credible measures of the optimum. By pressure optimization, the optima appear to change only 9ms between the slow and fast rate (expressed as SDD). Since this is no different from the test-retest variability of the optimization process itself, it indicates that this change in heart rate does not genuinely cause a change in the optimal VV delay (Figure 6-8).

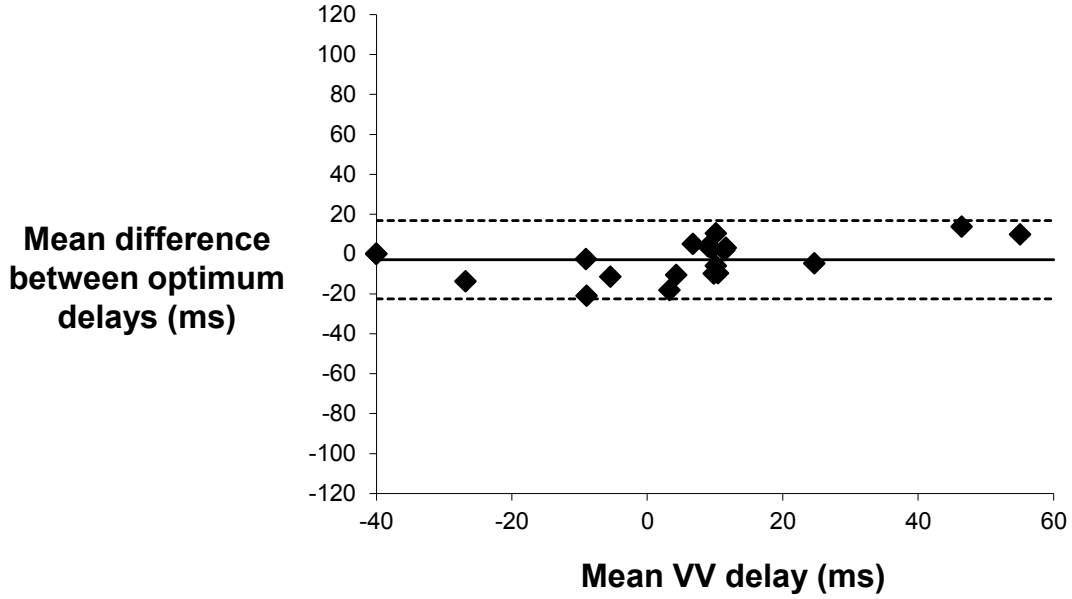


**Figure 6-8. Figure 8. Bland-Altman plot showing the agreement of the beat-to-beat SBP determined optimum settings between the slow and fast heart rates.**

There is very good agreement between the slow and fast rate optimal VV delay, standard deviation of the difference (SDD) of 9ms. This level of agreement would imply that the optimal VV delay in independent of heart rate.

### *6.4.6 Effect of the passage of one year on the optimal VV delay*

Five patients had previously undergone pressure optimization a mean of 1.1±0.2 years previously, allowing the effect of passage of time to be evaluated. The standard deviation of the difference between the optimum VV delays of their first and second visits, at the fast heart rate, was 8ms. Again, this was no different from the same day reproducibility (SDD=9ms). This suggests that there is no underlying change in the optimal VV delay over one year, other than the small random scatter between any successive pair of optimizations even if conducted within the hour.

## 6.5 Discussion

This study evaluated the performance of three potential approaches for VV optimization, using the three key criteria for internal validity of an optimization. Of the approaches tested, optimization by pressure appears to offer all 3 criteria: *singularity, reproducibility* and biological *plausibility.* QRS minimization offers singularity and reproducibility, but the distribution of optimum settings obtained appears biologically implausible. Optimization by flow performed disappointingly in our study, on all 3 criteria of internal validity.

### 6.5.1 Three criteria for internal validity

*Reproducibility* is a key criterion for any method of optimization. If an individual patient is given multiple discrepant proposed 'optima' in rapid succession by a single method, most of these apparent optima must be incorrect. While reproducibility alone is not sufficient criterion to judge an optimization approach to be internally valid, it is a necessary one.

*Singularity* indicates that having conducted the optimization process, there is only a single region which appears to be optimal, rather than two optimal regions separated by non-optimality. This is relevant because the principle of CRT is to improve cardiac function by bringing the walls of the heart into more closely coordinated times of contraction (although not necessarily to VV 0ms). Moving away from this optimal timing of contraction in either direction should worsen cardiac function. In some cases (when the true optimal region is at the extremes of the range of tested settings) there might reasonably be only one non-optimal region, but singularity can still be tested by the shape of the curve. Because the shape of the curve should be almost flat at the optimal region, becoming steep as one moves away, fitting a parabola will still verify singularity (i.e the orientation of curvature would indicate that there would have been 2 non-optimal regions, if more settings beyond the optimal had been tested).

Biological *plausibility* of the distribution of the obtained optima is the final criterion. It is less fundamental than the others because it relies on a collateral belief of what distribution of optima is expected. CRT is generally accepted to exert benefits by decreasing rather than increasing dyssynchrony

of the myocardial walls. It is therefore rational to expect the distribution of the optima to show that for many patients, their optimum setting is near to the VV delay of 0ms, with only few patients being at an optimum with marked pre-activation of one lead. It is left, rather than right, bundle branch block in which the salutary effects of biventricular pacing are most prominent, and invasive studies (Auricchio A. 2002, Kass D.A. 1999, Butter C. 2001, Auricchio A. 1999) have shown that left ventricular pacing can achieve most of the effect of biventricular pacing but right ventricular pacing cannot. These prior observations of others are reasons to expect the VV delay optimum to more often involve pre-activation of the left ventricle than the right.

### 6.5.2 Internal validity as an endpoint in a "basic science" of optimization

This study specifically focussed on the three key characteristics of internal validity of an optimization approach. I did this because these are essential criteria that may be definitively established in controlled circumstances, and which enables early identification of potentially unsuitable optimization approaches. It also establishes the internal validity of these optimization measures, wise to establish before embarking on large clinical event trials.

Only optimization by pressure fulfilled all 3 criteria. Flow maximization disappointed on all 3 criteria. QRS minimization, although it showed good reproducibility and singularity, provided a biologically implausibly high frequency of proposed optima with marked pre-activation of one lead or the other (35% of optima at the slow heart rate and 40% at the fast heart rate had at least 40 ms pre-activation of one lead).

### 6.5.3 Atrial Fibrillation as a model for isolated VV optimization

In sinus rhythm, it is not possible to adjust the VV delay without disturbing the AV delay of one ventricular lead or the other. In some CRT devices, the programmed AV delay corresponds to one particular chamber only. For example, in most Medtronic devices, the programmed AV delay always sets

the delay to activation of the RV lead. The delay to activation of the LV lead is determined by the VV delay, which may be negative (RV lead first) or positive (LV lead first).

In Guidant devices, the computational convention is different, but the ultimate constraint, which arises from physiology itself, is the same. The programmed AV delay sets the delay to the first paced ventricular lead to be. Which lead that is, and how much later the other lead is paced is determined by the VV delay setting. In both families of CRT device, any VV delay change must affect the AV delay of either the LV or the RV lead, and therefore the transmitral filling time of either the left or right ventricle (Figure 6-1). As a result, in sinus rhythm, it is impossible to measure the haemodynamic effect of an isolated, pure change in the VV delay because there will always be superimposed haemodynamic effects from a simultaneous, unwanted change in AV delay of the left or right heart.

### 6.5.4 LVOT VTI as a modality for VV optimization

There is a strong *a priori* rationale for the use of LVOT VTI (flow) as a marker of cardiac function, for optimization. Given that the diameter of the LVOT remains constant, changes in stroke volume are solely dependent on velocity and duration of blood flow. Therefore, the LVOT VTI is a perfect index of stroke volume which in turn is, in principle, an ideal marker of cardiac function. Our study does not contradict the principle that optimal flow is desirable, but rather only indicates that in patients such as ours it is not possible to measure changes with sufficient precision to prevent noise overwhelming the signal.

In this study, conducted in a research setting with much less time constraint than occurs in routine clinical practice, I applied a rigorous methodology, including measuring a number of LVOT VTIs (6 beats) that would be considered large by routine clinical standards. The reason was to improve the signal-to-noise ratio and therefore improve the reproducibility of the optimal VV delay (Pabari P.A. 2010). Inability to deploy resources to analyse multiple independent beats at each VV setting often limits routine clinical practice to only 1, 2, or 3 replicate beats.

However, despite the special precautions I took, LVOT VTI optimization performed poorly, which may be an explanation for the inconsistent findings reported by other studies testing clinical outcomes following VV optimization (Boriani G. 2006, Rao R.K. 2007, Leon A.R. 2005). Notably, singularity, reproducibility and plausibility have rarely been commented upon in studies assessing optimization.

### 6.5.5 QRS minimization as a modality for VV optimization

QRS minimization superficially appears to have better properties for suitability as an optimization tool. It is a highly reproducible measurement that can be quickly and cheaply acquired, potentially automatically, it avoids the problems of needing good echocardiographic windows and a trained operator with enough time to perform and analyse a lengthy series of measurements. Indeed, a wide QRS is part of the selection criteria for CRT device implantation so it would be consistent to seek to narrow the QRS width as far as possible during optimization. There are studies showing some association between a reduction in the QRS width and clinical benefits (Pitzalis M.V. 2005, Lecoq G. 2005). However, our findings showed that although reproducible and generally singular, QRS minimization frequently proposed optimal VV delays that had marked right ventricular pre-activation (Figure 6-7). This is not biologically plausible if the current understanding of cardiac resynchronization process is correct. Moreover, in our study, QRS reaches its minimum at a VV delay very different from that at which arterial pressure is maximized. Because I have quantitative data on reproducibility of these techniques in the same patients at the same session, I know that the discrepancy between methods is not due to imprecision of my ability to establish each optimum, but rather that the two optima are providing fundamentally distinct information.

It is inescapable from our data, that adjusting VV delay to minimise QRS definitely results in a lower blood pressure. Forced to choose between a pressure maximum and a QRS minimum, I believe that the pressure maximum is both intrinsically a better physiological target as well as showing a biologically more plausible distribution of VV optima.

The numerous elements contributing to mechanical dyssynchrony, and cardiac function overall, go far beyond QRS width, as has been documented in several studies (Ghio S. 2004, Bleeker G.B. 2005). Therefore, even though wide QRS may predict benefit for CRT (Chung E.S. 2008, Linde C. 2008, Moss A.J. 2009, Gorcsan J. 2008) first principles do not require that QRS minimization must be the ideal approach to VV optimization.

Several studies have shown that during biventricular pacing the QRS, although in theory may be expected to shorten by approximately 50%, only shortens by 20% (Gervais R. 2009). Moreover, LV pacing does not seem to shorten QRS width, yet it has been shown that LV pacing is not inferior to biventricular pacing both acutely and long term (Verbeek XA. 2006).

When measuring simply the width of QRS as potential tool for optimization, another consideration is the activation time across the septum. This can be as high as 100ms or more (Prinzen FW. 2008). A recent study has confirmed that transseptal conduction in LBBB and heart failure can be very long indeed: 67±9ms (Strik M. 2013). This slow transseptal conduction will therefore limit the extent by which the QRS could narrow during VV optimization. Moreover, the patterns of electrical activation in heart failure, both endocardially and epicardially, are still largely unknown and unless these are further investigated and understood the application of the QRS, especially its width, as an optimization modality should be used with caution.

### 6.5.6 VV optimum unchanged by heart rate, and after 1 year

Using the only method in our study with internal validity, pressure optimization, I saw that heart rate had no discernible effect on optimal VV delay. The agreement of individual patients' optimal settings between the slow and fast heart rates was no worse than the reproducibility of the optimal VV delay at either the slow or fast rate, suggesting that patients' optimum settings do not change with heart rate.

