Temporary biventricular pacing after cardiac surgery in patients with severe left ventricular dysfunction.

Short title: Pacing after cardiac surgery.

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APPENDIX 1: Specimen Layout for Declaration/Statements page to be included in Taught Master's

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Summary

Background:

Left ventricular (LV) function is an important predictor of outcome after cardiac surgery. Severely impaired LV function (EF<20%) carries a 4-fold increase in the risk of in-hospital mortality compared to patients with EF >40%.

Optimising LV function in the peri-operative setting may improve outcomes. Haemodynamic studies of permanent BiV pacing have reported a relative 25% increase in EF compared to dual-chamber right ventricular pacing.

Methods:

38 patients in sinus rhythm, ejection fraction ≤35%, undergoing on-pump cardiac surgery were enrolled into the main study. All patients received temporary pacing wires attached to the right atrium, right ventricular outflow tract and left ventricle.

Patients were randomly assigned to post-operative biventricular pacing or atrial-inhibited/dual-chamber right ventricular pacing. The primary endpoint was the transition from level 3 to level 2 care.

The cardiac output measurements obtained using the PA catheters were compared to simultaneous measurements obtained from a FloTrac device (Edwards Lifesciences, arterial pulse-wave analysis). The measurements were compared using a Bland-Altman analysis.

Results:

The median duration of level 3 care was 22.0 (IQR: 16.0-66.5) hours and 37.5 (IQR: 16.3-55.0) hours in the BiV and standard pacing groups respectively (log-rank p=0.58, 95% CI: 0.43-1.61).

At 18 hours, cardiac output with biventricular pacing (5.8 L/min) was 9% higher than dual chamber right ventricular pacing (5.3 L/min), (p=0.001). Optimisation of the VV interval produced a further 4% increase in cardiac output (p=0.005).

Analysis of the cardiac output measurements taken simultaneously from the PA catheter and FloTrac system yielded a bias -0.33L/min±2.2 L/min and a percentage error of 42%.

Conclusions:

Patients who require post-operative pacing or a prolonged haemodynamic support after surgery may benefit from optimised BiV pacing. However, for the majority of patients BiV pacing does not alter the clinical outcome compared to atrial-inhibited or dual chamber RV pacing.

Although the FloTrac system is easy to use and rapidly reports changes in cardiac output, its precision requires refinement before it can be used instead of a PA catheter.

Publications from this thesis

1. Russell SJ, Tan C, O'Keefe P, Ashraf S, Zaidi A, Fraser AG, Yousef ZR. Temporary epicardial cardiac resynchronisation versus conventional right ventricular pacing after cardiac surgery: study protocol for a randomised control trial. Trials. 2012;13:20.

2. Russell SJ, Tan C, O'Keefe P, Ashraf S, Zaidi A, Fraser AG, Yousef ZR. Optimized temporary bi-ventricular pacing improves haemodynamic function after on-pump cardiac surgery in patients with severe left ventricular systolic dysfunction: a two-centre randomized control trial. Eur J Cardiothorac Surg. 2012;42(6):e146-51.

Presentations to Learned Societies

1. A randomised study of temporary epicardial cardiac resynchronisation versus conventional right ventricular pacing in cardiac surgical patients. Poster at the British Cardiac Society Annual Conference and Welsh Cardiovascular Meeting 2012.

2. Resynchronisation therapy after cardiac surgery. Presentation to the Welsh Cardiovascular Society Annual Meeting 2012.

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Finally, I would like to say a special thank you to my wife Louise for her support during the project and while writing up the thesis.

For Louise, Amélie and Finley

XXX

Abbreviations

AAI	Atrial-inhibited pacing
AV	Atrio-ventricular
AF	Atrial fibrillation
BiV	Biventricular
BNP	Brain natriuretic peptide
BPM	Beats per minute
CI	Cardiac index
CO	Cardiac output
CPB	Cardio-pulmonary bypass
CRT	Cardiac resynchronisation therapy
CVE	Cerebro-vascular event (stroke)
CW	Continuous wave Doppler
DDD	Dual chamber (atrium and ventricle) pacing
DFT	Diastolic filling time
DSE	Dobutamine stress echo
EF	Ejection fraction
FAC	Fractional area change
IABP	Intra-aortic balloon pump
IL	Interleukin
IMA	Internal mammary artery
IQR	Inter-quartile range
IR	Ischaemia-reperfusion injury
IVRT	Isovolumic relaxation time
MPI	Myocardial perfusion imaging

NO	Nitric oxide
NT BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
LA	Left atrium
LV	Left ventricle
LVEDD	Left ventricular end-diastolic dimension
LVEDP	Left ventricular end-diastolic pressure
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
LVOT	Left ventricular outflow tract
LVSWI	Left ventricular stroke work index
MAP	Mean arterial pressure
PA	Pulmonary artery
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PDE	Phosphodiesterase inhibitor
PEEP	Positive end-expiratory pressure
PET	Positron emission tomography
PW	Pulsed wave Doppler
RA	Right atrium
RVOT	Right ventricular outflow tract
SBP	Systolic blood pressure
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SR	Sinus rhythm

SVC	Superior vena cava
$SV0_2$	Mixed venous oxygen saturations
TDI	Tissue Doppler imaging
TnT	Troponin T
VTI	Velocity time integral
VVI	Ventricular only pacing

Word total for this thesis= 29,314

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Chapter 1 –Background

1.1 Introduction

Coronary artery disease is the leading cause of heart failure in the United Kingdom with a prevalence of 2% in the general population and 7.5% in patients over the age of 75 years (1-3) . Heart failure patients may benefit from surgical revascularisation especially in the context of left main stem or proximal left anterior descending coronary artery disease and viable myocardium (4).

A meta-analysis of 24 trials of patients with multi-vessel coronary artery disease, impaired left ventricular (LV) function and myocardial viability, reported a 79.6% reduction in mortality with surgical revascularisation compared to optimal medical therapy at 25±10 months follow up (3.2% v 16%; Chi^2=147, p<0.0001) (4). Viability was analysed using dobutamine stress echocardiography, position-emission tomography or cardiac magnetic resonance imaging. A multivariate analysis also demonstrated a relationship between pre-operative LV ejection fraction (EF) and the prognostic benefit from surgery. Patients with significant LV dysfunction achieved the greatest improvement in prognosis compared to lesser degrees of LV impairment. There was no prognostic benefit with surgery in the absence of viability.

However, patients with severe LV systolic function (EF <20%) are at increased risk of in-hospital complications after surgery compared to patients with EF >40%. The New York State Database contains information on over 55,000 patients who had surgery between 1997-9 (5). Patients with EF <20% had a 3-fold increase in the risk of respiratory failure, and a 4-fold increase in renal failure, sepsis and in-hospital mortality compared to patients with EF >40%. The discharge-to-home rates were lower in the EF <20% group compared to EF >40% group (73.1% v 87.7%; p <0.001). Therefore,

treatments directed at optimising peri-operative LV function may potentially improve outcomes in this high risk surgical group.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) has identified risk factors for mortality after cardiac surgery. Data was obtained from almost 20,000 patients, across 128 surgical units in different 8 countries in 1995 (add ref roques F). The odds ratios (OR) for mortality increased with progressive LV dysfunction, EF 30-50% (OR 1.5; standard error 0.138; $p < 0.001$) and EF <30% (OR 2.5; standard error 0.340; $p < 0.001$). Both databases have identified that LV dysfunction increases the risk of cardiac surgery. However, other baseline characteristics including: age, female gender, creatinine >200 μmol/L, extra-cardiac arteriopathy, lung disease, neurological dysfunction, PA pressure, pre-operative state and the nature of the operation need to be combined with LV function to calculate the patients' operative risk. This may explain why the EuroSCORE predicts a lower mortality based on the published odds ratios compared to the New York database.

During on-pump cardiac surgery the myocardium is arrested with a mixture of blood and cardioplegia solution with mechanical circulatory support. Although cardioplegia solution and volatile anaesthetic agents protect the heart during surgery, the protection is not perfect and the heart is subjected to an ischaemia-reperfusion (IR) injury. All patients develop a systemic inflammatory response (SIR) syndrome that may compromise organ-perfusion if severe or prolonged.

The next sections discuss IR and the SIR syndrome in more detail along with the conventional treatments for low cardiac output including inotropes and intra-aortic balloon pumps and vasoconstrictors to attenuate the SIR syndrome. These treatments

do have limitations and biventricular pacing after cardiac surgery may benefit such patients with low cardiac output following surgery.

1.1.1 Peri-operative management of heart failure medications

ACE-inhibitors (ACE-I), β blockers and aldosterone antagonists improve heart failure symptoms, LV ejection fraction and prognosis in heart failure patients (2, 6-11). The SOLVD (Studies of LV Dysfunction) group reported a 16% relative reduction in death at 40 months follow up, in heart failure patients (NYHA II/III) with EF <35%, taking enalapril v placebo (35.2% v 39.7%; p=0.004) (12). Pitt et al reported a 30% relative risk reduction in mortality with spironolactone compared to placebo at 24 months in patients with heart failure (EF <35%) treated with an ACE-I (mortality 35% v 46%; p <0.001 respectively) (6). The prognostic benefits of β blockers was also demonstrated in the CIBIS II trial (Cardiac Insufficiency Bisoprolol Study II) (13). This trial reported a 5.5% absolute risk reduction with bisoprolol v placebo at 1.3 years follow up in symptomatic heart failure patients (NHYA III/IV) with EF <35%, treated with ACE-I (11.8% v 17.3%; p <0.0001 respectively).

Although these therapies are well established for the treatment for chronic heart failure, they are often discontinued before cardiac surgery. ACE-I and aldosterone antagonists may increase the risk of peri-operative hypotension and subsequent vasoconstrictor requirements. There is limited evidence to support this argument. One study of 40 patients reported that stopping the ACE-I before surgery did not prevent post-operative hypotension (14). β blockers are usually continued before surgery especially in patients with a recent myocardial infarction or impaired LV systolic function.

1.1.2 Systemic Inflammatory Response syndrome after cardio-pulmonary bypass

Cardiac surgery stimulates an aggressive inflammatory response by activating cytokines, complement and other modulators of inflammation (15). A report from the Society of Thoracic Surgeons National Database found that 20% of low risk patients developed a post-operative systemic inflammatory response syndrome (SIRS) (16). 11% developed multi-organ dysfunction syndrome, which carried 41% mortality (17). Acquired multi-organ dysfunction syndrome was the best predictor of mortality in cardiac surgical patients who required prolonged ventilation (17). To diagnose the systemic inflammatory response syndrome, 2 or more of the following criteria must be achieved:

- Temperature: >38°C or <36°C
- Heart rate: >90 beats/min
- Respiratory rate: >20 breaths/min or $PaCO_2$ <32 mmHg
- Leukocytes: >12,000, <4,000/mm^3 or >10% immature forms

The SIR syndrome can be activated through a variety of mechanisms including tissue trauma, blood transfusion, hypothermia, cardio-pulmonary bypass, mechanical ventilation, ischaemia-reperfusion injury during aortic cross-clamping, and sepsis (18-20). Patients with impaired LV function and diabetes appear to have more pro-inflammatory cytokine release, which increases the incidence of post-operative complications (21, 22).

Cardio-pulmonary bypass induces mediators of inflammation, including IL-6, which are associated with myocardial stunning, ischaemia and β-adrenergic receptor desensitisation (23). TNF-α, IL-1β and IL-6 are associated with myocyte refractoriness to adrenergic stimulation after cardio-pulmonary bypass. LV wall motion abnormalities

and ischaemic episodes correlate with IL-6 and IL-8 concentrations (23, 24). Pro-inflammatory cytokines also increase nitric oxide production via iNOS (nitric oxide synthase) which has been shown to depress myocardial contractility (25).

The SIR syndrome is also associated with acute lung injury, pleural effusions, stroke (1-3%) and seizures (5-10%), renal insufficiency requiring haemofiltration (1%), hepatic injury and activation of the clotting cascades (19, 20, 26-30).

Anaesthetic agents, including propofol and sevoflurane, opiates and haemofiltration have anti-inflammatory properties and help down-regulate the SIR syndrome (31-33). Haemofiltration can remove mediators of inflammation, including TNF-α and IL-1β from the circulation (34, 35). Other possible treatments include: the use of off-pump cardiac surgery, heparin-coated bypass circuits, leukocyte filters, and anti-inflammatory agents including serine protease inhibitors, aprotinin, anti-oxidants, corticosteroids and cyclooxygenase inhibitors. However, there is limited evidence to support these therapies.

1.1.3 Ischaemia-reperfusion injury after cardiac surgery

The concept of the ischaemia-reperfusion injury was first described by Jennings et al, in the 1960s (36). Jennings observed that reperfusion, after ligation of a canine coronary artery was associated with accelerated myocardial necrosis on histological samples. The necrosis observed after 30-60 minutes of reperfusion was similar to that observed, 24 hours after permanent occlusion of a coronary artery.

Ischaemia-reperfusion injury after cardio-pulmonary bypass is associated with stunning injury after reperfusion of the ischaemic myocardium (37). Ischaemia induces

the accumulation of intra-cellular sodium, hydrogen and calcium ions, culminating in tissue acidosis (38). Subsequent reperfusion reverses this flux in ions with rapid correction of the cellular acidosis leading to enhanced cytotoxicity (39, 40). High sodium concentrations increase sarcoplasmic reticular calcium, leading to calcium over-load, myofibrillar hyper-contraction, adenosine triphosphate depletion, structural damage to mitochondria and myocardial stunning (41, 42). Calcium over-load leads to the production of reactive oxygen species from the mitochondria, which triggers cellular injury.