From previous work (Whinnett Z.I. 2006) it was shown that the signal to noise ratio of haemodynamic optimization, using our multiple transitions protocol, is higher at faster heart rates and as a result the

optimization process can be quicker. Therefore, in clinical practice, where time is limited, it may be advisable to carry out VV optimization by pressure at a faster heart rate, as this will reduce the time required to accurately optimize the VV delay (Pabari P.A. 2010).

### 6.5.7 Distribution of optimal VV delay

This study was primarily designed to compare the optimal VV delays identified by pressure (Finapres), flow (echocardiography) and ECG during a controlled environment i.e same individual, at the same heart rate and same posture of the individual. Optimization with all three modalities was performed within a period of 1-2 hours in order to minimize any changes is fluid volume status.

Although not designed to assess whether there may be a difference in the optimal VV delays between subgroups of patients, I attempted to investigate whether there was any difference between the ischaemic and non-ischaemic patients. The average optimal VV delay was 9 (SD 11) in the non-ischaemic and 10 (SD 27) in the ischaemic patients; therefore both subgroups requiring a small degree of LV preexcitation but this was not significantly different between the two ($p=0.85$). However, this observation is very unlikely to reflect the true distribution of VV optima in the two subgroups because the number of patients in each group was small and probably confounded by other variables. Only a much larger, prospective trial, designed for this purpose, will be able to answer the patterns of VV optima distribution in various subgroups.

### 6.5.8 Clinical implications

Using pressure, the only marker with internal validity in our study, all of our patients had a clearly identifiable optimum, frequently not the default device setting of synchronous excitation (VV 0ms), suggesting that optimization of the VV interval away from zero might potentially confer improved cardiac function, although this needs to be tested formally with a randomised, double blinded clinical trial. In the majority of patients (80%) the optimum had some amount of LV pre-excitation, consistent the theoretical concept of CRT mechanisms.

However, many of the optimum settings were close to VV 0ms. Optimization techniques vary in their ability to detect the optimum reliably as I have seen in this study and have reviewed with a generalizable framework previously (Pabari P.A. 2010). If a measurement modality is prone to beat-to-beat variability, its reliability can always be increased by simply taking the average of multiple replicates. However, the number of replicates required may be large, if there is a relatively large amount of such noise to be abated (Pabari P.A. 2010).

If there is insufficient time to conduct enough replicates to perform a reliable optimization, it is not wise to perform an unreliable optimization as this is worse than placebo (which has the saving grace of never truly causing harm). Unreliable optimization of the VV delay can easily shift patients away from default settings (which may not be far from their true optimum) to VV delays far away which could worsen cardiac function. This concern is sound grounds for a clinician to leave default VV settings unchanged until optimization methods with good reliability become available for clinical application.

It may take some courage to act in this way, against guidelines (Gorcsan J. 2008) and peer pressure. However, this study is scientific support and provides quantitative reasoning based on carefully conducted measurement. For example, if one's local clinical service uses LVOT VTI to optimize the VV delay, at the slow heart rate the scatter between repeated optimization using flow is 34ms. This means after one optimization, the next identical procedure will report an optimization with ±1.96x34, i.e ±67ms; in other words a range as wide as all the settings tested. Wisdom may prevail, preventing extreme values being selected, but if so, what is the net effect other than random selection amongst clinically-reasonable VV delays?

Finally, from a small number of patients in our study that underwent two optimizations a year apart, it appears that the optimal VV delay does not change with time, and that VV optimization in AF patients may not need to be performed frequently. However, fuller evaluation in a larger group, perhaps studied over longer time periods, is essential before drawing definite conclusions. All that can be said for certain is that only a standard deviation of difference between optimizations over time, that is wider than the

standard deviation of immediate optimization, is genuine evidence of change in the true optimum over time.

### 6.5.9 Study Limitations

This study was not designed to test the clinical benefit of VV optimization, nor to attempt to separate responders from non-responders. The only aim of this study was to evaluate the qualities of non-invasive candidate measures for VV optimization that are relevant to internal validity, and to do so in a cohort of patients in whom VV optimization is the dominant form of optimization of CRT lead timings, namely AF patients.

Although the study's measurements were performed in a teaching hospital by experienced clinical research staff, there may be centres with greater skills in, for example, echocardiography which might be able to achieve better performance from flow optimization than what I achieved. Superficially, that would appear to be the case from the fact that guidelines recommend flow optimization of the VV delay (Gorcsan J. 2008). Nevertheless, I note that the guidelines do not cite independent data on the 3 key principles of internal validity (singularity, reproducibility and plausibility) of flow optimization, or any comparison of these principles between flow and any other alternatives, and therefore it is possible that flow optimization was recommended only because there appeared to be no alternative.

Although ventricular ectopy was completely excluded from echocardiography images and from QRS measurements, it was not eliminated from the semi-automated analysis of pressure optimization. This may have adversely affected the precision of the pressure data. However, results in terms of singularity, reproducibility and plausibility, were still no worse for pressure than for flow and QRS. The real practical advantage of pressure over flow is that it could be monitored by automated systems without manual beat-by-beat calculation, and therefore it is fitting that pressure measurement was calculated in this in the same way that might happen in a real-world clinical system operating without beat-by-beat supervision.

Optimal VV delays were calculated using data taken with the patient lying down, and this may not necessarily reflect the optimal VV delay during other physiological states such as exercise. However, for

the purpose of genuine head-to-head comparison of several optimization methods I had to select a posture suitable to all modalities including echo, and which did not introduce unnecessary noise.

Finally, this is a study of AF only. Sinus rhythm may be different, not least because changes in the VV delay always change the AV delay on either the left or right side of the heart.

## 6.6 Conclusions

Programming a 0ms VV delay may currently be a rational day-to-day clinical strategy if one's environment does not have a means of optimization that provides, at the very least, singularity, reproducibility and plausibility.

Applying a method that does not have these characteristics may be, unintentionally, a random selection amongst settings. At best this could be useless. At worst, since the patients would be moving away from the vicinity of the optimum in which they begin by factory default (0ms), optimization might be on average somewhat harmful.

In our study, only pressure optimization satisfied all three criteria. Given the unsatisfactory performance of flow and QRS, I cannot recommend their use for VV optimization.

# 7 Increasing the heart rate shortens the programmed optimal AV delay, but enlarges the difference in the optimal AV delay between sensed and paced atrium

## 7.1 Abstract


**Introduction**

The effect of heart on the optimal AV delay during atrial sensing and atrial pacing is under-investigated in the CRT population; as is the effect of atrial pacing on optimal AV delay. In this study, I investigated these two effects and echocardiographically examined the mechanism of the sensed-paced difference in the optimal AV delay at two heart rates.

**Methods**

20 patients were haemodynamically optimised using non-invasive beat-to-beat systolic blood pressure at rest ($A_{sensed,rest}$), during exercise at 22±4 bpm above rest ($A_{sensed,ex}$) and at 3 atrially paced rates; ~5 ($A_{paced,r+5}$), 25 ($A_{paced,r+25}$) and 45 ($A_{paced,r+45}$) bpm above the resting sinus rate ($A_{sensed,rest}$).

Three echocardiographic parameters (septal and left lateral mitral ring TDI and mitral inflow VTI) were used to estimate changes in the timing of the left atrial contraction with increasing atrial rate and between sensed-paced atrium.

**Results**

During atrial sensing, the move from $A_{sensed,rest}$ to $A_{sensed,ex}$ decreased the optimal AV delay from 136 ± 6ms to 111± 5ms ($p<0.001$). During atrial pacing, higher heart rate also progressively shortened optimal AV delay; at $A_{paced,r+5}$ 212±6ms, $A_{paced,r+25}$ 196±5ms and at $A_{paced,r+45}$ 179±6ms ($p<0.001$ for all comparisons).

Atrial pacing prolonged the optimal AV delay by 76±6ms between $A_{sensed,rest}$ and $A_{paced,r+5}$ ($p<0.0001$) and by 85±7ms between $A_{sensed-ex}$ and $A_{paced,r+25}$ ($p<0.0001$); a difference of 9±4ms between the two rates ($p=0.017$).

Independent, blinded echocardiographic measurements showed prolongation in left atrial contraction between sensed and paced atrium was 58±3ms at rest and 68±3ms during exercise ($p=0.00002$). Left atrial contraction was shortened by 7±2ms ($p=0.001$) between rest $A_{sensed,rest}$ and $A_{sensed,ex}$, but was not significantly different between $A_{paced,r+5}$ and $A_{paced,r+25}$.

**Conclusions**

Higher heart rate leads to a shorter optimal AV delay. Earlier mechanical activation of the left atrium during exercise leads to a larger difference in the optimal AV delay between a sensed and paced atrium at higher heart rate.

## 7.2 Introduction

Left ventricular filling time (LVFT) is an important determinant of stroke volume. LFVT is critically short in patients with left bundle branch block (LBBB) and long PR intervals (i.e a very high proportion of cardiac resynchronization therapy, CRT, recipients). This marked reduction in LVFT is evident at resting heart rates (Mbassouroum M. 1992); as a result increasing the heart rate does not significantly worsen LFVT.

In patients with a long PR interval and a narrow QRS, the LFVT is better at resting rates. However, with increasing heart rate, the LFVT and consequently stroke volume drop significantly (Mbassouroum M. 1992).

Therefore, although resynchronization would improve the LVFT at rest, a long PR interval will be detrimental at higher heart rates (Mbassouroum M. 1992). This rate of fall in LVFT with increasing heart rate can be partially overcome by adjusting the PR interval (rate adaptive pacing). Although in theory the adjustment would be to shorten the AV delay, interestingly, a review (Bogaard M.D. 2010) of the very few studies available, has suggested that this is not universally true; in some patients the AV delay may need to be prolonged or left unchanged for best cardiac output.

Nevertheless, if AV is not adjusted as the heart rate increases, the fall of stroke volume and consequently fall in blood pressure become progressively larger (Whinnett Z.I. 2006, Whinnett Z.I. 2008, Whinnett Z.I. 2008, Whinnett Z.I. 2006).

At present, routine optimization of the AV delay is not universally performed (Gras D. 2009). Where it is done, it is generally reserved for non-responders of CRT and only carried out at rest. How the optimal AV delay changes with increasing heart rate has not been explored in detail, and is therefore not sufficiently understood how rate adaptive pacing pacing should be programmed in the CRT population (Bogaard M.D. 2010). This is of particular clinical importance since at elevated heart rates (by exercise or atrial pacing) patients may receive additional benefit from a rate adaptive optimal AV delay.

Physiologically, the optimal AV delay is the one which allows for maximal contribution of the atria to ventricular filling and therefore maximal stroke volume (Ng K.S. 1989). At elevated heart rate, the intrinsic AV conduction shortens to allow for earlier ventricular contraction and consequently increased time for passive (E wave) and active (A wave) ventricular filling; a result of maximal separation of the E and A waves (Figure 7-1).

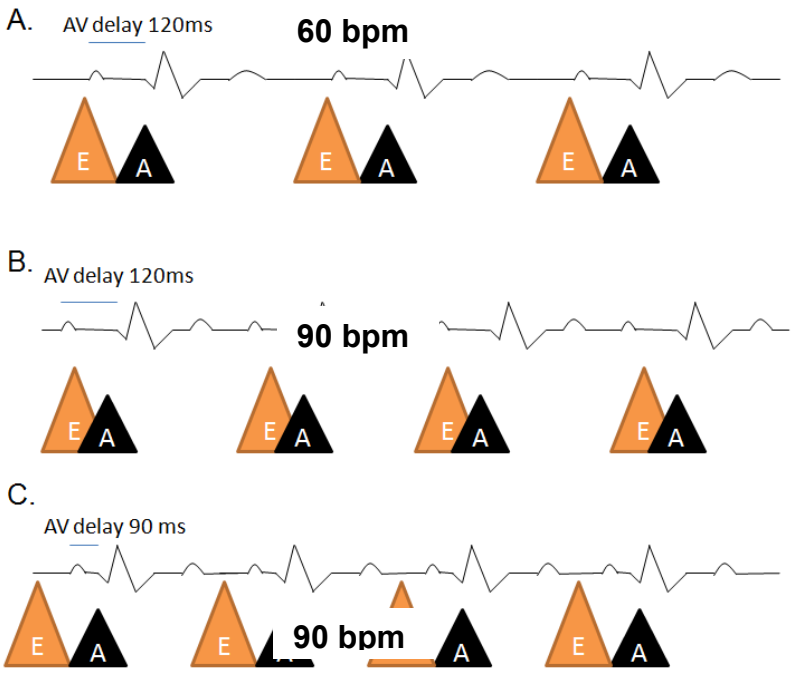


**Figure 7-1. A conceptualized diagram of the inter-relationship between the echocardiographic trans-mitral Doppler inflow pattern and heart rate**

A, when the AV delay is optimal at slow heart rate, E and A waves are fully separated and contribute maximally to ventricular filling. B, Hypothetical LV filling pattern if AV delay remains fixed (at the optimal AV delay of slow heart rate) during elevated heart rate. The AV delay is now too long, resulting in delayed ventricular contraction and consequently delayed onset of the (pressure dependent) E wave. This causes E/A fusion and resultant diminished ventricular filling. C, By shortening the AV delay with increased heart rate, ventricular contraction and thus the E wave occur earlier in the cardiac cycle. This maintains E/A separation and optimal ventricular filling.

Prior studies have suggested that the intrinsic AV conduction shortens linearly with increased heart rate (4 - 21 ms/ 10 bpm) in healthy subjects in order to maintain optimal haemodynamics (Daubert C. 1986, Barbieri D. 1990). If such behaviour has evolutionary advantage in health, then it is possible that

replicating it in disease might also have value in heart failure even if the disease process typically impairs the natural processes in these patients.

Modern CRT devices do provide a 'rate-adaptive' AV delay function, and all major manufacturers have provided guidelines as to how the programmed AV delay should shorten with increased rate. However, manufacturers' recommendations, vary, and rather widely, perhaps because they are based on data in different states of health and disease – or not based on data at all. In addition, for the same heart rate CRT devices recommend a different AV delay depending on whether the atrium is sensed or paced. In general if the atrium is paced then the AV delay is prolonged by 30-40ms. This is to compensate for intra and inter atrial delays caused by atrial pacing.

At first sight, the conflict (Scharf C. 2005, Valzania C. 2008, Melzer C. 2008, Tse H.F. 2005, Grimm R.A. 2009) between studies examining the relationship of heart rate and optimal AV delay in CRT may seem surprising. At elevated heart rate, the optimal AV delay has been seen to increase, stay the same, and decrease both during exercise (Mokrani B. 2009) and with atrial pacing (Whinnett Z.I. 2008).

It is likely that several limitations in these studies' designs have masked the anticipated response of shorter optimal AV delays with elevated heart rate. Change in measured AV delay optimum from one state to another is only meaningful if AV delay optimum has close test-retest reproducibility, otherwise the value in the second state may be different simply through chance alone rather than because of a genuine change in optimum. Test-retest reproducibility (i.e. from independent data) is a prerequisite before designing a study of the effects of an intervention on the optimum AV delay.

Previous studies have used a wide range of cardiac response markers during AV optimization. However, many of these markers suffer from poor reproducibility, preventing precise identification of an optimal AV delay.

In one study (Mokrani B. 2009), for example, use of echocardiographic measurements of left ventricular outflow tract velocity time integral and left ventricular filling time yielded different optimal AV delays, in the same patient at rest.

A second way to confirm that changes in AV delay optimum are genuine and not noise is to see dose dependency from the intervention. For example, if by increasing the heart rate by 10 bpm, for example, the optimal AV delay shortens, then, if the optimization process is reproducible, a further increase (by 10bpm) in heart rate would result into a further reduction in optimal AV delay i.e consistency of direction. Consistency of direction should be observed if the optimization is reproducible.

Random variation caused by unreproducibility of the optimization process may create what appears to be individualised direction of change in response to an intervention, but it will not be able to show consistency of direction of two doses (i.e two increases in heart rate) of intervention.

Several prior studies have simply compared one increased heart rate with the resting rate. Therefore this may be insufficient to permit accurate characterisation of the intra-individual trend of optimal AV delay with increased heart rate. Moreover, had they tested two or more increased heart rates then the reproducibility of the optimization process would have been revealed by examining the consistency of direction and also it would have been scientifically a more robust methodological approach to examine the intra-individual trend of the optimal AV delay with increasing heart rate.

Finally, a third way of assessing a genuine change from an intervention, in this case a change in optimal AV delay as a result of change in heart rate or because of atrial pacing, is to evaluate its concordance with the independent assessment of the mechanism underlying the change. For example, assess whether any difference in the optimal AV delay between sensed and paced atrium is concordant with the change in the intra/interatrial delays caused by atrial pacing.

In this study, I used methods with good reproducibility and systematically set out to assess dose dependency (by testing more than two pacing states). I investigated separately the influence of increased heart rate and atrial pacing on optimal AV delay.

I hypothesized that with increasing heart rate the optimal AV delay will tend to shorten and that the optimal AV delay will be different between a sensed and paced atrium at the same heart rate, and that this difference may change with increasing heart rate.

## 7.3 Methods

### 7.3.1 Subjects

Twenty patients (13 male), with an age of 65 ± 8.7 years, were enrolled into this study. Subjects were recruited from a heart failure outpatient clinic. Inclusion criteria dictated that all patients had a biventricular pacemaker or biventricular defibrillator in line with current guidelines (NYHA III-IV despite maximal medical therapy and QRS>120 ms). Exclusion criteria included the absence of sinus rhythm and the inability to exercise on a supine bicycle. Aetiology of heart failure was ischaemic in seven, dilated cardiomyopathy in twelve and hypertension in one.

### 7.3.2 Study design

Haemodynamic optimization of the AV delay was carried out in 5 states. Two states used atrial sensing mode and three rates used atrial pacing:

1. Atrial-sensing, resting sinus rate; $A_{sensed,rest}$
2. Atrial-sensing, at 22±4bpm above resting sinus rate; $A_{sensed,ex}$
3. Atrial-pacing at ~ 5 bpm above resting sinus rate; $A_{paced,r+5}$
4. Atrial-pacing at 20 bpm above $A_{paced,r+5}$; $A_{paced,r+45}$
5. Atrial-pacing at 40 bpm above $A_{paced,r+5}$; $A_{paced,r+45}$

Elevation of heart rate during exercise was achieved using a supine bicycle (Medical Positioning Inc, Kansas City, MO, USA). To ensure continuous atrial-sensed operation during exercise, the lower rate pacing limit was set to below the resting rate.

Patients were positioned supine during all five haemodynamic optimizations.

### 7.3.3 Haemodynamic optimization protocol

Changes in systolic blood pressure were measured on a beat-to-beat basis by a Finometer (Finapres Medical Systems, Amsterdam, Holland) (Peňàs J. 1973, Wesseling K.H. 1995, Smith N.T. 1985, van Egmond J. 1985, Petersen M.E. 1995, Jellema W.T. 1996, Imholz B.P. 1998) using an algorithm of repeated alternations from a reference AV delay of 120 ms and a tested AV delay. A range of AV delays were tested in a random order: 40, 80, 160, 200, 240, 280, 320 ms, up to but excluding the AV delay at which atrio-ventricular conduction became solely intrinsic.

Changes in SBP (SBPrel) was calculated by subtracting the mean SBP of the beats in one respiratory cycle immediately following an AV delay transition from the mean SBP of the beats in one respiratory cycle immediately preceding the AV delay transition. I deliberately aimed for high reproducibility of optimization by performing at least 12 alternations, each of two respiratory cycles in duration (therefore a total of 24 replicates of data), for each AV delay tested at each heart rate. The reproducibility of this algorithm using SBP has been studied extensively by Whinnett et al (Whinnett Z.I. 2006, Whinnett Z.I. 2011, Whinnett Z.I. 2008).

It has been shown that the haemodynamic effects of changing AV delay progressively are curvilinear and fit a parabola. I therefore used parabolic interpolation to determine the optimal AV delay at each heart rate (Whinnett Z.I. 2006).

An ECG signal was recorded using Hewlett-Packard 78351A monitor. Analogue signals were taken via a National instruments DAQ-Card AI-16E-4 (National Instruments, Austin, TX) and Labview (National Instruments, Austin, TX). Results were analysed off line with custom software based on the Matlab platform (MathWorks, Natick, MA).

### 7.3.4 Echocardiographic estimation of change in left atrial contraction timing

I measured the time of the left atrial contraction from the onset of QRS (the most reliably identifiable reference time point) during both atrial-sensed and atrial-paced measurements, at both rest and during

exercise. For consistent identification of atrial contraction I used the peak of the 'A' wave on tissue Doppler, Figure 7-2, (at both the septal and lateral points of the AV ring) and also to the peak of the A wave on flow Doppler across the mitral valve. For valid comparisons, the AV delay was maintained at the same value during both atrial-sensed and atrial-paced measurements, at both rest and during exercise.

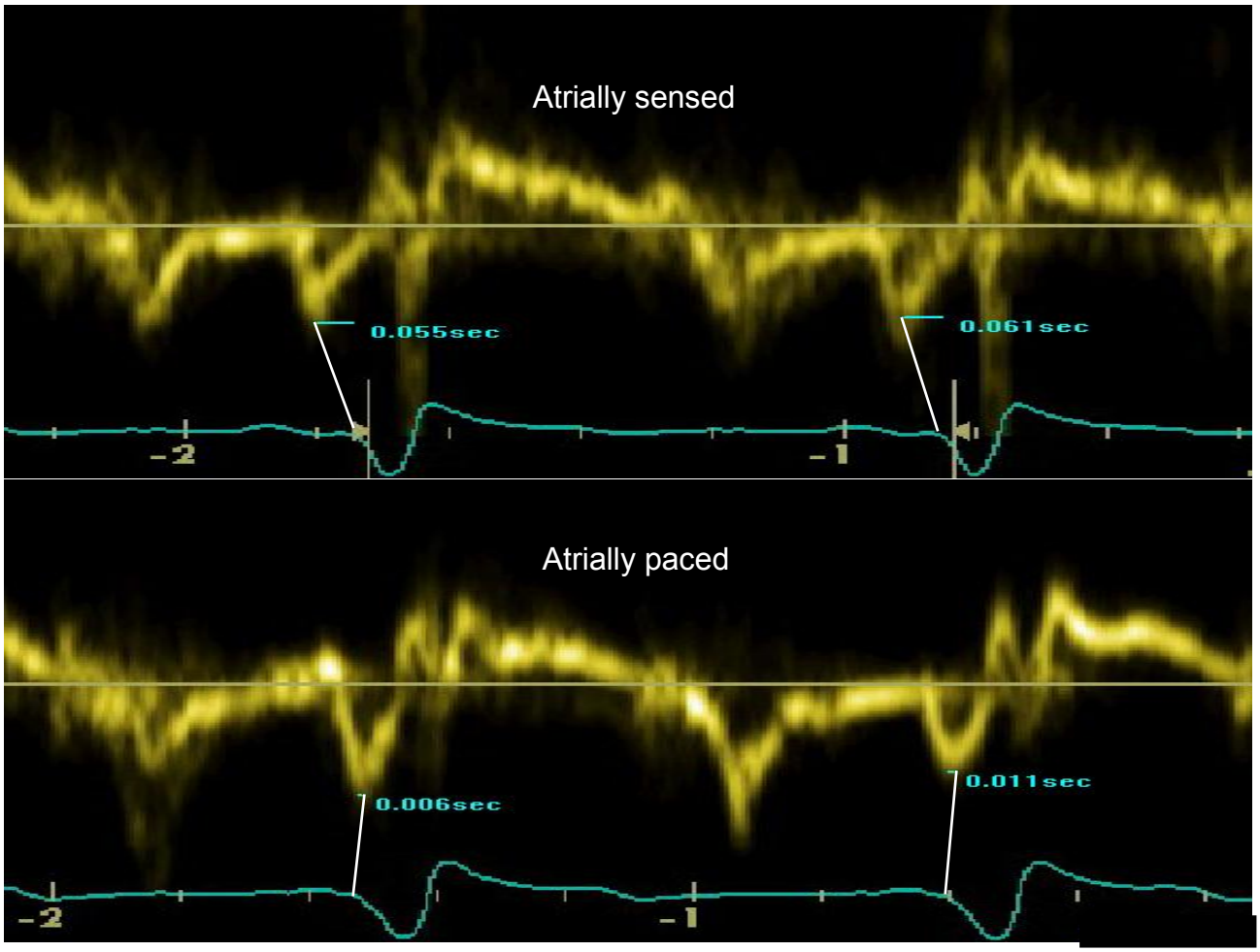


**Figure 7-2. Example measurement of change in the time of left atrial contraction when changing from a sensed to a paced atrium**

Tissue Doppler imaging across the septal wall of the AV annulus, during sensed and paced atrial modes of biventricular pacing. The same AV delay was programmed for both modes. The time of contraction of the left atrium (peak of A') was measured from a fixed time point (the onset of the QRS) in order to allow precise mesurements of alterations in the time of left atrial contraction as a result of pacing changes. In this example the A' wave can be seen to be shifted to the right when atrially paced and this change denotes delay of left atrial contraction during atrial pacing.