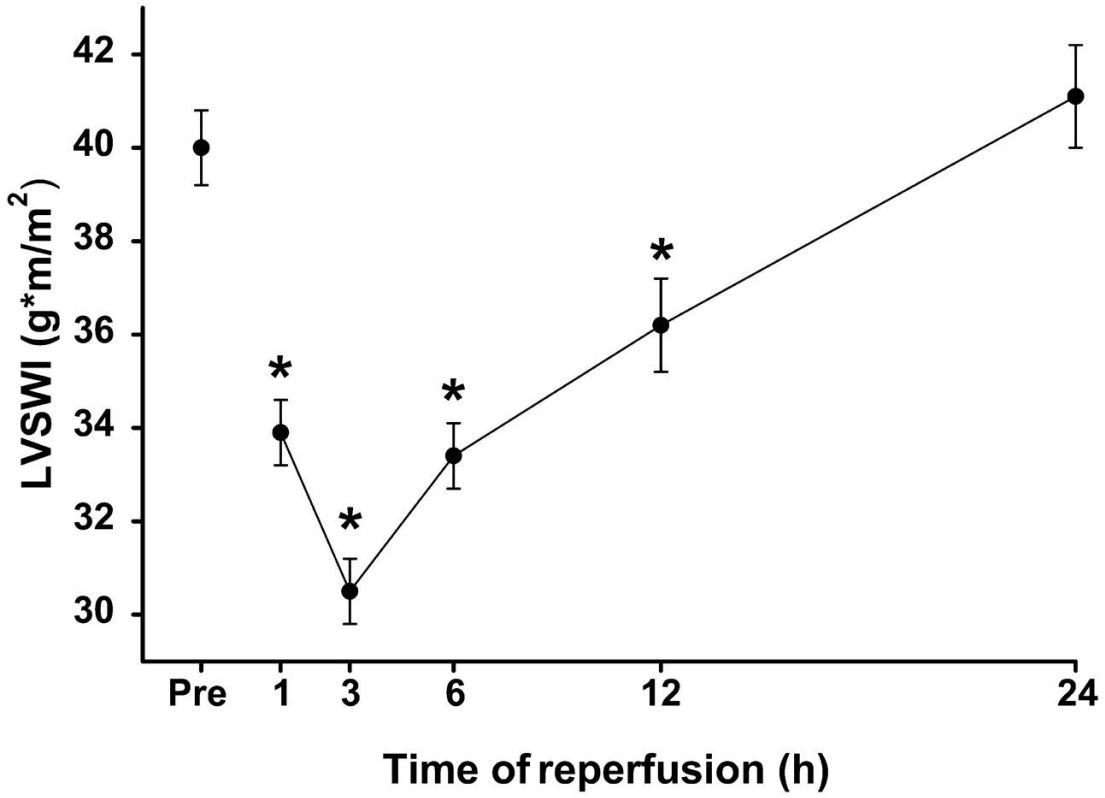
Endothelial nitric oxide is released during IR injury. Nitric oxide is normally a vaso-protective agent, leading to vasodilation and preventing platelet aggregation. However, in high concentrations, nitric oxide paradoxically potentiates the toxic effects of the reactive oxygen species leading to further IR injury.

Cardioplegia solution mixed with cold-blood is designed to reduce the ischaemic injury during cardiac surgery. This potassium-rich solution reduces myocardial metabolism and oxygen consumption during this vulnerable period. IR after cardiac surgery may manifest as arrhythmias, low-output states, peri-operative myocardial infarction or myocardial stunning. Inotropic agents are required after surgery to increase cardiac output and prevent low-output states.

1.1.4 Inotropes

Inotropes are used to increase cardiac output especially in the critical first 6 hours after surgery. A study by Lalu et al, identified a nadir in LV stroke work at 3 hours after surgery in 15 patients with no prior history of myocardial infarction and normal pre-operative LV systolic function (43), see figure 1.

Figure 1: LV stroke work index before cardioplegia and after reperfusion.



*= p<0.01 compared to pre-operative LV stroke work index. Adapted from Lalu et al, 2005 (43).

In clinical practice, inotropic agents are used in combination with vasoconstrictors to increase cardiac output and mean arterial pressure, and intra-aortic balloon pumps (IABP) to increase cardiac output, coronary perfusion and to reduce after-load, following bypass surgery.

Inotropes are used to increase cardiac output in the peri-operative period. Inotropes recruit stunned-reperfused myocardium to contract. Although not an ideal strategy to counter IR injury, inotropes are not associated with worse functional recovery or increased tissue necrosis after surgery (44).

In heart failure patients, phosphodiesterase inhibitors (PDE-III) including enoximone and milrinone are routinely used after cardiac surgery. The PDE-III agents

have a positive inotropic effect by increasing intramyocardial levels of cAMP, promote vasodilatation and reduce systemic and pulmonary vascular resistance but at the expense of increasing myocardial oxygen demand (45-48).

A study of 99 patients receiving elective cardiac surgery, reported after a 50 µg/kg bolus of milrinone, cardiac index increased by 54% in patients with low pre-operative cardiac index (<1.6L/min/m^2; p <0.05). Milrinone reduced pulmonary vascular resistance (PVR) by 26% after a 60 minute infusion (0.75-0.75 µg/kg/min) in patients with elevated pre-operative PVR >200 dynes.sec.cm^{-5} compared to baseline measurements before milrinone infusion (p <0.005) (49, 50). In another study of 44 patients with an EF >30%, milrinone increased graft flow by 48% in venous conduits and FAC (%) on TOE (+3% v -7%; p=0.002) 10 minutes after bypass compared to baseline v placebo (51).

Enoximone has been reported to reduce post-operative TNI levels compared to dobutamine. In a non-randomised study of 216 patients, 70% with preserved LV function, enoximone reduced troponin I levels >50% at 12 hours compared to dobutamine (p =0.003) (52).

1.1.5 Intra-aortic balloon pump

An alternative method of optimising peri-operative cardiac output is to insert an intra-aortic balloon pump (IABP). IABPs improve coronary perfusion, protect against myocardial ischaemia and augment cardiac output by reducing after-load. This device may be inserted before or after surgery and in combination with inotropes and vasoconstrictors.

A propensity matched analysis of 478 pairs of high risk surgical patients with a Euroscore >8, reported that patients without an IABP had 64% increased risk of in-hospital mortality (p=0.001), 45% higher risk of peri-operative MI (p=0.01), and 45% risk of a longer ITU admission (p=0.001) compared to patients with an IABP (53). IABP increased mean flow in the arterial mammary grafts by 18% and by 10% in vein grafts (p=0.04) (54).

A meta-analysis of 110 papers on the peri-operative utilisation of IABP has recommended the routine use of IABP for patients with 2 of the following: EF <30-40%; left main stem disease; unstable angina or re-do operation (55).

Despite these potential advantages, IABPs have an associated 4% risk of vascular complications including limb ischaemia or groin haematoma from the device (56, 57). The device also requires the patient to remain immobile in bed and as an indwelling device is a potential source of infection. These factors limit the clinical application of this device.

Inotropes and IABP are both used in routine clinical practice to wean patients from cardio-pulmonary bypass and improve cardiac output after surgery. Although these methods are effective, they have several drawbacks including: increased myocardial oxygen demand and vascular complications. This has created interest in temporary biventricular (BiV) pacing for acute haemodynamic support after separation from cardio-pulmonary bypass (CPB). If BiV pacing can augment cardiac output by reversing electro-mechanical dyssychrony after surgery, it may reduce the requirements for inotropes and IABP. In practical terms this can be achieved by upgrading the conventional temporary dual chamber epicardial pacing system implanted before weaning from CPB with the addition of LV pacing wires.

1.1.6 A brief history of biventricular pacing

Biventricular (BiV) pacing has been investigated as a heart failure treatment for over 40 years (58). Pioneering work by Cazeau et al in the 1990s (59) led to it being established as a therapy to improve prognosis in chronic heart failure patients with dyssynchrony (60). Multi-centred randomised controlled trials focused on long-term outcomes including LV remodelling and mortality (60, 61); however BiV pacing also has an acute haemodynamic effect. Previous trials have reported an absolute increase in ejection fraction of 25% (see section 1.3). This has been demonstrated by conducting acute haemodynamic studies in patients receiving a permanent BiV pacing system (2, 62, 63).

This principle can be applied to patients after cardiac surgery by attaching pacing wires to the right atrium, right ventricle and left ventricle before separation from the cardio-pulmonary bypass circuit. Therefore, temporary BiV pacing can be performed in the post-operative setting with the aim of improving cardiac efficiency, acute haemodynamic function and may reduce the length of ITU admission, in patients with severe LV systolic dysfunction.

The following sections of this review will focus on electromechanical dyssynchrony as a potential target for BiV pacing, the acute haemodynamic effects of BiV pacing, including previous trials of BiV pacing after cardiac surgery, and the potential benefits of optimising the AV and VV timing intervals.

1.2 Dyssynchrony

The term dyssynchrony is used to describe the inefficient and in-coordinated filling and contraction of the heart. The normal heart is composed of myocardial fibres

with a longitudinal orientation in the sub-endocardium and epicardium and circumferential orientation in the mid wall. During systole there is both circumferential and longitudinal contraction with shortening from the base to the apex of the LV. This complex matrix of myocardial fibres is activated in a temporal order by the His-Purkinje network which achieves optimal pump efficiency. A wave front of electrical depolarisation starts at the endocardial surface of the heart at the apex of the LV and spreads towards the base of the LV and the epicardium. This wave-front of electrical depolarisation takes 80-100 ms to disperse through the LV (64).

The following sections review the literature on electro-mechanical dyssynchrony and the utility of identifying dyssynchrony to predict a response to BiV pacing.

1.2.1 Electrical dyssynchrony– QRS duration and morphology

LBBB is a significant predictor of LV systolic dysfunction, mortality and response to BiV pacing in patients with heart failure (65-67). The MADIT-CRT trial investigated the response to BiV pacing in heart failure patients with mild symptoms (NYHA I-II), severe LV systolic dysfunction (EF <30%) and QRS duration >130 ms (61). A post-hoc analysis of the trial compared the primary outcome of death or heart failure hospitalisation in patients receiving CRT-D v ICD-only with respect to their baseline QRS morphology (68). The subgroup with LBBB had a 53% reduction in the primary endpoint with CRT-D v ICD-only ($p < 0.001$) whereas there were no beneficial effects in the non-LBBB subgroup (HR 1.24; $p=0.257$). Fewer ventricular arrhythmias were observed in the LBBB group and LV end-systolic volumes were reduced compared to the non-LBBB subgroup.

In contrast, there are limited data to support the routine implantation of BiV pacemakers in subjects with a narrow QRS duration (<120 ms). The majority of studies reporting a clinical benefit are small, single-centre studies with limited follow up (69-71). Achilli et al investigated 52 patients with NHYA 3-4 symptoms, EF <35% and either an inter-ventricular mechanical delay >20ms or intra-ventricular dyssynchrony (71). Intra-ventricular dyssynchrony was defined as the onset of the diastolic E wave before maximal apical displacement of the basal lateral LV wall. Only 14 patients had a QRS duration ≤120 ms. BiV pacing increased the QRS duration by 10 ms (p=NS) but BiV pacing reduced NHYA class (3.3±0.5 v 1.7±0.6 at baseline v 6-months; p <0.001) and increased 6 minute walk distance (276.4±88.9m v 369.9±70.2m; at baseline v 6-months; p <0.01) in patients with QRS duration ≤120 ms.

Bleeker et al studied the effects of BiV pacing in 33 heart failure patients, NHYA 3-4, QRS <120 ms, EF <35% with a septal to lateral wall delay of at least 65ms, to peak systolic velocity using TDI (70). A control group of 33 patients with QRS >120 ms was created and both groups followed up for 6 months. Improvements of equal magnitude were observed in both groups: reduction in LV dyssynchrony (68±37 ms v 78±39 ms; p=NS); improvement in 6 minute walk distance (89±107 m v 130±95 m; p=NS) and improvement in EF (8±8 % v 9±7 %; p=NS). The comparisons are for variables measured at 6 months compared to baseline values in the narrow QRS v wide QRS duration groups respectively.

The ESTEEM-CRT (Evaluation of CRT in narrow-QRS patients with mechanical dyssynchrony from a multicenter study) included 68 patients with NYHA class III heart failure, QRS <120 ms, LVEF <35% and intra-ventricular dyssynchrony. Dyssynchrony was assessed using a 12 segment model of the LV and calculating the standard deviation of time to peak systolic velocity, using TDI (72). After 6 months

follow up, BiV pacing improved NYHA score and quality of life score ($p < 0.01$ for both comparisons) but there was no statistically significant improvement in peak $V0_2$ or reduction in LV volumes or improvement in ejection fraction.

The 'Cardiac resynchronisation therapy in heart failure with narrow QRS complexes', RETHINQ trial investigators studied the effect of BiV pacing in 172 patients with a standard indication for an ICD (73). The patients were randomised to receive either BiV pacing with ICD or ICD-only (control group). Enrolment included NYHA class III patients with EF ≤35%, QRS <130 ms and mechanical dyssynchrony. The primary endpoint was a ≥1 ml/kg/min increase in peak oxygen consumption during cardio-pulmonary exercise testing after 6 months. The primary endpoint was not significantly different between the 2 groups at the end of the study, neither was there a significant difference in 6 minute walk time, LV volumes or quality of life score. The only significant finding was an improvement in NYHA score in the BiV group v control (54% v 29%, $p = 0.006$).

A pre-specified analysis of outcome was performed for subject with QRS ≥120 ms v <120 ms. Peak oxygen consumption increased in the QRS ≥120 ms group ($p = 0.02$) but not in the QRS <120 ms group ($p = 0.45$). Therefore, patients with prolonged QRS durations above 120ms and with LBBB morphology are most likely to benefit from BiV pacing.

BiV pacing is an effective therapy to improve heart failure symptoms, exercise capacity and promote LV remodelling in patients with severe LV systolic impairment and prolonged QRS durations (2, 74). Therefore, this group of patients may also benefit from post-operative BiV pacing after cardiac surgery.