This approach provided three independent echocardiographic measurements of the time of left atrial contraction.

Change in the time of left atrial contraction between atrial-sensed and atrial-paced states at the same heart rate (the 'sensed-paced difference') is a result of the sum of atrial sensing delay, atrial pacing delay and inter/intra-atrial conduction times.

Change in the time of left atrial contraction between atrial-sensed or atrial-paced states, at different heart rates, is a result of primarily changes in the interatrial conduction times (IACT).

Ten consecutive beats from the four-chamber view were acquired, for each of the 3 echocardiographic measurements, at four pacing states ($A_{sensed,rest}$, $A_{sensed,ex}$, $A_{paced,r+5}$, $A_{paced,r+25}$). All traces were recorded from the supine position including those taken during exercise on the supine bicycle.

Images were acquired using a Vivid I system (GE Healthcare, Waukesha, Wisconsin, USA) and offline analysis was carried out using Medcon software (McKesson, San Francisco, USA).

Using Doppler echocardiography for estimating changes in IACT has been used and validated against an invasive electrogram-based study (Cozma D. 2003).

### 7.3.5 Statistical Analysis

Paired comparisons of Normally-distributed continuous variables were made using Student's paired *t* test, and one-way ANOVA where appropriate. A p-value of $<0.05$ was taken as statistically significant. Statview 5.0 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

## 7.4 Results

### 7.4.1 The effect of increase in heart rate on optimal AV delay

The optimal AV delay shortened from rest to exercise, Figure 7-3A. Across all patients the optimal AV delay was 136 ± 6ms at rest ($A_{sensed,rest}$) and 111± 5ms during exercise ($A_{sensed,ex}$), $p<0.001$.

Pacing the atria at incremental rates, progressively shortened the optimal AV delay (Figure 7-3B): $A_{paced,r+5}$ 212 ± 6ms, $A_{paced,r+25}$ 196 ± 5ms ($p<0.001$ versus $A_{paced,r+5}$) and $A_{paced,r+45}$ 179 ± 6ms ($p=0.0001$, versus $A_{paced,r+25}$).

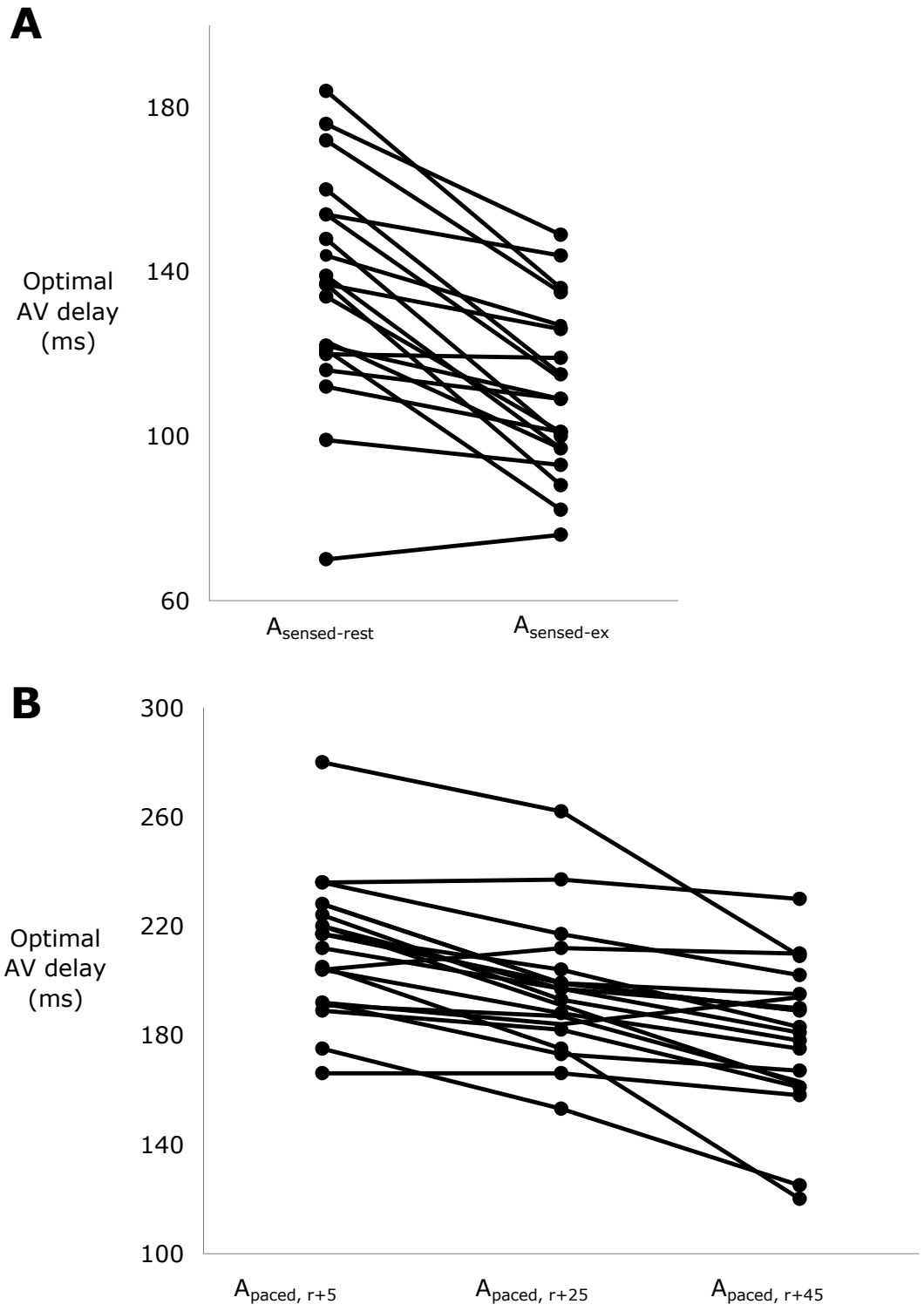


**Figure 7-3. Individual patient data showing the effect of increased heat rate on the optimal AV delay.**

A; during exercise to 20bpm above the resting rate there is a significant decrease in the haemodynamic optimal AV delay. B; pacing the atria to 20 ($A_{paced,r+25}$) and 40 ($A_{paced,r+45}$) beats above $A_{paced,r+5}$, results in progressive shortening of the haemodynamic optimal AV delay.

During atrial pacing, the relative proportion of the RR interval that was occupied by the optimal AV delay increased with elevation of heart rate: 23.5±0.8% at $A_{paced,r+5}$, 28.3±0.9% at $A_{paced,r+25}$ and 31.7±1% at $A_{paced,r+45}$ ($p<0.00001$, for all comparisons), (Figure 7-4).

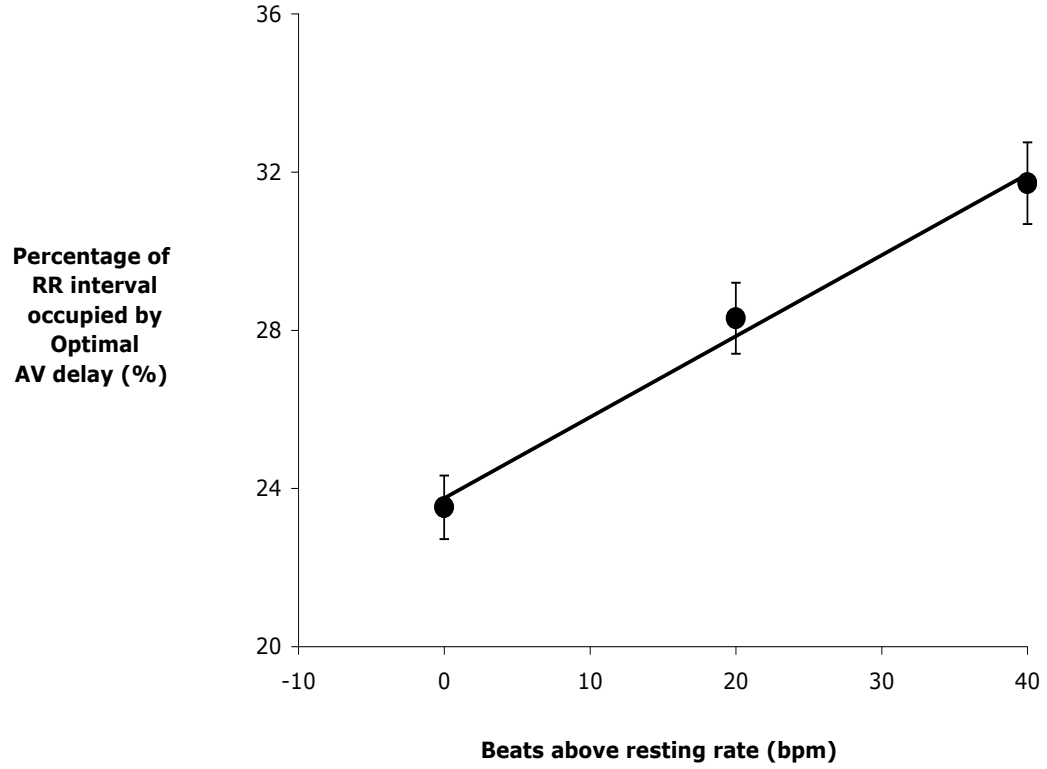


**Figure 7-4. The effect of pacing the atria at incremental heart rates on the percentage of RR interval (cycle length) occupied by the optimal AV delay**

With 20bpm increments in paced atrial rate the optimal AV/RR ratio increases linearly, $r=0.997$, $p<0.05$.

### 7.4.2 Sensed-paced difference in electrical AV delay that must be programmed to maintain optimal haemodynamics

In all patients, the optimal AV delay required to be programmed during atrial pacing was significantly longer than during atrial sensing, at the equivalent heart rate, as is shown in Figure 7-5.

At $A_{sensed,rest}$ the optimal AV delay was 136 ± 6ms versus 212 ± 6ms ($p<0.0001$) at $A_{paced,r+5}$. During $A_{sensed,ex}$ the optimal AV delay was 111± 5ms versus 196 ± 5ms ($p<0.0001$) at $A_{paced,r+25}$.

The difference between sensed and paced haemodynamic optimal AV delays, was slightly, but statistically significantly greater at the higher heart rate; 76±6ms versus 85±7ms, p=0.017, (Figure 7-5).