1.2.2 Non-responders to BiV pacing

The 12-lead ECG is a useful tool for identifying electrical dyssynchrony and a prolonged QRS duration has been used as a selection criterion in previous trials of BiV pacing, see table 1. However, clinical trials consistently report a non-response rate to BiV pacing in the region of 25-30%.

Table 1: Inclusion criteria for randomised control trials of BiV pacing.

Trial	**n**	**NYHA class**	**LVEF (%)**	**LVEDD (mm)**	**SR/AF**	**QRS criteria (ms)**
MUSTIC-SR **(75)**	58	III	≤35%	≥60	SR	≥150
MIRACLE **(76)**	453	III,IV	≤35%	≥55	SR	≥130
PATH-CHF **(77)**	41	III,IV	≤35%	NA	SR	≥120
MIRACLE-ICD **(78)**	369	III,IV	≤35%	≥55	SR	≥130
CONTAK CD **(79)**	227	III,IV	≤35%	NA	SR	≥120
MIRACLE ICD II **(80)**	186	II	≤35%	≥55	SR	≥130
PATH CHF II **(81)**	89	III,IV	≤35%	NA	SR	≥120
COMPANION **(82)**	1520	III,IV	≤35%	NA	SR	≥120
CARE-HF **(60)**	814	III,IV	≤35%	≥30	SR	≥150 or ≥120+echo.
REVERSE **(83)**	610	I,II	≤30%	≥55	SR	≥120
MADIT-CRT **(84)**	1800	I,II	≤30%	NA	SR	≥130
RAFT **(85)**	1800	II,III	≤30%	>60	SR/AF	≥130 or paced ≥200

AF=atrial fibrillation

SR=sinus rhythm

The mechanisms of non-response to BiV pacing are multi-factorial. The level of functional block is variable in LBBB and dyssychrony may be limited if it occurs at the

terminal fibres of the conduction system. However, patients with narrow QRS complexes exhibit mechanical dyssynchrony with a prevalence of 30-50% (86-88), indicating a sub group of patients that may potentially benefit from BiV pacing. In addition, 30-40% of patients with QRS >120 ms have no evidence of mechanical dyssynchrony which may explain the non-response rate to BiV pacing in patients with QRS >120 ms.

Sub-optimal LV pacing is important. Apical and anterior LV locations are sub-optimal and targeting the region of latest LV activation may improve response rates (89-91). Non-viable myocardium causes conduction delay and is detrimental to resynchronisation, especially if it is present in the basal posterior/lateral LV region, at the preferable site of LV pacing. Enlargement of the left atrium is an adverse marker of response to BiV pacing especially if it is associated with atrial arrhythmias. Finally, for effective LV resynchronisation, a high percentage of BiV pacing (ideally 100%) is required. Atrial arrhythmias, ventricular ectopy and LV lead failure can inhibit BiV pacing leading to non-response (61, 68, 89, 92).

Acute changes in LV after-load can also cause dyssynchrony, even in the presence of normal electrical conduction. In a canine study, clamping the aorta increased after-load, prolonged LV relaxation time and regional shortening became dyssynchronous (93). These findings were supported by Wang et al, demonstrating that reducing after-load with diuretics and vasodilators reversed dyssynchrony in heart failure patients (94). In the absence of electrical dyssynchrony, BiV pacing is ineffective at reversing this load-dependent mechanical dyssynchrony. This is another potential explanation for the reported non-responder rate to BiV pacing.

Echocardiography and CMR techniques have been developed to analyse mechanical dyssynchrony in an attempt to refine the selection criteria for BiV pacing and reduce the non-responder rate. Mechanical dyssynchrony can be observed between the atria and ventricles, between the left and right ventricle and within the left ventricle- AV, inter- and intra-ventricular dyssynchrony respectively (95). In reality, heart failure patients may develop all 3 types of mechanical dyssynchrony to varying degrees of severity.

1.2.3 Intra-ventricular dyssynchrony

Patients with heart failure may develop regional conduction delays that alter the pattern of myocardial depolarisation and reduce stroke volume. Left bundle branch block (LBBB) is a marker of delayed electrical activation and is present in 15-27% of heart failure patients (96). Although there is heterogeneity in the pattern of LV contraction in patients with LBBB, the left basal postero-lateral wall is most frequently the site of late activation. The right antero-septal wall is activated rapidly by the intact right bundle and contracts early but the contralateral wall is quiescent. The basal postero-lateral wall contracts in late systole/early diastole against a relaxing septum. This inefficient pattern of contraction delays the rise in intra-cavity pressure (dP/dT_{max}); reduces ejection fraction by 23%; reduces regional coronary blood flow by 11-19% and myocardial metabolism (97, 98). Late activation of the postero-lateral papillary muscles distorts mitral valve closure and results in mitral regurgitation.

Intra-ventricular dyssynchrony can be assessed using TDI, (figure 2). In this 2 segment model, tissue velocities are measured at the basal septum and lateral walls.

The difference in time to peak systolic velocity is the measurement of intra-ventricular dyssynchrony.

Although it appears logical that intra-ventricular dyssynchrony would be more prevalent in patients with broad QRS widths, a study by Bleeker et al failed to identify a relationship (99). A time delay of >60 ms between peak velocity of the basal septum to lateral wall was used to define mechanical dyssynchrony, (table 2 and figure 2). In a sample of 90 subjects with heart failure and severe LV systolic dysfunction using linear regression analysis, there was no correlation between electrical and intra-ventricular mechanical dyssynchrony.

Figure 2: Measurement of intra-ventricular dyssynchrony- Time to peak velocity in the septal (yellow) and lateral walls (green) for 3 cardiac cycles.

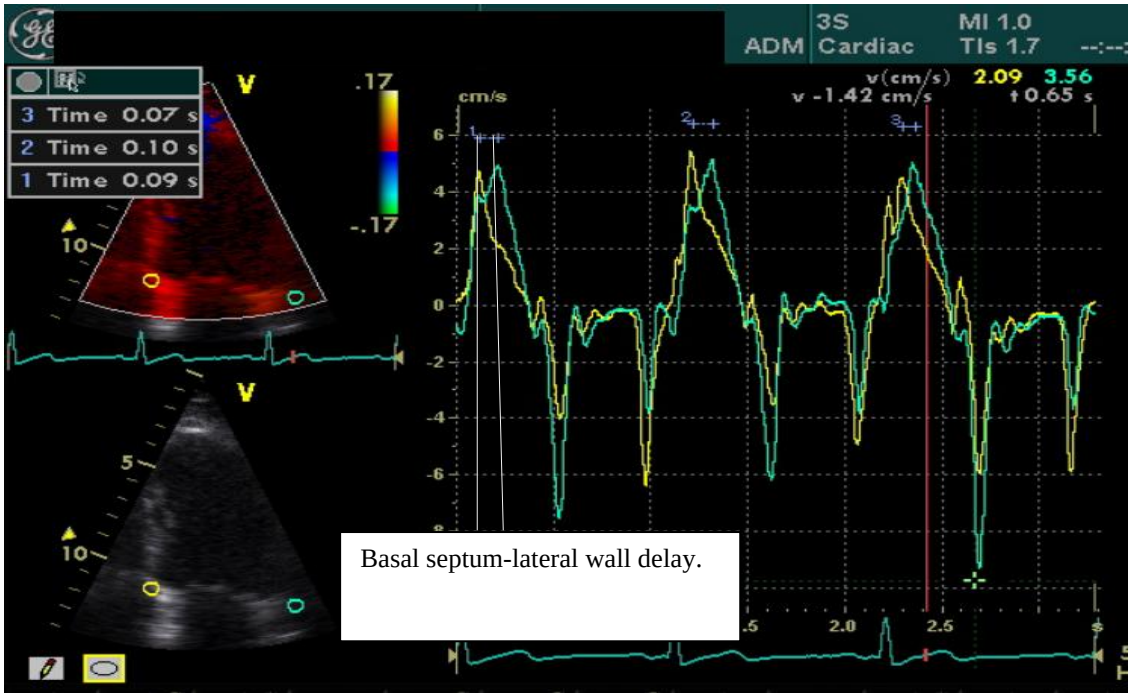
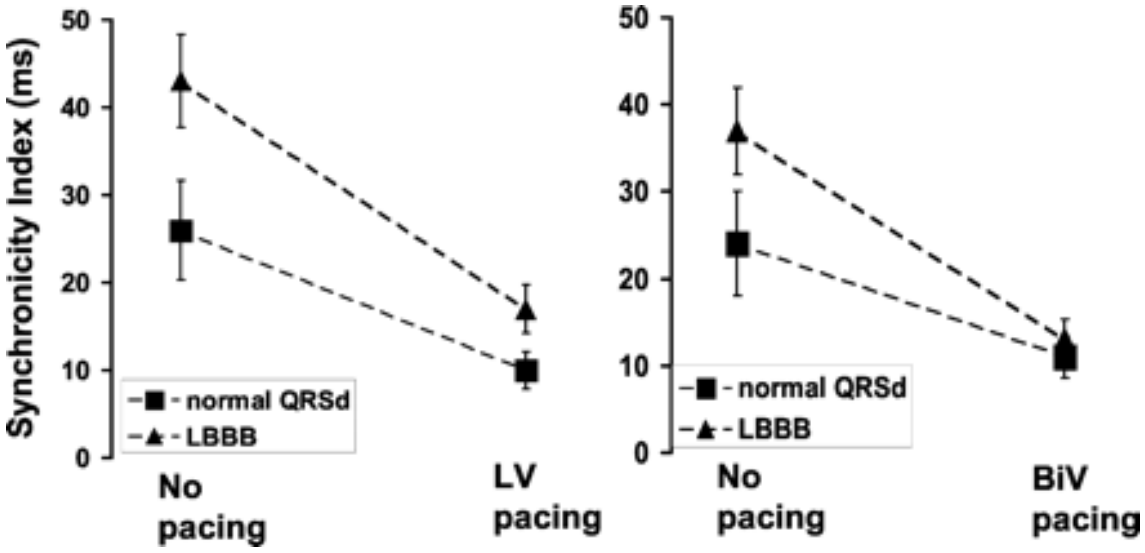


Table 2: Relationship between electrical and intra-ventricular dyssynchrony.

QRS duration /ms	**Mechanical dyssynchrony/%**
<120	27
120-150	60
>150	70

A study by Turner et al investigated the activation patterns of the LV free wall in patients with LBBB compared to narrow QRS durations and severe LV systolic dysfunction. (100). LV free wall activation was prolonged in the LBBB group compared to the narrow QRS group (155±23 ms v 65.5±25 ms; p =0.05). However, late activation of the LV free wall was observed in the narrow QRS group and LV synchronicity could be improved with BiV and LV pacing, see figure 3.

Figure 3: The synchronicity index at baseline and during LV and BiV pacing. LV synchronicity index is improved in both patient groups and with both pacing modes.



Adapted from Turner et al, Circulation 2004 (100).

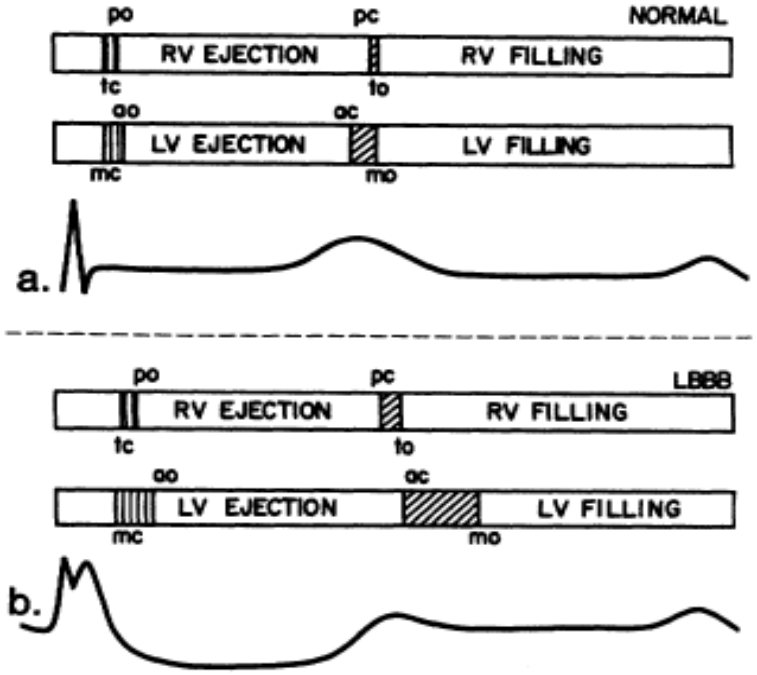
1.2.4 Inter-ventricular dyssynchrony

In healthy individuals, the LV is activated before or at the same time as the RV. A delay in LV activation has been observed in patients with LBBB and reverses this relationship (101). In a study by Grines et al, the pattern of septal wall motion was studied in 18 patients with preserved LV function and QRS >120ms with LBBB morphology (101).

LBBB delayed LV activation by 85 ms compared to normal subjects ($p < 0.001$). The times to aortic valve opening and closing and mitral valve opening were also delayed in the LBBB group. However, the times to mitral valve closure remained constant due to a high proportion of 1^0 AV block in the LBBB group. Therefore, LV filling time was reduced in the LBBB group, reducing pre-load and stroke volume. The

duration of LV isovolumic relaxation was also prolonged (94±31 ms v 36±20 ms in healthy subjects; p <0.0001), see figure 4.

Figure 4: Timing of mechanical events in normal patients (A) and LBBB (B).



In the normal group, LV events occurred before or at the same time as the RV. This relationship was reversed in patients with LBBB. po, to, ao and ao are time of pulmonary, tricuspid, aortic and mitral valve opening and pc, tc, ac and ac time of valve closure, respectively. Adapted from Grines et al, (101).