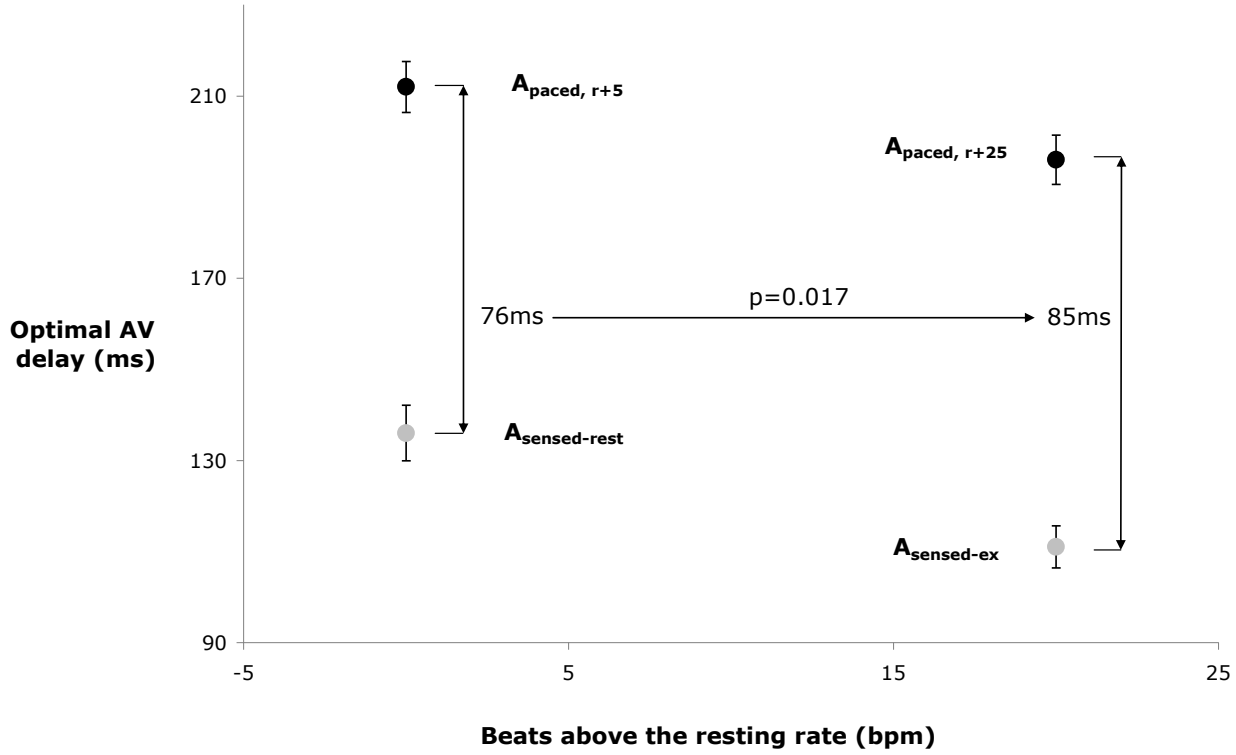


**Figure 7-5. The effect of atrial pacing on haemodynamic optimal AV delay**

Atrial-pacing increases the haemodynamic optimal AV delay at rest and at 20bpm above the resting rate by 76ms and 85ms respectively. The difference between these two increases is statistically significant (p=0.017).

### 7.4.3 Mechanical basis for the dynamic sensed-paced electrical difference of the optimal AV delay

**Timing of Left atrial contraction.** Left atrial contraction was delayed when the atria were paced instead of sensed. This delay was detected by all 3 echocardiographic markers used in this study, at both heart rates. For example, using septal TDI, at rest the delay in left atrial contraction was 63±5ms and at 20bpm this delay between sensed-paced atrium was larger at 73±5ms, $p<0.01$ (Table 7-1).

**Table 7-1 The delay of left atrial contraction due to atrial pacing using three echocardiographic parameters at rest and at 20bpm increment.**

Note that as well as the increment in sensed-paced delay between heart rates being statisitically significant for each echo parameter, the increment is approximately the same for all three parameters even though they were measured independently from separately acquired data. This suggests that the change in s-p delay between heart rates is real rather than an artefact of noise. (ANOVA was used for the difference in behaviour between different echocardiographic parameters).

| Echo parameter | Sensed-paced delay in left atrial contraction at rest (ms) | Sensed-paced delay in left atrial contraction at rest +20 bpm (ms) | P-value |
|---|---|---|---|
| Septal TDI | 63 ± 5.4 | 73 ± 5.4 | <0.01 |
| Lateral TDI | 56 ± 6.0 | 67 ± 4.8 | <0.05 |
| Transmitral | 56 ± 5.1 | 64 ± 5.1 | <0.05 |
| ANOVA | p=0.61 | p=0.48 | |

Increasing heart rate by atrial pacing from $A_{paced,r+5}$ to $A_{paced,r+25}$ did not significantly change the timing of left atrial contraction. However, a rise of heart rate by exercise, $A_{sensed,ex}$, caused an earlier left atrial contraction compared to $A_{sensed,rest}$; by 7±2ms (p=0.001).

**Contraction *within* the left atrium**. The septal-to-lateral delay in left atrial contraction remained unchanged regardless of heart rate; $A_{sensed,rest}$ versus $A_{sensed,ex}$ (19±5ms versus 21±5ms, respectively, p=0.7), and $A_{paced,r+5}$versus $A_{paced,r+25}$ (12±7ms versus 15±6ms, respectively, p=0.3).

The septal-to-lateral delay remained unchanged between sensed-paced atrium; $A_{sensed,rest}$ versus $A_{paced,r+5}$ (p=0.17) and $A_{sensed,ex}$ versus $A_{paced,r+25}$ (p=0.16).

### 7.4.4 Reliance on echocardiographic parameters

I compared the noise of the three echocardiographic parameters for measuring changes in the timing of the left atrial contraction, by comparing their standard errors of the mean of the measurements at $A_{sensed,rest}$ and $A_{paced,r+5}$ modes. Analysis of variance demonstrated no superiority of any of the echo

parameters: septal TDI 2.7ms, lateral TDI 2.64ms and mitral valve flow 2.72ms at $A_{sensed,rest}$ (F=0.02, p=0.98); septal TDI 2.6ms, lateral TDI 3.0ms and mitral valve flow 2.8ms at $A_{paced,r+5}$ (F=0.38, p=0.69).

## 7.5 Discussion

In this study I found that the optimal AV delay shortens with increasing heart rate, regardless of whether the heart rate is increased by exercise or atrial pacing.

To achieve optimal haemodynamics the programmed AV delay must be programmed longer with atrial pacing than with atrial sensing, at the same heart rate. Independent investigation with Doppler echocardiography showed that a delay in the left atrial contraction from sensed to paced atrium may be the cause for the prolongation of the programming, in relation to the pacemaker's atrial fiducial time point. Measurement of the mechanism of this discrepancy by echocardiography was found to be concordant across three independent Doppler measures.

Finally, I found that this sensed-paced discrepancy in optimal AV delay is dynamic and enlarges at higher heart rates. This is explained by an earlier left atrial contraction during exercise compared against rest, coupled with no change in the time of left atrial contraction during atrial pacing with increasing heart rate.

### 7.5.1 Effect of heart rate on optimal AV delay

In our study I found that elevation of heart rate results in shortening of the optimal AV delay. To our knowledge, no other study has explored the change in optimal AV delay of biventricular pacing at three heart rates in 20bpm increments. I have shown that the optimal AV delay shortens by on average 6.5ms per 10bpm of increase in heart rate. This slope is concordant with the current devices' algorithms (based on bradypacing algorithms) which use slopes ranging from 5 to 10ms reduction in AV delay per 10bpm increase in heart rate.

In this study I showed a positive correlation between an increase in heart rate and the proportion of the RR interval occupied by optimal AV delay. With increasing heart rate, the optimal AV delay occupied a bigger proportion of the cardiac cycle (Figure 7-4). In other words, although the optimal AV delay does shorten with increasing heart rate, it shortens by a less proportion than the shortening of the RR interval.

This observation supports the importance of maintaining maximum possible ventricular filling at higher heart rates.

It appears that the duration of atrial contraction in diastole becomes more important than at slower heart rates. At slow heart rates most of the filling occurs by passive movement (transmitral E wave). As rate increases the E and A transmitral filling waves begin to merge, the extent of which is prevented by the shortening of the AV delay. However, too much shortening would eventually cause truncation of the A wave and reduction in filling. Therefore a balance between merging and truncation has to be achieved to allow maximal filling. I found that by looking at the AV optimum/RR ratio gives an insight to this balance.

This finding may be used clinically. By identifying the optimal AV delay at just one heart rate, the optimal AV delay can be predicted at all other heart rates (Figure 4). This may offer a reliable and time efficient method to determine a haemodynamic optimal AV delay at rest, from faster atrial-paced rates where haemodynamic optimization is more precise (Whinnett Z.I. 2008).

Rate adaptive AV delay is widely used in dual chamber pacing, where it has been shown to improve exercise tolerance and haemodynamic markers (Ritter P. 1989, Khairy P. 2001). Our results, which show a similar shortening of AV delay with increasing heart rates, suggest that it may be reasonable to extrapolate the benefits of rate adaptation of AV delay to the CRT population.

A study has shown that use of a combination of the rate-response and rate-adaptive functions improves peak exercise HR, exercise time, METs and VO2max in chronotropically incompetent patients with CRT devices (Tse H.F. 2005). It was suggested, however, that the rate-adaptive AV delay function did not add further benefit over the rate-response function. However, further studies are required to assess the short-to-medium term benefits on haemodynamics and functional capacity of the rate-adaptive AV delay function in DDDR pacing mode.

### 7.5.2 The effect of heart rate on the start of left atrial contraction

In this study I found that elevating heart rate by exercise caused an earlier left atrial contraction i.e shorter interatrial contraction time (IACT). However, elevation of heart rate using atrial-pacing had no such effect.

Intracardiac electrogram studies in patients with dual chamber pacemakers have shown that increases in heart rate have no influence on IACT in both atrially paced (Ausubel K. 1986), and atrially sensed modes' (Camous J.P. 1993, Ismer B. 1996).

There are very few reports on the effect of exercise on IACT in CRT patients; one invasive study found no significant effect. The most likely explanation for the shortening of IACT with exercise in our study, would be that sympathetic activation reduces inter-atrial conduction and/or atrial electromechanical coupling; however I am not able to distinguish which one of these two parameters shortened due to the fact that our assessment of changes in IACT incorporated both of these timings.

However, our measure of incorporating both changes in interatrial conduction and electromechanical coupling times may be more representative of the haemodynamic effects of increasing heart rate on ventricular filling and therefore its effect on optimal AV delay.

The absence of sympathetic discharge during atrial-paced elevation of heart rate could explain the lack of an effect on IACT. An invasive study of IACT in CRT patients has also shown no effect of incremental atrial-pacing on IACT, consistent with our findings (Levin V. 2011).

### 7.5.3 The effect of atrial pacing on the start of left atrial contraction

A consistent large increase on the start of the left atrial contraction was observed when the atria were paced as opposed to sensed, at the same rate. This discrepancy became larger with increasing heart rate.

Delayed onset of left atrial contraction due to atrial-pacing may be explained by 3 main factors. Firstly, there is a pause between the delivery of the pacing stimulus to the onset of right atrial capture – this delay is termed the 'atrial pacing latency'. Secondly, right intra-trial depolarisation time may increase due to

initiation of depolarisation outside the specialised fast atrial conduction pathways; both of the 2 factors contribute to a delayed depolarisation wave reaching the interatrial connection bundles (such as the Bachmann bundle).

Thirdly, during atrial-sensed mode, the CRT device only detects the intrinsic atrial depolarisation when it has propagated from the sino-atrial node to the right atrial pacing electrode. This 'atrial sensing latency' results in a longer actual right sided AV delay, than the programmed one. The inter-relationship of these three factors is shown in Figure 7-6.