LBBB also changed the motion of the inter-ventricular septum. Early RV filling displaced the septum into the LV and impeded LV filling. RV ejection occurred during LV isovolumic contraction and displaced the septum towards the RV. LV systole continued after pulmonary valve closure which displaced the septum towards the RV. In diastole, the tricuspid valve opened before the mitral valve displacing the septum towards the LV with a similar pattern with atrial contraction.

Therefore, in patients with LBBB there are several oscillations of the inter-ventricular septum during systole and diastole, hence the term inter-ventricular mechanical dyssynchrony (IVMD). LBBB reduced LV ejection fraction compared to the control group (40±16% v 67±7; $p < 0.001$). BiV pacing is a therapeutic option to reset the timing of filling, contraction and relaxation and reverse IVMD.

Abnormal septal wall motion has also been reported after sternotomy. In an animal study, septal wall motion was observed in 11 pigs, after induction of anaesthesia and sternotomy. Wall motion was recorded, both with the pericardium open and closed and after closing the chest with the pericardium closed and then subsequently re-opened (102).

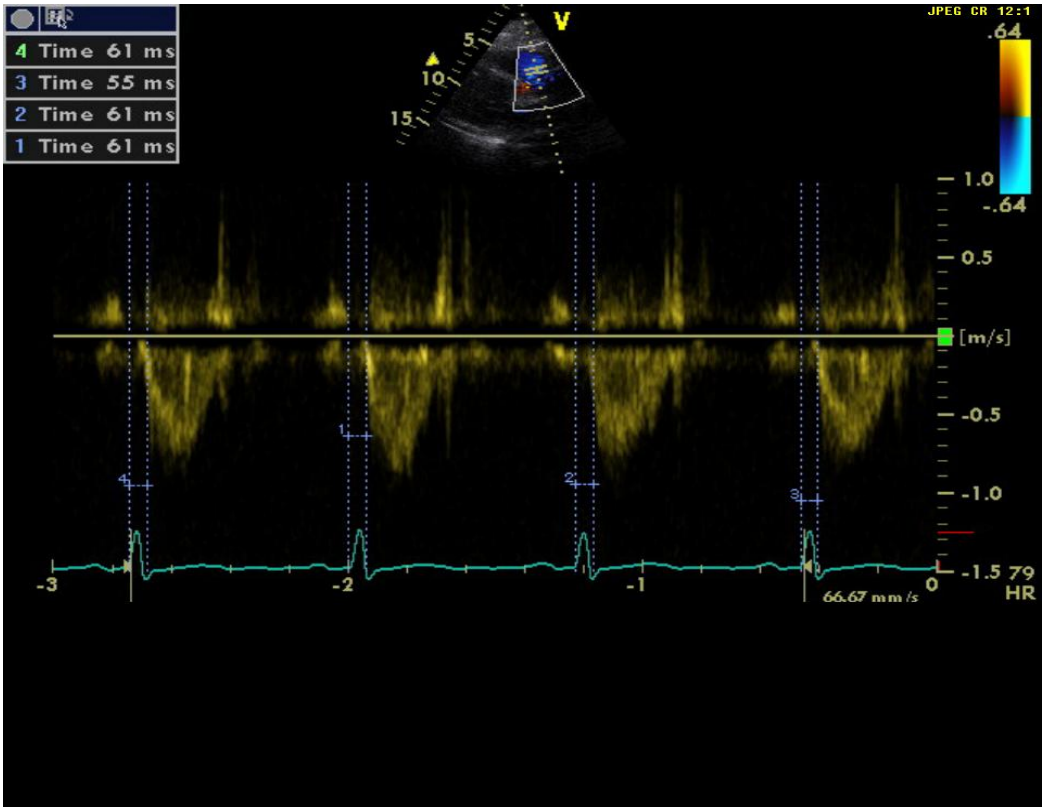
Closing of the pericardium, while the chest wall was open, reduced stroke volume by 19% ($p < 0.05$). Systemic vascular resistance increased by 19% with the chest wall and pericardium both closed ($p < 0.05$). These effects were reversed by re-opening the pericardium. Chest wall closure resulted in a paradoxical motion of the inter-ventricular septum with the pericardium open or closed. Closing the pericardium reduced stroke volume due to the external constraint of the pericardium.

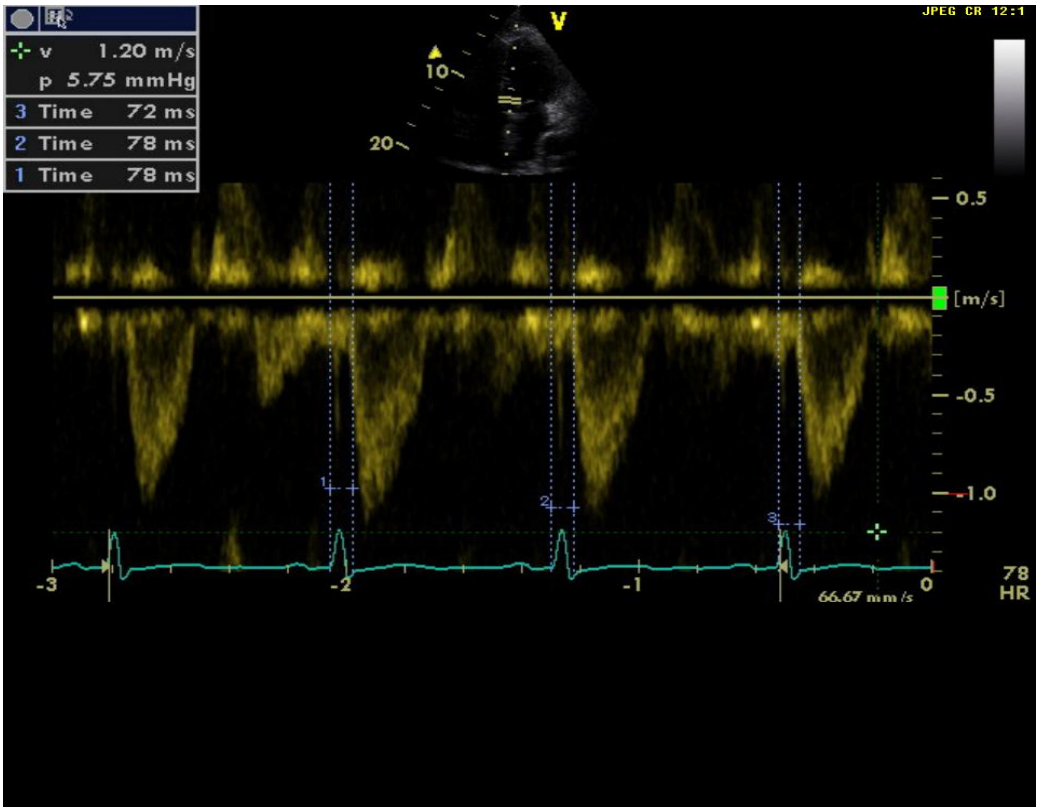
The pattern of septal wall motion is also altered in the presence of RV pressure overload (103). The pattern of septal wall motion was studied in 20 children with congenital heart disease and raised RV pressures and compared to 29 control subjects. Elevated RV pressures (>50% systemic pressure) reduced septal curvature, which was most prominent at the end of systole. Therefore, elevated RV pressure also affects septal wall motion.

The inter-ventricular mechanical interval can be measured using pulsed wave Doppler in the outflow tract of both ventricles (figure 5). Pulsed wave Doppler is

obtained from both the LV and RV outflow tract. The inter-ventricular mechanical interval is calculated by subtracting the LV to RV pre-ejection intervals. This measurement has been used as part of the enrolment criteria in large randomised control trials of BiV pacing including the CARE-HF study (60).

Figure 5: Measurement of inter-ventricular mechanical interval (B-A) using pulsed wave Doppler. A: Pulmonary pre-ejection interval and B: Aortic pre-ejection time.





1.2.5 Diastolic (AV) dyssynchrony

There are 4 phases of diastole: isovolumic relaxation; rapid filling; slow filling (diastasis) and atrial contraction. In healthy hearts, LV filling occurs at low LA pressure into a compliant LV but elevated filling pressures are the principal consequence of diastolic dysfunction. An LVEDP >16mm Hg or pulmonary capillary wedge pressure >12 mm Hg are used as reference values to define raised LV filling pressures (104).

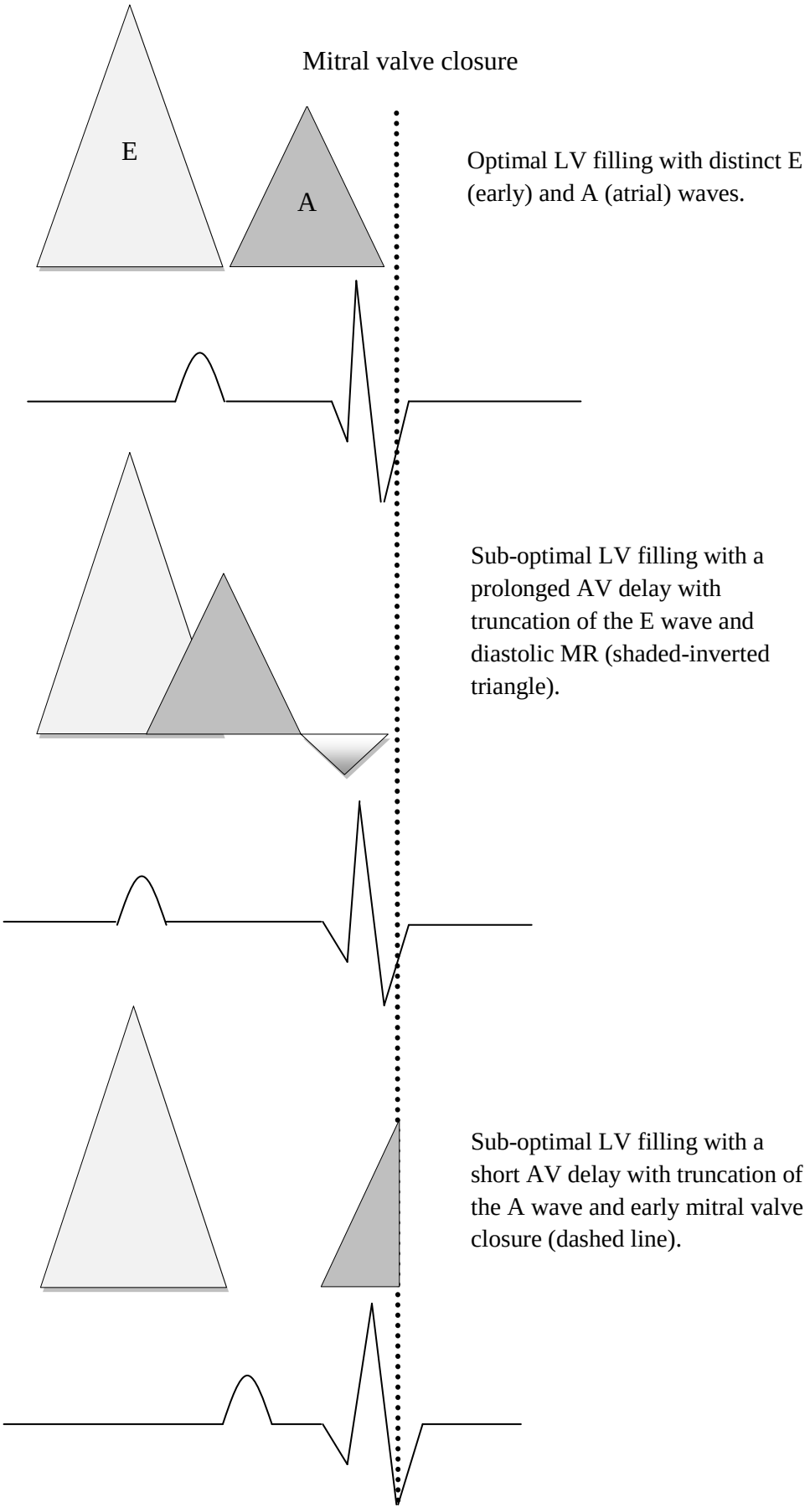
Filling pressures depend on LV compliance and loading conditions. Compliance is affected by myocardial fibrosis, chamber geometry and wall thickness, and extrinsic factors including external pericardial constraint and diastolic ventricular interaction. Increased after-load delays myocardial relaxation and also increases LV filling pressures.

Echocardiography can be utilised to assess diastolic filling (figure 6). To maximise LV filling/pre-load, atrial contraction should occur after a period of early LV filling and before the onset of LV contraction. Prolongation of the AV interval, which can also be indicated by first degree AV block on a 12-lead ECG, truncates early filling due to the premature onset of atrial contraction and blood refluxes back through the mitral valve during diastole (105). A pathologically short AV interval truncates atrial filling with the abrupt onset of LV contraction.

Prolongation of the PR interval is a common problem. 35% of heart failure patients have a PR interval >200 ms. A study of pacing after on-pump cardiac surgery reported that 38% of patients had PR interval >200 ms after separation from the bypass circuit (106). Reversing AV dyssynchrony using an AV optimisation protocol increased cardiac index by 20% compared to intrinsic rhythm (140ms v 220 ms

respectively). The greatest benefit was observed in patients with significant LV systolic impairment.

Figure 6: Patterns of LV filling with optimal and sub-optimal AV intervals.



1.2.6 The utility of mechanical dyssynchrony- The PROSPECT trial

A multi-centre prospective trial was conducted to assess the utility of mechanical dyssynchrony to predict a response to BiV pacing. Twelve measurements were performed for each patient with standard indications for BiV pacing including EF ≤35% and QRS ≥130 ms. The markers of dyssynchrony showed only modest value in both sensitivity and specificity in predicting a response to BiV pacing using both a clinical composite endpoint (table 3) and ≥15% reduction in end-systolic volumes.

Table 3: The predictive value of each individual marker of mechanical dyssynchrony in predicting a response to BiV pacing using the composite clinical score. Adapted from the PROSPECT trial.

Marker	**Yield/%**	**Sensitivity/%**	**Specificity/%**	**AUC**	**p for AUC**
SPWMD	71.0	55.4	50.0	0.54	0.27
IVMD	92.4	55.2	56.4	0.59	0.013
LPEI	94.6	66.3	47.1	0.6	0.001
Ts-(L-S)	66.8	42.4	57.0	0.5	0.85
Ts-SD	50.0	74.1	35.3	0.6	0.024
Ts-peak	82.0	51.9	53.8	0.55	0.19

Key:
SPWMD- septal to posterior wall mechanical delay ; IVMD- inter-ventricular mechanical delay; LPEI- LV pre-ejection interval; Ts-(L-S)- time delay from septal to lateral wall peak velocity; Ts-SD- SD time to peak velocity in 12 segments of LV; Ts-peak (basal)- maximum difference in time to peak velocity in 6 basal LV segments.

There were limitations in the methods used to analyse the data in this trial. The investigators used 3 core laboratories with limited standardisation of protocols especially for the analysis of TDI data. Re-evaluation of data in the core lab also identified that 20% of patients had an EF >40% (107). In addition, PROSPECT only analysed 12 markers of dyssynchrony and excluded techniques such as speckle tracking and more complex 3D models of mechanical dyssynchrony. The time to peak transverse and longitudinal strain predicted a response to BiV pacing in the MADIT-CRT trial but these measurements were not analysed in the PROSPECT trial (61, 95).

Therefore, in spite of the non-responder rate, QRS duration remains the gold standard for selecting patients for permanent BiV pacing, in the absence of a reliable echocardiographic marker of dyssynchrony, from randomised-control trials. This conclusion has been reinforced by the findings of the recently published 'CRT in heart failure with a narrow QRS complex' (ECHO-CRT) trial.

The 'CRT in heart failure with a narrow QRS complex' (ECHO-CRT) investigators reported that BiV pacing (CRT-D) did not reduce mortality or heart failure hospitalisation compared to a control group (ICD-only) with NHYA 3-4 heart failure, QRS <130 ms, EF <35% and mechanical dyssynchrony (108). Dyssynchrony was defined as either an 80 ms delay in opposing-wall time to peak systolic velocity using TDI in the apical 4-chamber or 2-chamber views or 130 ms delay using speckle tracking with radial strain in the mid-parasternal short axis between the septum and posterior wall. The study was stopped on the grounds of futility, after enrolling 809 patients with an average of 19 months follow-up. BiV pacing group had a higher death rate compared to the control group (11.1% v 6.4%; HR 1.81, 95% CI: 1.11-2.93; p=0.02) and more inappropriate ICD discharges, 20 (5%) v 7 (1.7%), p=0.01.

1.2.7 Peri-operative tissue Doppler imaging

Peri-operative TDI has also been investigated as a method of predicting regional recovery after coronary artery bypass surgery (109). Experimental models have shown a close relationship between tissue Doppler velocities and sub-endocardial blood flow (110, 111).

TDI measurements were taken using TTE before induction of anaesthesia and at 6-weeks post-discharge and using TOE after induction and sternotomy but before going into bypass and 4-hours post surgery, while ventilated. Acute changes in peri-operative TDI were highly variable and did not predict functional recovery at 6-weeks after discharge.

1.2.8 Summary

There are limitations in using both electrical and mechanical markers of dyssynchrony to predict a response to BiV pacing. QRS duration and morphology are currently used to select patients for permanent BiV pacing but about 1/3 patients fail to respond to cardiac resynchronisation. Mechanical dyssynchrony is more prevalent in heart failure patients than controls but the clinical utility and reproducibility of these measurements limits their clinical application.

Dyssynchrony may develop *de novo* after cardiac surgery due to IR injury. Invasive ventilation/sternotomy, inotropes, increased loading conditions, ischaemia-reperfusion injury and RV-only pacing are potential explanations. Therefore, in patients with severe LV dysfunction, temporary BiV pacing may be beneficial after on-pump surgery irrespective of baseline QRS duration.

1.3 Acute haemodynamic response to biventricular pacing

Biventricular pacing is achieved by attaching pacing wires to the right atrium, right ventricle and left ventricle. To stimulate the left ventricle, wires are either deployed via the coronary venous network or attached to the epicardial surface of the heart. Biventricular pacing has several mechanisms of optimising cardiac function leading to an acute augmentation of stroke volume and LV filling:

- Systolic resynchronisation: correcting LV lateral wall delayed contraction.
- Increasing LV filling time, reducing LV filling pressures and optimising the AV interval.
- Relief of pericardial constraint/minimising diastolic ventricular interaction
- Reducing secondary and pre-systolic mitral regurgitation.

Pacing studies have been performed to investigate the relationship between haemodynamic status and pacing mode, see table 4. Most studies have compared either intrinsic rhythm or atrial-inhibited pacing (AAI) to atrial synchronous right ventricular pacing (DDD-RV); atrial synchronous BiV pacing (DDD-BIV) and atrial synchronous left ventricular pacing (DDD-LV). The studies listed in table 4 are in patients who had been prescribed optimal medical therapy for heart failure. The 'relative effect' is the relative change in haemodynamic parameter compared to intrinsic rhythm/AAI pacing unless otherwise stated.

Table 4: Acute haemodynamic effect of BiV pacing in heart failure patients–NYHA 3-4.

Investigator	**n**	**PR**	**QRS**	**EF**	**Haemodynamic parameter**	**Relative Effect**	**p**
Yu **(62)**	33	217±53	158±22	24±12	EF	↑25%	0.02
Butter **(112)**	30	194±26	152±77	23±8	dP/dT_{max}	↑12%	<0.01
Blanc **(113)**	27	NA	171±31	27±6	Systolic BP †	↑6%	<0.01
Auricchio **(114)**	27	211±37	168±29	21±6	$+dP/dT_{max}$ †	↑13%	<0.01
Breithardt **(115)**	24	181±41	176±25	21±6	EF dP/dT_{max}	↑24% ↑37%	<0.01 <0.001
Leclerq **(116)**	18	221±52	170±37	19±5	CI	↑35%	<0.001
Kass **(117)**	18	204±69	157±36	19±7	dP/dT_{max}	↑13%	0.001
Breithardt **(118)**	16	211±38	176±4	21±6	$+dP/dT_{max}$ †	↑18%	0.001

Key:

† Haemodynamic comparison of DDD-BiV pacing v DDD-RV pacing.

All other comparisons are between AAI pacing or sinus rhythm and BiV pacing.

NA- Information not available/ result not reported in the published manuscripts.

Yu et al compared BiV pacing to RV pacing and no pacing in 33 heart failure patients with severe LV dysfunction (EF 24.2±12.4%) and intra-ventricular

dyssynchrony (QRS 158±22ms) (62). Biplane ejection fraction, non-invasive $+dP/dT_{max}$ and tissue Doppler characteristics were measured using TTE, 2 days after device implantation. Each pacing mode was programmed for 30 minutes before haemodynamic evaluation. BiV pacing improved EF and $+dP/dT_{max}$ compared to RV pacing and no pacing (EF 30±14% v 25±10% v 24±10%; p=0.02) and ($+dP/dT_{max}$ 795±239 mm Hg/s v 686±227 mm Hg/s v 577±214 mm Hg/s; p=0.04) respectively. BiV pacing also reduced the percentage area of mitral regurgitation (24.0±20.4% v 35.3±25.9% v 34.5±24.6%; p=0.02). A 12-segment model of the LV (6-basal and 6-mid segments) was constructed and the time to peak systolic velocity was measured using TDI. BiV pacing reduced the SD of time to peak velocity of the 12-segments compared to RV and no pacing (32.8±13.5ms v 40.2±14.8 ms v 39.6±13.3 ms; p=0.04).

Blanc et al studied the acute haemodynamic effects of BiV and LV pacing compared to RV pacing (113). 23 patients with EF <35% and mean QRS 171±31ms were included in this study. Transvenous pacing catheters were inserted into the RA appendage, RV apex and then moved to RVOT. The lateral wall of the LV was paced using a retrograde catheter inserted via the aortic valve. Cardiac index was measured using thermodilution PA catheters and blood pressure via a femoral arterial line. Pacing the RVOT did not improve SBP compared to RV apical pacing (116.6 mm Hg v 121.4 mm Hg; p=NS). LV and BiV pacing increased SBP and reduced capillary wedge pressure compared to RV pacing (SBP: 123.3±13.9 mm Hg v 122.1±13.6 mm Hg v 114.9±15.4 mm Hg; p <0.001) and (PCWP: 19.6±5.1 mm Hg v 20.7±5.6 mm Hg v 25.5±5.8 mm Hg; p<0.001) respectively.

Auricchio et al measured invasive $+dP/dT_{max}$ and intra-aortic pulse-pressure in 22 heart failure patients with QRS >120ms, during implantation of a permanent BiV pacemaker under general anaesthesia (114). Haemodynamic measurements were taken

during 5 paced beats followed by 15 non-paced beats in VDD mode with RV, BiV and LV stimulation. All measurements were repeated 5 times. BiV and LV pacing increased LV $+dP/dT_{max}$ by 14.4% and 15.3% compared to RV pacing ($p < 0.05$). The optimal AV interval producing the maximum LV $+dP/dT_{max}$ was 110±14 ms and 98±52 ms for LV and BiV pacing producing a 23% and 22% increase in SBP compared to nominal settings (PR interval-30 ms).

Therefore, acute BiV pacing augments cardiac output in heart failure patients who are prescribed optimal medical therapy, with severe LV systolic dysfunction and intra-ventricular conduction delay. BiV pacing increased ejection fraction by an absolute value of 5-6% (62, 115) and cardiac index 0.7 L/min/m^2 (116) compared to intrinsic rhythm ($p < 0.01$ and $p=0.02$ respectively).

1.4 Biventricular pacing after cardiac surgery

The studies in table 4 have shown a clear pattern than reversing dyssynchrony with BiV pacing produces an acute augmentation in cardiac function.

The next question is whether biventricular pacing can produce similar results and improve LV function after cardiac surgery. It is important to remember that the results in table 4 were produced in patients taking optimal heart failure medications including beta blockers and ACE inhibitors.

Before cardiac surgery, ACE inhibitors are frequently discontinued because of the risk of post-operative renal insufficiency and hypotension (14). Typically, heart rates are increased after surgery because of hypovolaemia and the chronotropic effects of dobutamine, PDE III inhibitors (milrinone/enoximone) or adrenaline.

After surgery, positive pressure ventilation and ischaemia-reperfusion injury may impede the potentially beneficial effects of BiV pacing (44). Positive pressure ventilation increases intra-thoracic pressure and right atrial pressure and reduces systemic venous return/RV pre-load and cardiac output (119-121). RV after-load remains relatively unchanged unless PEEP exceeds 10 mm H_20. Patients with asthma/COPD experience a rapid increase in PVR with ventilation due to collapse of extra-alveolar vessels and/or hypoxia with a significant rise in RV after-load (122). However, PEEP reduces LV after-load and can be beneficial in treating acute pulmonary oedema.

Around 9% of patients develop post-operative AV block and require temporary ventricular pacing (123). This is usually achieved by pacing the right ventricular free wall, which induces intra-ventricular dyssynchrony, which is equivalent to LBBB (123-127). In addition, inotropic 'stress' may prolong the QRS duration by up to 8 ms and prolong the isovolumic period ($p < 0.001$) (128). Therefore, patients with severe LV dysfunction may benefit from LV pacing wires to protect against RV-only pacing after surgery.

1.5 Temporary biventricular pacing after cardiac surgery

Despite the adverse effects of right ventricular pacing and the detrimental effects of cardiac surgery on mechanical dyssynchrony, studies of the beneficial effects of acute biventricular pacing in the post-operative setting have been inconclusive, see table 5. This table illustrates the relative effect of BiV pacing compared to AAI pacing or intrinsic rhythm unless otherwise stated.

Table 5: Results of acute biventricular pacing after cardiac surgery.

Investigator	**n**	**QRS**	**EF**	**Endpoint**	**Effect**	**p**
Straka (129) 2011	18	>120	24±4	Cardiac output	↑22%	<0.001
				Cardiac index	↑21%	<0.001
Eberhardt (130) 2009	94	110±16	35±4	Cardiac index	NS	NS
				NT-PRO-BNP	NS	NS
				SV02	NS	NS
				MAP	NS	NS
Hanke (131) 2009	21	98±17	29±6	Cardiac index†	↑11%	<0.05
				dP/dT_{max}	↑18%	<0.01
Evonich (132) 2008	40	111±30	23±6	Cardiac index	NS	0.83
				MAP	NS	0.52
Muehlschlegel (133) 2008	10	117±37	35±6	Cardiac output†	↑4%	0.3
Schmidt (134) 2007	26	132±25	27±7	Cardiac index	NS	NS
				PAP	NS	NS
				PCWP	NS	NS
Flynn (135) 2005	25	<120	33±10	Cardiac index*	↑12%	<0.02
				LVSWI	↑15%	<0.01
				MAP	↑5%	<0.01
Saxon (136) 1998	11	139±39	<35%	FAC (TOE)	↑21%	<0.01
Foster (137) 1995	18	NA	>40%	Cardiac Index	↑8%	<0.05

Key:

*= comparison of atrial-LV posterior wall pacing to dual chamber RV pacing.

†= comparison of BiV pacing to dual chamber RV pacing.

NS= p value non-significant, exact value not published.