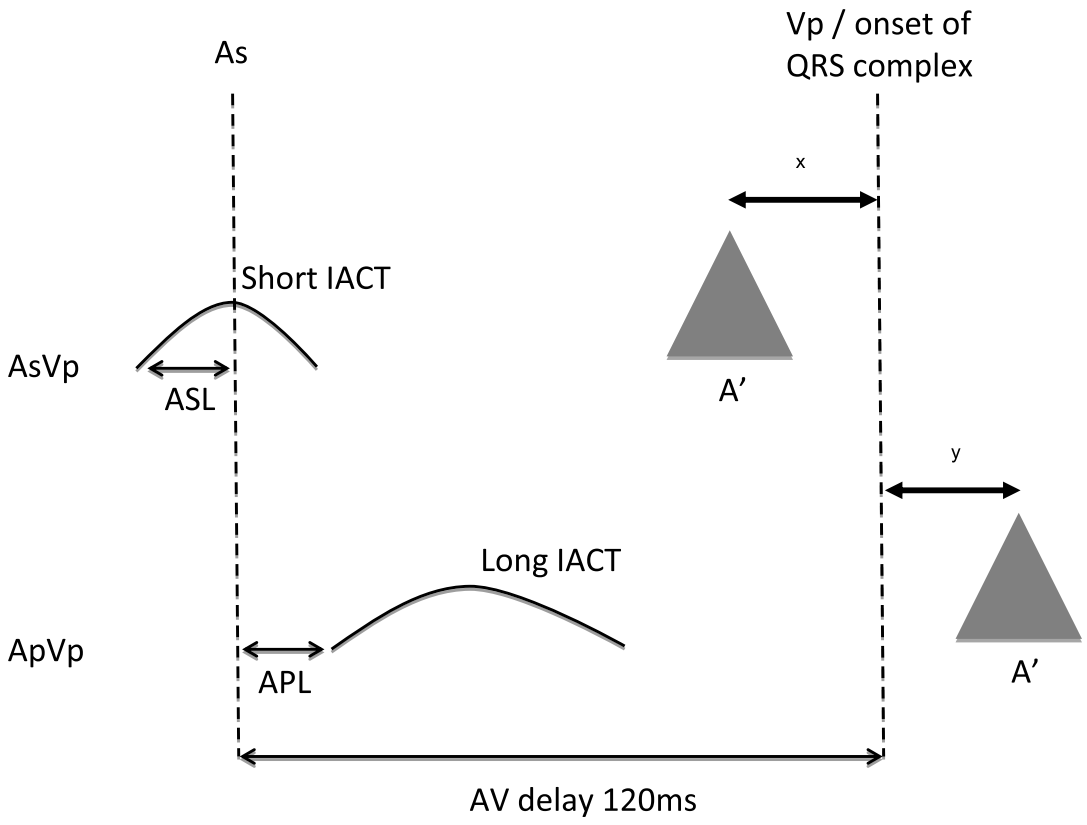


**Figure 7-6. Schematic explanation of the increase in IACT causing an increase in optimal AV delay with atrial pacing**

When right atrial pacing is introduced the left atrial contraction (A') is delayed due to atrial pacing latency (APL) and prolonged intra/interatrial conduction. The change in the timing of the left atrial contraction (A') from a sensed to a paced right atrium, is the sum of atrial sensing latency (ASL), APL and IACT.

Several invasive studies have demonstrated this relationship in dual chamber pacemakers (Ausubel K. 1986, Camous J.P. 1993) and in CRT devices (Levin V. 2011) whereby the IACT increases dramatically with atrial-pacing.

Although I did not measure IACT directly, I have demonstrated that the delay (55-65ms) in the onset of the left atrial contraction is similar to the measurement of the increase in IACT with atrial-pacing by other studies; (36ms (Levin V. 2011) and 50ms (Camous J.P. 1993)).

The prolongation in the onset of the left atrial contraction time with atrial-pacing was highly variable across patients (21-98ms). This may be explained by the relative position of the right atrial pacing wire to the right intra-atrial and interatrial conduction pathways.

### 7.5.4 The effect of atrial-pacing on optimal AV delay

The programmable AV delay in CRT devices represents the electrical AV delay, however it is the mechanical coupling of the left atrium and ventricle that determines acutely systemic haemodynamics (Wish M. 1987, Chirife R. 2003, Cha Y.M. 2002, Janosik D.L. 1989). In theory, introducing a delay in the onset of left atrial contraction by atrial pacing, a compensatory increase in the programmable electrical AV should be applied to ensure unchanged mechanical atrioventricular interaction.

In this study I found that pacing the atria significantly increased the optimal electrical AV delay. The majority of the increase in haemodynamically optimal electrical AV delay was explained by the delay in the left atrial contraction time; there was a fixed difference of 10-20ms between the two times.

Several studies have reported the dependence of optimal AV delay on IACT in dual chamber pacemakers (Wish M. 1987, Melzer C. 2007). Invasive experiments by Levin et al (Levin V. 2011) reported a high correlation between paced and sensed IACT and the corresponding optimal AV delays in CRT devices.

In this study, I did not measure IACT, however I was able to estimate, using echocardiography, change in the left atrial contraction time from atrial sensed to paced modes, which accounted for most of the change in the  in haemodynamic optimal electrical AV delay.

### 7.5.5 Left intra-atrial conduction delay

By comparing the time of atrial activation at the septal and lateral mitral valve annulus with tissue Doppler imaging I found that left intra-atrial conduction time is not significantly altered by either an increase in heart rate (regardless of how this is achieved), or by changing from atrial-sensed to paced modes. This is of value as it confirms previous findings in the bradypacing population (Ausubel K. 1986) that conduction within the left atrium does not contribute to changes in the optimal AV delay.

### 7.5.6 Study limitations

Ideally, to permit full comparison between sensed and paced elevation of heart rate, I would also have exercised the subjects to 40 beats above their resting rate. This would have allowed intra-individual trends to be established for both atrial overdrive pacing and dynamic exercise. However, many patients struggled to maintain a target of at least 20bpm above the resting rate – suggesting a further goal of 40bpm above the resting rate would be unrealistic. Additionally, this issue is exacerbated by the fact that chronotropic incompetence is particularly prevalent (estimated 21%) in this population (Maass A.H. 2009).

Finometry uses peripheral pressures as a surrogate measure for cardiac output. Therefore patient specific factors affecting the peripheral vasculature may affect the results. However, the finometer cuff was placed in the same position in each patient, throughout the full protocol, therefore any systematic error would be constant. Since I was simply observing the relative changes in SBP between different AV delay states and a reference AV delay, the effect of this issue was minimized. Additionally, this non-invasive technique of blood pressure monitoring is not subject to many of the errors in data acquisition using echocardiography, such as inconsistencies in position and angle of the ultrasound probe when measuring LVOT-VTI and operator variability during data analysis.

Subjects were positioned supine for all aspects of the protocol, even whilst performing dynamic exercise, so that any positional effects on haemodynamics were minimised. This was also advantageous as echocardiography could be carried out whilst the patient was exercising. However, it could be argued that

real-life exercise occurs mainly in an upright position and therefore our measurements of haemodynamic changes with reprogramming of the AV delay may not accurately reflect those encountered with day-to-day exercise.

Most of the subjects in this study were within the NYHA II classification. This reflects the requirement for patients to be able to perform sufficient exercise to raise the heart rate by a minimum of 20bpm for the time required for optimization (approximately 5 minutes). Therefore, this could be regarded as a form of selection bias, and further study would be required to ensure that our results are representative of the full spectrum of CRT patients.

## 7.6 Conclusion

The optimal AV delay of CRT devices shortens with elevation of heart rate. At the same heart rate the optimal AV delay lengthens when atrially paced. The sensed-paced difference is a result of the delay in the left atrial contraction, and this difference increases at higher heart rates, primarily due to earlier atrial contraction during exercise.

# 8 Synthesis

This thesis has challenged the several beliefs of optimization of biventricular pacing by using carefully designed experiments in prospectively recruited patients under strict scientific conditions.

Optimization of the AV and VV delay of cardiac resynchronization therapy can be achieved using non-invasive haemodynamic technologies. For these technologies to be used appropriately, optimization protocols should be designed to provide an efficient optimization process which reduces noise and therefore maximises the signal to noise ratio which can in turn identify, as reproducibly as possible the optimal AV and VV delays.

Only achievement of this would allow exploration of the effects of optimization and the identification of the underlying physiological mechanisms which are dominant in defining the optimal AV and VV delay at different pacing states.

Therefore aim of this thesis was to use an efficient optimization protocol with good reproducibility of the optimal AV/VV delay (as described in the Methods section – Chapter 2) that would allow:

- Investigation of the cardiac mechanoenergetic effects of biventricular pacing at a nominal AV delay and of AV optimization during acute biventricular pacing (Chapter 3)
- Evaluation of coronary physiology during acute biventricular pacing (Chapter 4); a severely underexplored area of cardiac resynchronization therapy
- Head-to-head comparison of the reproducibility and potential clinical applicability of two non-invasive haemodynamic technologies (Finapres and Simple photoplethysmography) with distinctly different modes of measuring haemodynamic changes (Chapter 5)
- Evaluation of the internal validity (singularity, reproducibility and biological plausibility) of three commonly used modalities (flow using ECHO, electrical using QRS width, and pressure using Finapres technology) for optimization of VV delay (Chapter 6)

- Investigation of the underlying physiological mechanisms (using Doppler Echocardiography) for the differential optimal AV delays during atrially sensed and atrially paced modes, and the effect of heart rate on the optimal AV delay (Chapter 7)

## 8.1 Biventricular pacing generates more cardiac work but at the cost of more oxygen consumption; nevertheless it is good value

My invasive study showed that the LV pressure developed and stroke volume generated, and consequently the cardiac work, increases when biventricularly paced at the nominal AV delay of 120ms. Cardiac work further increased, significantly, at the haemodynamic optimal AV delay. The optimal AV delay was determined using non-invasive haemodynamic optimization (by Finapres) prior to any invasive haemodynamic measurements. In addition, setting the AV delay to a very short (40 ms) delay, and despite ventricular resynchronization, did not generate a statistically significant change in cardiac work compared against LBBB.

I found that there was an increase in the myocardial oxygen consumption with biventricular pacing but this was proportionally less than the increase in external cardiac work, which signifies improved mechanoenergetic efficiency. The improved efficiency during biventricular pacing was ~80% higher than LBBB.

The optimal AV delay had the same mechanoenergetic efficiency as the nominal AV of 120 ms but generated a one-third higher external cardiac work.

This means that haemodynamic optimization of biventricular pacing not only does not appear to affect the mechanoenergetic efficiency improvement, when paced from a dyssynchronous ventricle to a nominal AV delay (120ms), but it also increases the useful work done by the heart.

The long term significance of this acute study's finding may be tested in the future in an appropriately designed clinical endpoint trial. The real challenge, however, of designing such a clinical trial would be the very large sample size that would be required for recruitment to satisfy adequate power. Instead, it

may just be simpler to accept that external cardiac work maximization from the optimal AV delay is beneficial (and not harmful) to the patient and therefore justify optimizing in all patients.

## 8.2 Evaluation of coronary physiology during acute biventricular pacing

I was able to show that coronary physiology improved when left ventricular contractility was enhanced by biventricular pacing, compared against LBBB. I applied wave intensity analysis to quantify the left coronary waves. These waves can explain the mechanism of flow within the coronary artery throughout the cardiac cycle.

The coronary flow was higher at the optimal AV delay and AV 120 ms, when compared against the LBBB. The left ventricular $dP/dt_{max}$ and $_{neg}dP/dt_{max}$ were increased at these two AV delays. Wave intensity analysis demonstrated that the diastolic backward decompression wave (suction) wave which is responsible for diastolic coronary blood flow was enhanced with biventricular pacing at AV delays which produced a better contractility than LBBB; this suction wave correlated well with the temporally corresponding $_{neg}dP/dt_{max}$. There were also enhancements of the systolic forward and backward compression waves, and these correlated well with LV $dP/dt_{max}$.

Interestingly, biventricular pacing at AV 40 ms did not improve LV contractility and there was no difference in coronary flow or wave intensity against LBBB.

This means that in the case of biventricular pacing both resynchronization (synchronous contraction of ventricular walls) and AV delay (left ventricular filling) affect left ventricular contractility, and therefore both contribute to the observed improved coronary physiology.