Eberhardt et al (130) performed the largest haemodynamic study of temporary post-operative BiV pacing (n=96). This trial included patients undergoing CABG with an EF <40% and pacing was continued for 96 hours after surgery. 94% had narrow QRS durations <120ms, mean duration 100±16 ms and 6% had a bundle-branch block. Patients were excluded if they developed post-operative atrial fibrillation and did not cardiovert with amiodarone or electrical defibrillation.

Patients were randomly assigned to either post-operative BiV pacing, DDD-RVOT pacing or AAI pacing. Pacing was initiated prior to separation from cardio-pulmonary bypass circuit, at a rate of 90 beats per minute for 96 hours with an AV interval 120ms for BiV pacing and 150 ms for DDD-RVOT pacing. Cardiac index was measured using a PA catheter. The index was the average of 3 thermodilution measurements.

BiV pacing did not improve haemodynamic function (cardiac index or LV cardiac power index) or reduce the median duration of ITU admission compared to AAI or atrial synchronous-RVOT pacing: (ITU duration: 20 hours v 19 hours v 21 hours respectively; p=NS). The frequencies of post-operative arrhythmias, renal failure and IABP insertion were not influenced by pacing mode. Post-operative NT-pro-BNP, TnT and mixed venous oxygen saturations were similar in all 3 groups. 3 patients in the BiV group required post-operative IABP and 1 patient in the AAI group and 2 patients in the BiV group and 1 patient in the DDD-RVOT group required post-operative haemofiltration.

At 30-days, 1 patient in each group had died (n=3) and 1 patient in the DDD-RVOT group had a stroke. This trial concluded that BiV pacing was feasible after

cardiac surgery but there was no clear advantage with BiV pacing compared to AAI or atrial synchronous-RVOT pacing.

Although Eberhardt reported that BiV pacing was similar to atrial inhibited and RV pacing, an initial study by Hanke et al reported improved haemodynamic function with BiV pacing compared to RV pacing in the operating theatre (131). Hanke et al, studied the haemodynamic effect of temporary BiV pacing (n=21) in patients with narrow QRS and EF <35%. Haemodynamic function was measured using pressure-volume (PV) loop analysis, 15-30 minutes after separation from the cardio-pulmonary bypass circuit. PV loops were recorded 30 seconds after changing pacing mode. Haemodynamic data were collected during AAI pacing and dual chamber BiV and LV pacing compared to RV outflow tract pacing.

BiV pacing improved cardiac index by 0.22 L/min/m^2 compared to RV pacing. All pacing modes improved $+dP/dT_{max}$ and $- dP/dT_{max}$, end-systolic elastance and ventriculo-arterial coupling compared to RV pacing- (991±263 mm Hg/s v 841±236 mm Hg/s; 0.87±0.24 mm Hg/ml v 0.79±0.22 mm Hg/ml; 0.775±0.667 v 0.682± 0.232 BiV v RV pacing respectively; $p<0.05$). This study only measured cardiac parameters for a brief period of time while the sternum was open. However, it suggests that BiV or LV pacing is superior to RVOT pacing in patients with post-operative AV block. However, there was no advantage to BiV/LV pacing compared to AAI pacing in patients with intact AV conduction.

Straka et al studied the effect of BiV pacing compared to LV and RV pacing within 72 hours of bypass surgery in 21 patients with severe LV dysfunction EF <35% and either QRS >150ms or >120 ms with mechanical dyssynchrony on 3D TOE (129). Mechanical dyssynchrony was assessed using the systolic dyssynchrony index. This index is the standard deviation of the time to minimum LV systolic volume in all of the 16 segments of the LV. The index is expressed as a percentage of the RR interval to eliminate the effects heart rate variability. The site of LV pacing was also defined by the site of latest activation using a bull's-eye map of LV segment activation before surgery. The RV leads were attached adjacent to the septum in the lower third of the anterior wall. The AV and VV intervals were also optimised using the velocity time integral (VTI) of mitral inflow and LV outflow tract VTI respectively.

Haemodynamic measurements were taken on arrival to the ITU and at 24, 48 and 72 hours after surgery using thermodilution catheters. 11 patients had valve surgery but the cardio-pulmonary bypass time was similar to Eberhardt's study (130): 113±34 mins v 105±39 mins, respectively. The sites of latest LV activation were mid-anterolateral (33%), basal-anterolateral (19%) and basal inferolateral (19%) segments. The optimal AV interval was 152±19 ms, and 11/20 patients benefited from LV pre-activation.

BiV pacing and LV pacing were superior to RV pacing: they increased MAP (77±10 mm Hg v 78±9 mm Hg v 73 mm Hg; p=0.03); cardiac output (6.7±1.7 L/min v 6.2±1.5 L/min v 5.4±1.4 L/min; p=0.01) and LV stroke work index g.m/m^2 (8.6±2.7 v 8.1±3 v 7±2.4; p=0.0025). There was no difference in pulmonary vascular resistance between pacing modes. The durations of inotropic support and ITU admission were shorter in the BiV and LV paced groups compared to RV pacing: inotropic duration

/days (2.8±2.3 v 1.9±1.5 v 5.1±2.6 days; $p < 0.05$) and ITU duration /days (3.1±1.9 v 2.6±1.2 v 4.1±2.1) respectively.

Evonich et al (132) enrolled 40 patients with severe LV dysfunction and narrow QRS duration into 3 treatment groups after cardiac surgery: 'usual care', atrial-right ventricular and atrial-BiV pacing. The primary endpoint was the duration of ITU admission and secondary endpoints included haemodynamic studies using a PA catheter. 29/40 patients completed the haemodynamic studies at 12 hours. This study included patients with IABP (n=11) and valve surgery (n=16). There was no overall difference in cardiac output, stroke volume or mean arterial pressure between atrial only and BiV pacing. A trend was observed that BiV pacing may be beneficial in patients with lower ejection fractions compared to atrial-only pacing. However, atrial-only pacing was superior to atrial-right ventricular pacing.

The duration of ITU admission was not influenced by pacing mode. There was a high cross-over of patients from their assigned pacing mode (n=10) and the primary endpoint was analysed using both intention to treat and on-treatment analyses. This study suggested that if patients require ventricular pacing because of AV block, BiV pacing would appear preferable to right ventricular only pacing.

Flynn et al (135) studied the acute haemodynamic effects of BiV pacing using similar pacing modes to Foster et al (137). The patients enrolled by Flynn had a lower ejection fraction and narrow QRS durations. This study of 25 patients also compared LV pacing in 2 separate sites, the anterior and posterior walls of the LV. Both LV sites improved LV stroke work index compared to RV pacing. However, only posterior wall LV pacing improved cardiac index by 12% compared to RV pacing.

Foster et al (137) studied the acute haemodynamic effects of pacing mode on cardiac index using thermodilution catheters 12-36 hours after cardiac surgery. Pacing leads were attached to the right atrium, and the para-septal regions of the right and left ventricle. Haemodynamic studies were performed after 10 minutes of over-drive pacing using AV sequential pacing and stimulation of the right ventricle, left ventricle and both ventricles simultaneously. Most patients (14/18) had an ejection fraction greater than 40%. BiV pacing produced a significant 8% improvement in cardiac index compared to the other pacing modes ($p<0.05$) but no overall change in mean arterial pressure or pulmonary diastolic pressures.

In summary, the largest study of post-operative BiV pacing reported that BiV pacing was similar to RV pacing (130). The results may have been influenced by the site of RV pacing (RVOT rather than RV apex), the exclusion of AV/VV optimisation protocols, and LV pacing at a fixed location rather than the site of latest LV activation.

The study by Straka et al (129) addressed these issues and also enrolled patients with pre-operative dyssynchrony defined as QRS >120ms. The investigators reported that BiV pacing improved cardiac index by 24% and reduced the duration of inotropic support by 2.3 days. Therefore, selecting patients with either baseline dyssynchrony or including optimisation protocols may be required for patients to benefit from BiV pacing after cardiac surgery.

1.5.1 Permanent biventricular pacing after cardiac surgery

Pokushalov et al conducted the largest trial of post-operative BiV pacing. 178 patients received a permanent epicardial CRT pacemaker after surgical revascularisation and half received BiV pacing (CRT 'on') and the other half did not (CRT 'off'). All

patients had a diagnosis of heart failure with severe LV systolic dysfunction (EF ≤35%) and baseline dyssynchrony (138). Baseline dyssynchrony included: QRS duration >120 ms; aortic pre-ejection delay >140 ms; inter-ventricular mechanical delay >40 ms or intra-ventricular dyssynchrony using tissue tracking or tissue Doppler imaging.

The primary endpoint of total mortality at 18 months and duration of ITU stay was lower in the BiV pacing group compared to the control arm of the study (10% v 26.1%; p=0.006 and 2.5±0.5 days v 3.9±0.6 days respectively). Remodelling and reversal of dyssynchrony was only observed in the CRT 'on' group with a 12% increase in EF compared to baseline (p<0.001). Heart failure hospitalisation was reduced in the CRT arm of the study (6.6% v 21.9%) and NYHA class (2.2±0.7 v 3.5±0.3, p<0.001) compared to CABG-only. Dyssynchrony was identified as an independent marker of all-cause mortality and heart failure hospitalisation.

However, this study did not measure acute haemodynamic function after cardiac surgery. It would have been interesting to see if the reversal of dyssynchrony with BiV pacing improved acute haemodynamic function. In addition, the study protocol did not address the issue of protecting patients from sudden arrhythmic cardiac death. The patients were not assessed after revascularisation for an implantable defibrillator in either treatment group. Finally, the investigators did not report any improvement in LV ejection fraction with CABG-only. Although myocardial viability was not formally assessed, revascularisation of viable/hibernating myocardium should yield an improvement in ejection fraction (4).

1.5.2 Left ventricular size

Dzemali et al (139) studied the effect of temporary BiV pacing in 80 patients after cardiac surgery with pre-operative EF <35%. Patients were divided into 2 cohorts depending on LV size: dilated (mean LVEDD 65±5mm) and normal/mildly dilated LV (mean LVEDD 52±4mm). Cardiac index and blood pressure were measured at baseline, 6 hours and 24 hours after the operation. 67.5% (n=27/40) in the dilated LV group and 55% (n=22/40) in the normal size LV group showed a haemodynamic response to BiV pacing.

In patients with dilated LV, BiV pacing reduced the duration of ventilation and intensive care admission compared to atrial synchronous right ventricular pacing and baseline QRS duration did not predict a haemodynamic response to BiV pacing. Therefore, patients with dilated LV respond better to BiV pacing after cardiac surgery compared to patients with normal sized LV but both groups had responders to BiV pacing. Acute BiV pacing did not augment cardiac index in around 1/3 patients with dilated LV.

1.5.3 Left ventricular pacing site

The previous haemodynamic studies of BiV pacing (see table 4 and 5) have implanted the LV leads in different locations, including: para-septal, anterior and posterior walls. Flynn et al (135) demonstrated that posterior but not anterior LV pacing during BiV stimulation improved cardiac index compared to RV pacing.

The investigators of the large randomised trials of BiV pacing have performed post-hoc analyses of outcome determined by the site of LV pacing. The data from MADIT-CRT (n=799) were analysed in reference to LV lead position and the primary

outcome of heart failure hospitalisation or death (89). The primary endpoint of heart failure hospitalisation or death and the secondary endpoint of total mortality were increased with apical v non-apical pacing (HR 1.72; 95% CI 1.09-2.71, p=0.019 and HR 2.91; 95% CI 1.42-5.97, p= 0.04 respectively). Pacing the anterior, lateral or posterior LV wall did not affect these outcome measures. The COMPANION trial (n=1520) found that a lateral LV lead positioning produced the best acute haemodynamic response to BiV pacing but all lead positions improved functional class, 6 minute walk distance and quality of life score (90). Therefore, non-apical pacing appears better than apical pacing (89) and the data also suggest that a lateral lead position is best although this is less robust (90). An advantage of attaching temporary wires to the heart after cardiac surgery is that lead position is not limited by the venous anatomy of the heart which is a constraint with transvenous pacing.

There are data to support post-operative pacing at the site of latest LV activation (129). This technique has been used when implanting permanent BiV devices to achieve optimal invasive $+dP/dT_{max}$ which may also predict LV remodelling (91). However, it is possible that the site of latest activation may alter after cardio-pulmonary bypass. In addition, the temporary leads are attached during weaning from the bypass circuit, when the heart is under-filled and hypo-contractile after cardioplegia. This makes this technique technically more difficult.

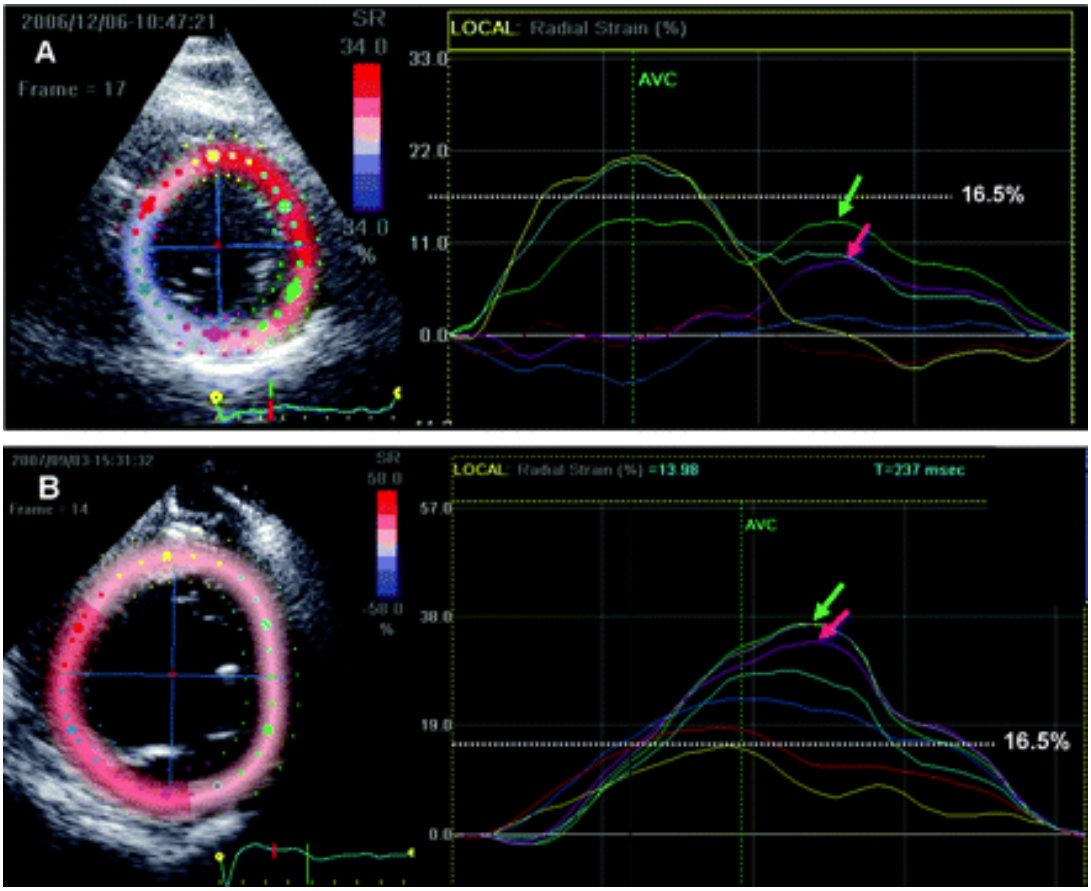
The trial by Straka et al (also discussed in section 1.5) investigated the acute haemodynamic effect of BiV pacing after cardiac surgery in 21 patients with QRS >150ms or QRS >120ms with mechanical dyssynchrony and EF <35% (129). 3D TOE tissue Doppler was used to identify the site of latest LV activation before surgery and the AV/VV intervals were optimised.

The mid-anterolateral segment of the LV was the most frequent site of latest activation, in 33%, but the optimal site was highly variable. BiV pacing also increased cardiac index by 25% ($p<0.001$) compared to RV pacing. However, the incremental benefits of AV/VV optimisation and optimal compared to nominal LV pacing sites were not reported.

Implanting the LV lead at the site of latest LV activation has also been investigated in patients receiving permanent BiV pacemakers (140). In the TARGET trial, 220 patients with conventional indications for BiV pacing had an echocardiogram. Using speckle tracking, radial strain was used to identify the region of latest LV activation and avoid pacing within scar tissue. Targeted LV pacing was compared to unguided lead implantation. The primary endpoint was a ≥15% reduction in LV end-systolic volume at 6-months. There was an absolute increase of 15% (70% v 55%) in LV remodelling with targeted lead implantation compared to unguided implantation (95% CI: 2-28%; $p=0.031$). The posterior or lateral walls were the latest site of LV activation in 70% of patients.

In a similar study, Delgado et al reported in 397 patients, that concordant LV pacing reduced mortality compared to discordant pacing at 3-year follow up (80% v 54%; log-rank $p <0.001$) (141). LV leads placed within a region of scar tissue (>50% LV wall thickness, identified by peak radial strain <16.5%) reduced survival by 29% at 3-years, compared to no scar tissue (58% v 87%; log-rank $p <0.001$) (figure 7).

Figure 7: Time to peak radial strain using speckle tracking.



Assessment of segmental peak radial strain by 2-dimensional speckle tracking imaging. From the time–radial strain curves, peak radial strain can be quantified for each segment in which the left ventricle is divided. A pre-established cutoff value of 16.5% defines the presence of transmural myocardial scar-A, An example of a patient with myocardial scar in the latest activated segments (lateral and posterior segments; peak radial strain <16.5%; arrows). B, In contrast, an example of a patient without myocardial scar in the latest activated segments (peak radial strain >16.5%; arrows).
Adapted from Delgado et al (141).

Therefore, pacing outside of scar tissue and at the site of latest activation is associated with improved LV remodelling and survival compared to standard unguided techniques. After cardiac surgery, transmural infarction may be identified by inspecting the heart, before implanting the temporary epicardial wires to avoid pacing over scar tissue. Likewise, imaging techniques can be utilised to guide LV lead position, at the

site of latest LV activation. If this is not feasible, then the posterior or lateral LV walls are the favoured locations for LV pacing.

1.6 Optimisation of timing cycles (AV and VV intervals)

The studies of haemodynamic response to BiV pacing listed in table 4 and 5, with the exception of the study by Straka et al (129), have used nominal AV intervals and simultaneous RV and LV activation. However, the haemodynamic response to BiV pacing may be enhanced by optimising the AV/ VV pacing intervals.

1.6.1 Atrio-ventricular interval (AV) optimisation

Optimisation of the AV interval can augment LV filling and subsequent stroke volume (figure 6). However, it appears that the optimal AV interval varies for each individual patient hence the variation optimal AV delays reported in table 6.

There are several methods of optimising the AV interval including: echocardiography; PA catheters (cardiac output/index); pressure-volume loops; invasive dP/dT_{max}; mean arterial blood pressure monitoring; finger plethysmography and impedance cardiography.

In clinical practice, optimisation of permanent BiV devices is usually performed using echocardiography due to its availability and non-invasive technique. Methods of optimisation include: measuring the VTI of the pulsed mitral inflow; direct visualisation of the E and A filling pattern, the 'iterative method' and measuring the VTI of the LV outflow tract (stroke distance) (142). Previous studies have reported significant improvements in haemodynamic function with optimisation of pacing intervals assessed

using serial measurements of invasive dP/dT_{max}, blood pressure and cardiac output (table 6).

Table 6: Beneficial effects of AV interval optimisation on haemodynamic function.

Trial	n	Opt Method	Effect of Opt	Timing of Opt	Optimal AV delay (ms)	VV opt
PATH-CHF **(77)**	41	Invasive LV dP/dT_{max}	↑17%	Implant	112±33	No
Auricchio **(114)**	27	Invasive LV dP/dT_{max}	↑22%	Implant	98±52	Yes
Van Gelder **(143)**	34	Invasive LV dP/dT_{max}	↑10%	Implant	147±32	Yes
Heinroth **(144)**	46	Impedance	↑11% CO	3-5 days	119	Yes
Butter **(145)**	57	FPPG	↑16.1 Invasive APP	Implant		No
Whinnett **(146)**	15	FPPG	↑21 mm Hg systolic BP	3-30 months	168	Yes
Meluzin **(147)**	18	Echo: mitral inflow	↑0.2 L/min CO by Swan Ganz	3 months	148±17	No
Riedlbauchova **(148)**	19	Echo: LVOT CO	↑0.6 L/min LVOT CO		140	Yes
Vidal **(149)**	100	Echo: Iterative MV inflow	↑0.7 L/min CO by aortic valve VTI	24-72 hours	137	Yes

Key:
APP- aortic pulse pressure
FPPG- Finger plethysmography.
Opt- Optimisation.

Auricchio et al reported a 22% increase in $+dP/dT_{max}$ by optimising the AV interval in 27 patients in sinus rhythm with moderate to severe heart failure and prolonged AV delay (PR interval ≥150ms) and intra-ventricular delay (QRS ≥150 ms) (114). There was substantial variation in the optimal AV interval, which measured 98 ±52 ms. Therefore, every patient required a haemodynamic study to define their optimal pacing intervals.

Likewise, the 'Pacing Therapies in Chronic Heart Failure' (PATH-CHF) trial investigated the acute haemodynamic response to AV optimised pacing and the long term benefit of resynchronisation, in subjects with heart failure and intra-ventricular delay (77). Optimisation of the AV delay at implantation augmented invasive $+dP/dT_{max}$ (+17 ±15.8%; $p < 0.001$) compared to intrinsic PR interval. The optimal AV interval was shorter than the intrinsic PR interval (112 ±15.8 ms v 190 ±34 ms, respectively). After 1 year, BiV pacing produced significant improvements in oxygen uptake during exercise, and in a 6 minute walk test ($p < 0.05$).

Prospective randomised control trials of cardiac resynchronisation have included AV optimisation protocols. The COMPANION trial (150) used a device-based algorithm and the MUSTIC (75), MIRACLE (78) and CARE-HF (60) trials used pulsed mitral inflow patterns on transthoracic echocardiography to predict the optimal AV delay. However, there is a limitation to these trials in that the clinical benefit of AV optimisation could not be quantified in the absence of a BiV pacing control group with nominal pacemaker settings.

1.6.2 Inter-ventricular interval (VV) optimisation

The presence of LV scar is a potential explanation for the failure to demonstrate a response to BiV pacing. Scar tissue may delay the propagation of LV depolarisation and hence lead to ineffective cardiac resynchronisation. Therefore, optimal LV lead placement should avoid scar tissue and target the region of latest LV activation.

LV lead placement is more of a problem with transvenous pacing. The options for LV pacing are limited by suitable conduits to accommodate a pacing wire but epicardial pacing is not restricted by the venous anatomy of the heart. Epicardial pacing wires can be placed away from transmural scar, but subendocardial scar may be difficult to visualise from the epicardial surface of the heart.

LV pre-activation may be a potential solution to sub-optimal LV lead placement and optimise response rates to BiV pacing. Pre-activation of the LV (or RV) may compensate for areas of slow conduction. The clinical benefit of VV optimisation is illustrated in table 7.

Table 7: Effects of VV optimisation of parameters of LV function.

Trial	n	Optimisation Method	Timing of Optimisation	Effect of Optimisation
Rao (151)	306	Device algorithm	2 weeks	None
Leon (152) (Insynch III)	359	Echo LVOT VTI	Pre-discharge	↑7.3% stroke volume ↑15.1m 6MWT
Boriani (153)	121	Echo LVOT VTI		None
Bordachar (154)	41	Echo LVOT VTI	Implant	↑0.8 L/m CO
Sogaard (155)	20	Tissue Doppler	24 hours	↑3.9% LVEF ↑7% DFT
Vidal (149)	100	Tissue Doppler	24-72 hours	↑0.7 L/min CO
Van Gelder (156)	53	Invasive dP/dT_{max}	<24 hours	↑8% dP/dT_{max}

These studies have used echocardiography, invasive $+dP/dT_{max}$ and CRT device algorithms to optimise the VV interval. The study by Rao et al (151) was designed to show equivalence of simultaneous BiV pacing, sequential BiV pacing and LV pacing. The sequential pacing group were VV optimised using a device based algorithm (CRT device- CONTAK RENEWAL, Boston Scientific). The device recorded intra-cardiac electrograms during device implant to predict the optimal VV interval. A similar algorithm was used to calculate the optimal AV interval for all patients. This aimed to maximise the percentage of BiV pacing.

An improvement in stroke volume and ejection fraction was observed in all groups compared to baseline. There was no additional advantage of VV optimisation compared to simultaneous BiV pacing with respect to LV remodelling, stroke volumes or indices of diastolic function.

However, echocardiogram guided optimisation using LV outflow tract VTI has been reported to improve stroke volume, 6 minute walk distance and cardiac output (152, 154). Leon et al (152) measured the change in stroke volume with VV optimisation compared to simultaneous pacing in 422 patients with NHYA III/IV, EF <35%, QRS >130ms, LVEDD >55mm. At 6 months, 88% of patients benefitted from VV interval optimisation, but only 7.3% achieved a >20% in stroke volume, compared to simultaneous VV pacing.

Boriani et al (153) compared simultaneous (n=31) to sequential (n=90) BiV pacing in heart failure patients with severe LV systolic impairment. Both treatment arms improved heart failure symptoms and 6 minute walk test but there were no differences between the 2 groups at 6 months.

Sogaard et al (155) studied the effects of VV optimisation in 20 patients with NHYA 3-4 symptoms, QRS >130ms, EF <35%. Post device implant echocardiography revealed a 7.3% increase in EF with BiV pacing compared to no pacing and a further 3.9% increase in EF and a 9% reduction in LV end-systolic volume with VV optimisation ($p < 0.05$).

Vidal et al (149) compared BiV pacing with a nominal AV interval of 120 ms and sequential BiV pacing to echocardiogram-guided AV and VV optimised patients with EF <35% and QRS >120ms. At 6 months, optimisation improved 6 minute walk distance by 104 m ($p < 0.01$) and cardiac output (4.3±1.4 L/min v 3.6±0.5 L/min;

p<0.05) compared to nominal settings but heart failure symptoms were similar in both groups. This study optimised both AV and VV intervals and did not report separate results on the incremental benefit of VV optimisation. However, Van Gelder et al (156) reported a significant improvement in invasive $+dP/dT_{max}$ with VV optimisation, in 53 heart failure patients, NHYA 3-4 patients, QRS >150 ms and EF <35%. VV optimisation increased $+dP/dT_{max}$ by 8% and LV pre-activation increased $+dP/dT_{max}$ in 73% of patients.

1.6.3 AV/VV interval optimisation of BiV pacing after cardiac surgery

The data in table 6 and 7 support the argument that the AV and VV intervals should be optimised in patients receiving BiV pacing. However, at the start of this research project in 2009, there were limited data on the clinical utility of optimising temporary BiV pacing after cardiac surgery.

Wang et al studied the effect of AV and VV optimisation in 20 patients in sinus rhythm with EF 33±15% and QRS 116±19 ms, after separation from the cardiac bypass circuit and using a flow probe attached to the aorta (157). The LV wire was attached to the basal segment adjacent to the circumflex artery. A range of AV intervals from 90 to 270 ms using 30 ms increments, and VV intervals from -80 to +80 ms using 20 ms increments, were selected: the negative vector indicated LV pre-activation.