This is the first study in humans with heart failure where such a close link between cardiac contractility and coronary blood flow physiology has been demonstrated.

## 8.3 Proof of concept for clinical application of a simple plethysmographic technology (pulse oximeter) for optimization of CRT devices

I was able to show that AV optimization using a simple and non-expensive haemodynamic technology can be as efficient as the more expensive, by a hundredfold, Finapres technology.

I compared the two technologies at an atrial rate just above sinus rate and at a 100bpm. The Finometer, at first look, appeared to have a better reproducibility at both heart rates. This was the case when peak of the haemodynamic signal was used for both technologies; the systolic blood pressure from the Finapres and the peak of the photopethysmogram from the pulse oximeter.

Further signal processing and use of the maximum rate of change of the haemodynamic signal appeared to have a favourable effect on the reproducibility of the optimal AV delay from the simple photoplethysmographic signal. In fact, the reproducibility of the optimal AV delay of both haemodynamic technologies is not dissimilar.

I also demonstrated that apart from appropriate signal processing there are two other important factors that improve the accuracy of optimization. First, increasing the number of replicates averaged, but at the cost of time, improves the reproducibility of the optimal AV delay, irrespective of haemodynamic technology used. Second, increasing the heart rate at which the optimization was performed also improved reproducibility of the optimal AV delay, again irrespective of haemodynamic technology used.

## 8.4 Comparison of the internal validity of three non-invasive modalities (pressure, flow, electrical) used for VV optimization

An elementary test of any VV optimization modality is its ability to demonstrate internal validity based on three criteria; singularity (the presence of only one optimum or optimal region), reproducibility and biological plausibility (the distribution of optimal settings should not contradict established physiological principles). Only modalities which fulfil all three criteria have any reason to be used further in clinical research. I have shown how this can be done in a straight forward experiment which is demanding on planning and execution but not demanding on the patient.

I found that optimization of VV delay by pressure (using the Finapres technology) fulfilled all 3 criteria of internal validity. The electrical optimization (width of the QRS on the 12-lead ECG) did not show plausibility and made it a weaker candidate for optimization. This was not surprising because the many factors that are contributing to mechanical dyssynchrony, and cardiac function overall, go far beyond QRS width, and even though wide QRS may predict benefit for CRT first principles do not require that QRS minimization must be the ideal approach to VV optimization.

Flow, by LVOT VTI, despite being a rationale marker to use to assess cardiac function, demonstrated poor internal validity. It performed poorly in all three criteria and therefore its use in clinical practice for optimization of CRT devices should be reconsidered.

Overall, through this study's findings it became apparent that optimization of VV delay by pressure seems to be the most internally valid approach.

## 8.5 Increasing heart rate requires a shorter AV delay for optimal haemodynamics, but the difference is small and requires careful experimental design to detect.

Optimization of AV delay during exercise on a supine bike, using non-invasive pressure, can be performed reliably when multiple replicates are averaged for each tested AV delay. Averaging multiple replicates reduces backround noise and the signal changes can be more reliably detected allowing evaluation of the effect of heart rate on the optimal AV delay.

In this study, I found that the optimal AV delay shortens with moderate exercise (~ 20-25 bpm above resting sinus rate). I also found that overdrive pacing the atrium by 20 and 40 bpm from an atrial rate just above the sinus rate, also led to progressive shortening of the optimal AV delay.

To my knowledge current rate adaptation algorithms of AV delay are generally extrapolated from the bradypacing algorithms from pacemakers implanted in normal LV patients. This the first study which has investigated the effect of heart rate on the optimal AV delay during exercise *and* during overdrive pacing in the CRT population. I found that the slope of optimal AV delay shortening with increasing heart rate is

very similar as the existing algorithms. This finding may not be so surprising because filling (principally determined by the AV delay) of the left ventricle should follow the same basic principles of passive (E wave on transmitral Doppler) and active (A wave on transmitral Doppler) transmitral flow, irrespective of the LV function.

It is therefore vital to programme these algorithms on, because adaptation of AV delay with heart rate will be an additional beneficial effect of biventricular pacing especially during exercise when patients are most likely to experience symptoms from their heart failure.

## 8.6 The prolongation of optimal AV delay from sensed to paced is quantitatively explained by left atrial mechanical delay measured independently under blinded conditions

I found that in all patients the optimal AV delay prolonged significantly when the atrium was paced instead of sensed, at the same heart rate. When the heart rate at which the optimization was carried out was increased by 20-25 bpm, the prolongation was significantly slightly bigger than at rest. Therefore, prediction of the optimal sensed AV delay from the optimal paced AV for any given heart rate cannot be extrapolated from the sense-paced difference in the optimal AV delays at rest.

This has not been demonstrated in previous studies, nor has the mechanism for such a change in the prolongation of the optimal AV delay between sensed-to-paced atrium at faster heart rate.

I was able to show that Doppler echocardiography can help investigate the mechanism for the prolongation in the optimal AV delay between sensed and paced atrium and explain why the difference in the optimal AV delays increases at faster heart rates.

I found that the longer optimal AV delay during atrial pacing was the result of a delayed left atrial contraction. This delay may be a result of a number of factors such as the introduction of atrial pacing latency and prolongation in the interatrial conduction.

I also found that the delay in left atrial contraction between sensed-paced atrium was larger at the faster heart rate. This was because the left atrial contraction occurred earlier during natural heart rate elevation

(i.e by exercise) as opposed to the rate of the already paced atrium being elevated by pacing, which did not result in any change in the timing of the left atrial contraction

## 8.7 Limitations to this thesis

This thesis was in part focused on investigating the impact of optimization of acute biventricular pacing on the cardiac mechanoenergetics and coronary physiology. It also focused on developing a simple haemodynamic technology for reliable and reproducible routine clinical optimization and comparing head-to-head existing non-invasive optimization modalities. In addition, the effect of heart rate on optimal AV delay was explored and a mechanistic explanation was investigated for the different optimal AV delays found at different pacing modes (sensed versus paced atrium) and heart rates.

This thesis was not designed to measure the effect of optimization on clinical outcomes; rather it casts light on how clinical outcome studies should be designed to prevent wastage of patients' good will on research that is doomed from the outset. It was not realistic for me to conduct a clinical trial because of the sample size that would be required to provide adequate power in order to answer this question. I found that for example the optimal AV delay can acutely improve cardiac work by an additional ~25% than the pacemaker's nominal AV 120 ms does from LBBB. To explore this effect in a clinical outcome study, it would require a sample size ($4^2$) 16 times more than the number of patients recruited in studies which looked at simply CRT on (at nominal pacemaker settings) versus CRT off.

In sinus rhythm I was unable to separate the differential effect of resynchronization from AV optimization because these two processes are intimately linked. For example when AV optimization is performed, a varying degree of ventricular resynchronization takes place by the intrinsic ventricular depolarisation (i.e through the AV node) and this would introduce haemodynamic changed in addition to the ones caused from AV delay modulation. To which extent one or the other contribute to the total haemodynamic benefit would be difficult to establish, although I think the majority of haemodynamic change could be attributed to the AV changes.

Also, VV optimization in sinus rhythm would involve changing the VV delay but by doing so that would inevitably affect the relative left and right sided AV delays and introduce haemodynamic effects on top of the effects caused from VV changes; calculating the relative contribution of each would be impossible.

I approached this as closely as possible in humans by studying AF where resynchronization could be studied in isolation, but although I found clear evidence of resynchronization effect in these patients it was not possible to be certain that patients in SR have the same size effect because they would be different patients. I cannot disprove the possibility that patients who are more prominent responders (greater acute haemodynamic curvature) to VV adjustment are more or less prone to be in AF. The only way to do this to study the same patient in sinus and AF which was not realistic to do in this thesis, but may be possible to do in future research which had ethical permission to conduct DCCV of a patient in persistent AF for research purposes.

## 8.8 Clinical implications of the findings of this thesis

Through the work of this thesis I have made significant steps in understanding the effect of the biventricular pacing and AV optimization on cardiac mechanoenergetics and coronary physiology.

Although there has been previous work looking at the changes in cardiac efficiency when patients are biventricularly paced compared against LBBB, no work had ever investigated the mechanoenergetic effect of AV modulation.

To my knowledge, this is the first time an invasive study has been carried out to investigate the effects of AV optimization on cardiac mechanoenergetics. I have shown that optimizing the AV delay improves cardiac work compared against the nominal AV of 120 ms and that programming a very suboptimal AV delay (40 ms), negates any of the benefits of cardiac resynchronization. This finding is an important piece of evidence that AV optimization is, at least acutely, more beneficial than the suboptimal nominal AV delay of cardiac pacemakers.

In addition, in this thesis I have proved that non-invasive optimization using beat-to-beat blood pressure identifies the optimal AV delay which provides more external cardiac work than the nominal AV delay. This finding strengthens the evidence that non-invasive haemodynamic optimization can be used to identify the AV delay which can deliver maximal cardiac performance.

Knowledge of this will lead to a wider uptake of the use of non-invasive haemodynamic optimization for routine optimization of CRT devices.

I have shown that the improved cardiac contractility of biventricular pacing leads to an increased coronary flow. The increase in coronary blood flow is principally through an increase in microcirculatory suction in diastole. Therefore it is critical that there is no significant epicardial coronary or microvascular disease otherwise the increase in demand in blood flow, as a result of biventricular pacing will not be met. This might tend to attenuate clinical benefits of CRT in CHF patients with ongoing ischaemia.

In this thesis I have demonstrated that optimization using different non-invasive technologies can be as equally effective in identifying the optimal AV delay. In previous work (by Whinnett et al, 2006, 2007) it was demonstrated that the optimization of CRT devices using beat-to-beat blood pressure can be very reproducible when a protocol of alternations from a reference to a number of tested delays is used.

In this thesis I found that using another non-invasive haemodynamic technology (simple plethysmographic signal of a pulse oximeter) to carry out optimization can be very comparative to the Finapres technology. The advantages of the simple plethysmographic technology are that it is cheaper by a hundredfold and the plethysmographic signal can form part of an implantable technology which potentially can be used in fully automated optimization.

I was also able to demonstrate that optimization can be performed reproducibly, either by Finapres or the pulse oximeter, in 12 minutes. This is much less time than the time required for an optimization using echocardiography, which would take on average 25 minutes which requires an experienced operator and as a modality is marred by inadequate reproducibility. This is important because it will facilitate a more

widespread use of a haemodynamic technology, over echocardiography, for optimization of CRT devices.

I found that VV optimization using echocardiography is flawed. The optimal setting is poorly reproducible and in most patients more than one supposedly optimal setting is generated and the distribution of such optimal settings are biologically implausible (i.e the RV is paced before the LV in a high proportion of patients which, goes against the physiological principle of biventricular pacing whereby LV is expected to be paced first). The consequence of such a poor internal validity would be selection of supposedly optimal settings which are much worse than even the nominal VV setting of 0 ms. It is therefore advisable that physicians who optimize by echocardiography, unless they are able to demonstrate internal validity of this modality, to stop using this technique and either programme VV delay to 0 ms or choose a more reliable optimization method, like the haemodynamic technologies tested in this thesis.

Additionally, although I found that electrocardiography was very reproducible, it also provided biologically implausible optimal settings which they did not agree with the optima identified by the non invasive haemodynamic technology. Forced to choose between the two, I would optimize haemodynamically instead of electrically because I feel haemodynamics as discussed above reflect cardiac performance accurately.

I found that non-invasive haemodynamic optimization can be performed at rest, during exercise and during atrial pacing. In routine clinical practice when optimization is performed it is most usually performed by echocardiography at rest in the atrially sensed mode. The atrially paced mode is not tested and instead a nominal increase of 20-30 ms from optimal sensed to optimal paced AV delay is commonly programmed, as advised by the device manufacturer.

I found that in the heart failure population the sensed AV and paced optimal AV delays have, on average, a bigger difference of 50-60 ms instead. This is very important because a lot of patients with CRT devices are atrially paced at rest and if not, a big proportion of them will be eventually atrially paced during daily activities because of the high prevalence of chronotropic incompetence in the heart failure

population. Therefore by not optimizing during atrial paced modes some of the benefit of CRT may be lost in many of these patients.

Finally I found that the optimal AV delay decreases with increasing heart rate, and that the rate of decrease is within the range of existing pacemaker algorithms (adopted from the bradypacing devices) used for rate adaptation of AV delay. It is important to programme the AV rate adaptation feature on all CRT devices as this will provide the optimal AV delay during exercise. Patients are more likely to feel more symptomatic during exercise, therefore having the correct optimal AV delay during exercise will provide more symptomatic relief than if the optimal AV delay was just left fixed to the one of the resting rate.

## 8.9 Future research work planned

As a result of this thesis's findings more research hypotheses have been generated. Specifically, I plan to investigate:

- the relative contribution of AV delay optimization to the overall benefit of biventricular pacing. I am planning to carry out non-invasive haemodynamic optimization studies to compare the haemodynamic improvement from baseline LBBB to optimal AV delay during biventricular pacing and from baseline LBBB to optimal AV delay during right ventricular pacing only. This will help clarify the relative contribution of ventricular resynchronization and AV optimization to the total haemodynamic improvement of biventricular pacing.
- the relative contribution of heart rate regularization (by atrially pacing just above the sinus rate) to the improved internal validity of haemodynamic optimization at faster heart rates. I plan to investigate the physiological changes in heart rate as the explanation for a potential difference in the internal validity of haemodynamic optimization between resting sinus rate and regularized rate.

- the underlying physiological explanation of why haemodynamic optimization during steady state pacing is inferior to the protocol of alternations that I used in this thesis. I will look specifically in the beat to beat variation in blood pressure as the predominant source of biological noise explaining the difference between these two approaches of optimization

- the feasibility of measuring the changes in the timing of left atrial contraction when the atrium is paced instead of sensed, by using right and left ventricular intracardiac electrograms from the implanted devices. I have already demonstrated, using tissue Doppler echocardiography, that the difference in the optimal AV delay between atrially sensed and paced modes at a given heart rate can be explained by the change in the left atrial activation time. If this change can be measured by the pacemaker leads then the atrial sensed-paced difference can be measured automatically and quite easily by the pacemaker at several heart rates during the patient's daily activities. Therefore haemodynamic optimization could then be performed by atrial overdrive pacing at several heart rates, when the patient is at rest. The equivalent heart rate optima at the atrially sensed mode can therefore be calculated using the sensed-paced difference already acquired and stored by the pacing device.

- the application of wave intensity analysis in the proximal aorta and coronary circulation to investigate several unanswered physiological questions: For example, can response to CRT be predicted by pre-implantation coronary physiology (for example the extent of coronary flow reserve); and how does proximal aorta and downstream blood pressure and flow physiology change with resynchronization and AV optimization.

- the feasibility of using pulmonary artery pressure for optimization of CRT devices. The technology for measuring PA pressure remotely using an implantable device is already available. This technology could therefore be of use for automated CRT optimization if a comparison study with, for example, a non invasive haemodynamic technology (for example the Finometer) or with

commonly used invasive markers of cardiac contractility (such as aortic pulse pressure and LV $dP/dt_{max}$) establishes its suitability.

## 8.10 Conclusion

Biventricular pacing at the nominal AV delay improves cardiac mechanoenergetics; and optimization of the AV delay, using non-invasive beat-to-beat blood pressure, improves external cardiac work further. Coronary physiology is closely linked to cardiac mechanics, therefore an improvement in cardiac contractility with biventricular pacing leads to an increase in coronary blood flow which is predominantly driven by the enhanced coronary microcirculatory suction during diastole.

Non-invasive haemodynamic optimization of CRT devices can be achieved reproducibly and relatively fast, using an appropriate optimization algorithm, regardless of the complexity and cost of the haemodynamic technology used. Simple photoplethysmography is a haemodynamic modality that can be implanted and provide automated optimization. Moreover, other commonly used optimization modalities, in particular echocardiography, lack internal validity and their use for optimization should be treated cautiously.

Finally, the optimal AV delay changes that occur from heart rate and pacing mode changes (atrially sensed versus atrially paced biventricular pacing) should be taken into consideration when programming cardiac resynchronization devices.

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# Publications arising from this thesis

## Publications

Kyriacou A, Pabari PA, Mayet J, Peters NS, Davies DW, Lim PB, Lefroy D, Hughes AD, Kanagaratnam P, Francis DP, Whinnett ZI. Cardiac resynchronization therapy and AV optimization increase myocardial oxygen consumption, but increase cardiac function more than proportionally. Int J Cardiol. 2014 Feb 1;171(2):144-52.

Kyriacou A, Whinnett ZI, Sen S, Pabari PA, Wright I, Cornelussen R, Lefroy D, Davies DW, Peters NS, Kanagaratnam P, Mayet J, Hughes AD, Francis DP, Davies JE. Improvement in coronary blood flow velocity with acute biventricular pacing is predominantly due to an increase in a diastolic backward-travelling decompression (suction) wave. Circulation. 2012 Sep 11;126(11):1334-44.

Kyriacou A, Pabari PA, Whinnett ZI, Arri S, Willson K, Baruah R, Stegemann B, Mayet J, Kanagaratnam P, Hughes AD, Francis DP. Fully automatable, reproducible, noninvasive simple plethysmographic optimization: proof of concept and potential for implantability. Pacing Clin Electrophysiol. 2012 Aug;35(8):948-60.

Kyriacou A, Pabari PA, Francis DP. Cardiac resynchronization therapy is certainly cardiac therapy, but how much resynchronization and how much atrioventricular delay optimization? Heart Fail Rev. 2012 Nov;17(6):727-36.

Kyriacou A, Li Kam Wa ME, Pabari PA, Unsworth B, Baruah R, Willson K, Peters NS, Kanagaratnam P, Hughes AD, Mayet J, Whinnett ZI, Francis DP. A systematic approach to designing reliable VV optimization methodology: assessment of internal validity of echocardiographic, electrocardiographic and haemodynamic optimization of cardiac resynchronization therapy. Int J Cardiol. 2013 Aug 10;167(3):954-64.

## Abstracts and presentations

*Heart Rhythm Congress 2011*

Fully automatable non-invasive plethysmographic optimization of cardiac resynchronization therapy: a miniaturizable and implantable technology. A Kyriacou, PA Pabari, K Willson, B Unsworth, D Lefroy, NS Peters, DW Davies, R Sutton, P Kanagaratnam, AD Hughes, J Mayet, DP Francis, ZI Whinnett. Europace 2011, Volume 13, Supplement 4 Pp. iv25-iv28

*British Cardiovascular Society 2011*

Evaluation of the impact of AV delay variation on the acute mechanoenergetic efficiency of cardiac resynchronisation therapy and assessment of performance of non-invasive vs invasive haemodynamic optimization. A Kyriacou, P Pabari, K Willson, R Baruah, S Sayan, D W Davies, J Mayet, N S Peters, P Kanagaratnam, Z Whinnett, D P Francis. Annual Conference of the British-Cardiovascular-Society (BCS), Manchester, England. Heart;97:A51-A52 doi:10.1136/heartjnl-2011-300198.88

*European Society of Cardiology Congress 2011*

The effect of cardiac resynchronisation therapy and of atrioventricular delay optimization on mechanoenergetic efficiency; simply, a better value for money. Kyriacou A, Pabari PA, Wright I, Cornelussen R, Lefroy D, Davies W, Mayet J, Hughes AD, Peters NS, Kanagaratnum P, Whinnet ZI, Francis DP. European Society of Cardiology, Paris. 27$^{th}$ – 31$^{st}$ Aug 2011.

*Heart Rhythm Society 2011*

Improvement in cardiac mechanoenergetics during CRT, results not only from ventricular resynchronization but also from atrioventricular optimization. Andreas Kyriacou, Punam Pabari, Ian

Wright, Richard Cornelussen, David Lefroy, Wyn Davies, Jamil Mayet, Alun Hughes, Nick S. Peters, Prapa Kanagaratnam, Darrel P. Francis, Zachary I. Whinnett

*European Society of Cardiology Heart Failure Congress 2010*

Applicability of low cost oximeter-type plethysmography as an alternative to volume clamp (Finapres-type) plethysmography in biventricular pacemaker optimization. A. Kyriacou, ZI. Whinnett, PA. Pabari, R. Baruah, D. Lefroy, DW. Davies, NS. Peters, P. Kanagaratnam, J. Mayet, DP. Francis.

Relative Contribution of Heart rate regularization, versus heart rate increase, to improved consistency of optimization of pacemakers at higher paced heart rates. A. Kyriacou, PA. Pabari, ZI. Whinnett, R. Baruah, D. Lefroy, NS. Peters, DW. Davies, J. Mayet, P. Kanagartnam, DP. Francis

Utility of Intraclass Correlation Coefficient to quantify efficiency of optimization markers. A. Kyriacou, ZI. Whinnett, PA. Pabari, R. Baruah, D. Lefroy, NS. Peters, DW. Davies, P. Kanagaratnam, J. Mayet, DP. Francis

*European Society of Cardiology 2010*

Adaptation of non-invasive haemodynamic technologies and development of algorithms for cost-effective, automated optimization of cardiac resynchronization devices. A Kyriacou, PA Pabari, ZI Whinnett, K Willson, D Lefroy, NS Peters, DW Davies, P Kanagaratnam, J Mayet, DP Francis.

# Grants awarded for this thesis

I was awarded a three year Clinical Research Training Fellowship (FS/08/027/24763) by the British Heart Foundation which financially supported all the research work carried out.

# Appendix

Ethics Committee Approval Letter.

**St Mary's REC**
Research Ethics Committees
Room 4W/12, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

Telephone: 0208 846 7251
Facsimile: 0208 846 7280

01 October 2008

Dr Darrel P Francis
Clinical Senior Lecturer and Hon. Consultant Cardiologist
International Centre for Circulatory Health
St Mary's NHS Trust
59-61 North Wharf Road
London
W2 1LA

Dear Dr Francis

**Full title of study:** **Maximising clinical applicability of noninvasive methods for optimisation of cardiac pacemakers and effect of optimisation on cardiac efficiency**
**REC reference number:** **08/H0712/65**

Thank you for your letter, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Sub-Committee of the REC. Your further information was reviewed by the Chairman Barrie Newton and the Vice Chairman Mr Vassilios Papalois.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Ethical review of research sites**

The favourable opinion applies to the research sites listed on the attached form.

**Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Investigator CV | | 14 December 2007 |
| Protocol | 1 | 30 May 2008 |
| Covering Letter | | 02 June 2008 |
| Peer Review | | 31 July 2008 |
| GP/Consultant Information Sheets | 1 | 30 May 2008 |
| Participant Information Sheet: Main Study: Patients with a biventricular pacemaker | 2 | 30 July 2008 |
| Participant Information Sheet: Invasive Substudy: Patients undergoing electrophysiological investigation | 2 | 30 July 2008 |
| Participant Information Sheet: Invasive Substudy: Patients undergoing coronary angiography | 2 | 30 July 2008 |
| Participant Consent Form: Consent form: Copy for Patient Notes | 2 | 30 July 2008 |
| Participant Consent Form: Consent form: Researcher Copy | 2 | 30 July 2008 |
| Participant Consent Form: Consent form: Patient Copy | 2 | 30 July 2008 |
| Response to Request for Further Information | | |
| Application for a clinical research training fellowship accompanying cover letter 17-4-08 | | 20 November 2007 |
| Letter from funder | | 17 April 2008 |

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

| **08/H0712/65** | **Please quote this number on all correspondence** |
|---|---|

With the Committee's best wishes for the success of this project

Yours sincerely

**Barrie Newton**
**Chairman**

Email: adriana.fanigliulo@imperial.nhs.uk

*Enclosures:* "After ethical review – guidance for researchers" *SL- AR2*
*Site approval form*

*Copy to:* *Gary Roper, Imperial College*
*Selvy Raju, Imperial College Healthcare NHS Trust*