The optimal AV interval was 171±8 ms and optimisation improved flow by 14% compared with the worst setting (111±11 ms; p <0.001) and 7% compared with the nominal AV interval (120 ms; p <0.001). VV optimisation increased flow by 10% compared with the worst settings (p <0.001) and 5% compared with nominal settings (p <0.001). Overall, optimised BiV pacing improved flow by 13% compared to atrial-

only pacing at a matched heart rate (5.5±0.5 v 4.9±0.6 L/min; p=0.003). These data were collected in the operating theatre before closing the chest wall.

The second phase of this trial was reported by Rubinstein et al in 2012 (158). Mean arterial pressure was recorded from 30 patients (this included the 20 patients enrolled by Wang et al), after closure of the chest. Optimising the AV interval increased MAP by 7% and 4% compared to the worst and nominal (120ms) AV intervals respectively ($p < 0.001$). Optimisation of the VV interval increased MAP by 7% and 3% compared to the worst and nominal (VV=0) VV intervals respectively ($p < 0.01$). Optimised temporary BiV pacing failed to augment MAP in approximately 30% of patients.

Garcia et al (159) studied the effect of pacing mode on cardiac output using thermodilution catheters in 50 patients after on-pump cardiac surgery. This was a heterogeneous population with 2/3 patients having valve replacements and only 1/3 coronary revascularisation. The whole spectrum of ejection fractions was studied with 50% having preserved EF and only 14% EF <35%. In addition, 16% of patients were in AF before surgery. The LV wires were attached to the posterior wall. A dual-chamber temporary pacemaker was used which allowed AV optimisation for patients in sinus rhythm. For patients in AF, VV optimisation was performed.

Atrial synchronous LV pacing increased the cardiac output by 7.5% (0.4 L/min) in patients with EF <35% compared to baseline measurements. However, atrial synchronous RV pacing decreased cardiac output by 2.3% in all groups of patients irrespective of baseline ejection fraction ($p<0.05$).

The study did not clearly define the ‘basal’ pacing mode and the heart rate was increased by 10% to perform the pacing studies, which would affect cardiac output.

Neither did the author report stroke volume, which would help compare the haemodynamic effect of pacing to baseline measurements. Finally, no data were presented for AV or VV optimisation, which was described in the methods section.

Therefore, only 2 studies have presented data on AV and VV optimisation of temporary epicardial pacing after cardiac surgery. Optimisation of pacing intervals improved cardiac output and MAP (157, 158) and appears to be beneficial. The data to support optimised BiV pacing after cardiac surgery are limited and further studies are required to confirm these findings.

1.7 Haemodynamic monitoring

Patients with impaired LV function are at increased risk of developing post-operative SIR syndrome, ischaemia-reperfusion injury and low-output cardiac failure (22, 23, 37). Therefore, monitoring central venous pressure, cardiac output and systemic vascular resistance can be helpful, to manage post-operative fluid resuscitation, and the requirements for inotropes and vasoconstrictors (160). Historically, pulmonary arterial (PA) catheters have been used to measure cardiac output. However, the invasive nature of this device along with its potential complications has led to interest in developing less invasive methods of haemodynamic monitoring.

The initial PA catheters were ‘stiff’ and the current design of a catheter with a balloon floatation device was only introduced in the 1970s. Further refinement of the catheters allowed measurement of cardiac output using thermodiluation, mixed venous oxygen saturations and PA wedge pressure. The principal complications associated with PA catheters include: complications from obtaining vascular access including arterial

puncture (1.9%); pneumothorax (0.5%); venous thrombosis (2-7%) and air embolus; ventricular arrhythmias (<1%); pulmonary infarction; injury to chordae of the tricuspid valve (0.9%); bacteraemia (1-2%) and pulmonary artery rupture (0.03%) (161).

A randomised clinical study of PA catheters compared to a control group (without PA catheters) was performed prospectively in over 1,000 patients in 65 critical care units in the UK (162). In a general population of intensive care patients, monitoring with a PA catheter failed to reduce in-hospital mortality compared to the control group (68% v 66%; HR 1.09; 95% CI 0.94-1.27; p=0.39). A complication rate of 9.5% was associated with using a PA catheter, although no complications were fatal. A prospective, observational study of 5735 patients admitted to critical care reported that PA catheters were associated with an increased 30-day mortality compared to patients who did not receive a PA catheter (OR 1.24; 95% CI 1.03-1.49) (163).

Alternative methods of measuring cardiac function include: the PiCCO (Pulsion Medical Systems, Munich, Germany) and LiDCO (LiDCO, Cambridge, UK) systems that analyse the arterial pulse-wave. However, both systems require invasive calibration by trans-pulmonary thermodilution and the PiCCO system also requires central venous access.

The Flotrac/Vigileo system (Edwards Lifescience, Irvine, CA) calculates continuous cardiac output from arterial waveform characteristics. Cardiac output is calculated from the pulse contractility and heart rate with corrections for gender, age and body surface area. The algorithms used in this device have been continually refined. At the start of writing this thesis in 2009, version 3 was the most recent algorithm. One of the main limitations of this device is that it cannot analyse the arterial pulse-wave in the presence of an intra-aortic balloon pump.

Validation studies for the Flotrac device have produced conflicting results. The results of previous validation studies using versions 1.07 and 1.0 of the FloTrac system compared to a PA catheter are displayed in table 8. The methods of agreement described by Critchley and Critchley suggests that ‘a percentage error of 30% or less between the FloTrac and the PA catheter indicates that the Flotrac is no less accurate than the PA catheter (164). However, 3/6 studies reported a co-efficient above 30%. As part of this thesis, a further validation study was conducted between the PA catheter and FloTrac/Vigileo system.

Table 8: Validation of the FloTrac/Vigelio system using PA catheters in cardiac patients.

Author	**Year**	**Software**	**Setting**	**Reference method**	**Data points**	**Bias ± 2 SD or LOA**	**Correlation**	**Percentage error**
Button (165)	2007	1.07	OP/ITU	TD	150	0.25±2.27	NA	54
Cannesson (166)	2007	1.07	OP/ITU	TD	166	-0.26±1.74	r=0.66	38
Lorsomradee (167)	2007	1.07	OP	CCO	550	Pre CPB: -3%±56% Post CPB: -1% ±50%	r=0.19	NA
Mehta (168)	2008	1.07	OP	TD	96	-0.27±0.44	NA	29
Staier (169)	2008	1.07	OP	TD	120	-0.06±0.91	NA	36
Chakravarthy (170)	2007	NA	OP	TD	438	0.15±0.66	r=0.49	NA
Prasser (171)	2007	1.1	ITU	TD	158	0.01±1.63	NA	26.9
Mayer (172)	2008	1.1	ITU	TD	282	0.19±0.63	NA	24.6

Key: OP=operating room; ITU= intensive care; TD= thermodilution; CCO=continuous cardiac output; CPB=cardiopulmonary bypass; LOA=limit of agreement. Adapted from Mayer et al (173).

1.8 Summary

Coronary artery disease is the leading cause of systolic heart failure. Patients with heart failure may also develop electro-mechanical dyssynchrony, which leads to a further decline in stroke volume and LV filling.

Surgical revascularisation is a therapeutic option for symptomatic heart failure subjects with coronary artery disease with ischaemic but viable myocardium. Pre-operative LV function is an important determinant of post-operative outcome in patients undergoing cardiac surgery.

BiV pacing improves haemodynamic function in non-surgical patients with prolonged QRS durations >120ms by reversing electro-mechanical dyssynchrony without adversely effecting myocardial oxygen requirements. The benefit of BiV pacing may be amplified by optimising the AV and VV pacing intervals and targeting LV lead placement. Therefore, optimised temporary BiV pacing may be a therapeutic option to augment cardiac output after cardiac surgery, in ventilated patients receiving inotropes and/or intra-aortic balloon counter-pulsation (IABP).

The question remains whether acute BiV pacing is beneficial in heart failure patients irrespective of baseline dyssynchrony and QRS duration and if optimisation of the AV and VV pacing intervals augments haemodynamic function after on-pump cardiac surgery.

1.9 Hypotheses

- On-pump cardiac surgery causes both inter and intra-ventricular mechanical dyssynchrony.
- Myocardial arrest with cardioplegia has a more profound effect on mechanical dyssynchrony in heart failure patients compared to patients with preserved LV function.
- Temporary BiV and LV pacing improves haemodynamic function after cardiac surgery compared to atrial synchronous RV pacing.
- BiV pacing will reduce myocardial and renal injury after on-pump surgery compared to standard atrial synchronous RV pacing.
- Optimisation of the AV and VV intervals during acute temporary biventricular pacing improves cardiac output compared to nominal settings.
- Assessment of the arterial pulse wave using the FloTrac device provides an accurate minimally invasive alternative to measurement of cardiac output using PA catheters.

1.10 Design of the thesis

This thesis contains three studies. A 'control' study was designed to investigate the effects of on-pump surgery with respect to the development of mechanical dyssynchrony. This study recruited patients with preserved left ventricular function (ejection fraction ≥45%), who were scheduled for elective on-pump surgery. If this group of patients developed *de novo* mechanical dyssynchrony, this would support the

hypothesis that biventricular pacing may be beneficial after on-pump surgery, even in patients without baseline dyssynchrony: the results are presented in chapter 3.

The main study enrolled patients with heart failure (ejection fraction ≤35%) who were scheduled to receive on-pump cardiac surgery. Patients were randomised to receive either biventricular pacing or standard pacing (atrial-inhibited or dual chamber right ventricular pacing) after surgery. The primary endpoint was the duration of intensive care defined as the time for which patients required "level 3 care" (section 3.2.5). All patients received left ventricular pacing wires to allow haemodynamic assessment of five different pacing modes in the post operative setting. The other secondary endpoints included: the duration of inotropic support; the presence of post-operative arrhythmias and the assessment of myocardial injury using NT-pro-BNP and TnT with BiV and standard pacing. These results are reported in section 3.2.6.

Finally, a haemodynamic study was conducted to compare two methods of measuring cardiac output. The FloTrac/Vigelio system that measures cardiac output using arterial pulse wave analysis was validated against the "gold standard" pulmonary arterial catheter. This is described in section 3.2.8.

Chapter 2 –Methods

2.1 Introduction

The first part of this chapter describes the inclusion criteria for the control study and the main trial of temporary biventricular pacing in patients with severe LV dysfunction, after on-pump cardiac surgery. The echocardiogram protocol listed in table 9 was used for both studies both before and after surgery.

2.1.1 Approvals

The initial application to investigate temporary biventricular pacing after cardiac surgery in patients with severe LV dysfunction was approved by the Research and Development departments at both the University Hospital of Wales, Cardiff (09/CAD/4628-main sponsor) and at Morriston Hospital, Swansea, UK (S10CardS961). The trial was also approved by the Dyfred Powys Research Ethics Committee-09/WMW01/27.

A substantial amendment was subsequently approved by all parties, to investigate the effect of cardiopulmonary bypass on cardiac dyssynchrony using echocardiography in patients with preserved LV function. All investigations were conducted in accordance with the 'Declaration of Helsinki' and all patients provided written consent. These trials were registered with clinicaltrials.gov NCT01027299.

2.2 Control study

2.2.1 Introduction

Patients awaiting elective on-pump coronary bypass surgery where invited to participate in this study. Patients were required to be in sinus rhythm on the 12-lead

ECG prior to surgery with a transthoracic echocardiogram reporting a Simpson's biplane ejection fraction ≥45%. The principal exclusions were: permanent AF, QRS duration >120 ms on 12-lead ECG, critical pre-operative status with on-going ischaemia, or valve surgery. All patients provided written consent to participate in this study.

2.2.2 Echocardiography

After written consent was obtained, a further echocardiogram was performed using the trial protocol, illustrated in table 9. The echocardiogram was performed at least 24 hours before surgery. The echocardiogram was repeated if the operation was performed 7 or more days after the original scan. Patients proceeded to the next phase of the trial if their EF remained ≥45%. For the purposes of this study, additional pacing wires and invasive haemodynamic monitoring were not required.

All echocardiograms were performed using a 3.5 mHz transthoracic transducer and GE, Vivid 7, Horten, Norway, ultrasound scanner. The echocardiograms were performed to evaluate LV systolic and diastolic function, valve function and cardiac dyssynchrony. Patients were scanned in the left lateral decubitus position.

Table 9: Echocardiography protocol–control study

Echo window	Modality	Measurement
Parasternal long axis	MMode	LV internal dimensions
		LV wall thickness
		Septum to lateral wall delay
	Colour flow	Mitral regurgitation
Parasternal short axis	PW Doppler	RVOT- pulmonary pre-ejection interval (PPEI)
	CW Doppler	PA acceleration time
Apical 4 chamber	2D	LA and RA area
		LVEDV and LVESV
	MMode	Long axis displacement- RV lateral/ LV septal and lateral walls
	Colour flow	Mitral regurgitation
	PW Doppler	Mitral inflow
		LVOT- aortic pre-ejection interval (APEI)
		LVOT- VTI
	TDI	IVRT
		Medial and lateral E’
		Basal segments- peak velocity.
Apical 2 chamber	2D	LVEDV and LVESV
	TDI	Basal segments- peak velocity.
Apical 3 chamber	TDI	Basal segments- peak velocity.

From these measurements a Simpson’s biplane ejection fraction and inter-ventricular mechanical delay were calculated. An inter-ventricular mechanical delay ≥40 ms was considered significant. This was calculated as the difference in time, from the onset of the QRS complex to the start of aortic and pulmonary ejection, measured using pulsed wave Doppler.

Tissue Doppler (TDI) 3-beat loops were acquired from the apical window to measure intra-ventricular mechanical delay between the basal septal and basal lateral walls. Gains, filters and sector width were optimised to improve frame rates. A time delay ≥65 ms between peak systolic velocities in the left ventricular septum and lateral wall was used as the threshold for intra-ventricular mechanical dyssynchrony (figure 2).

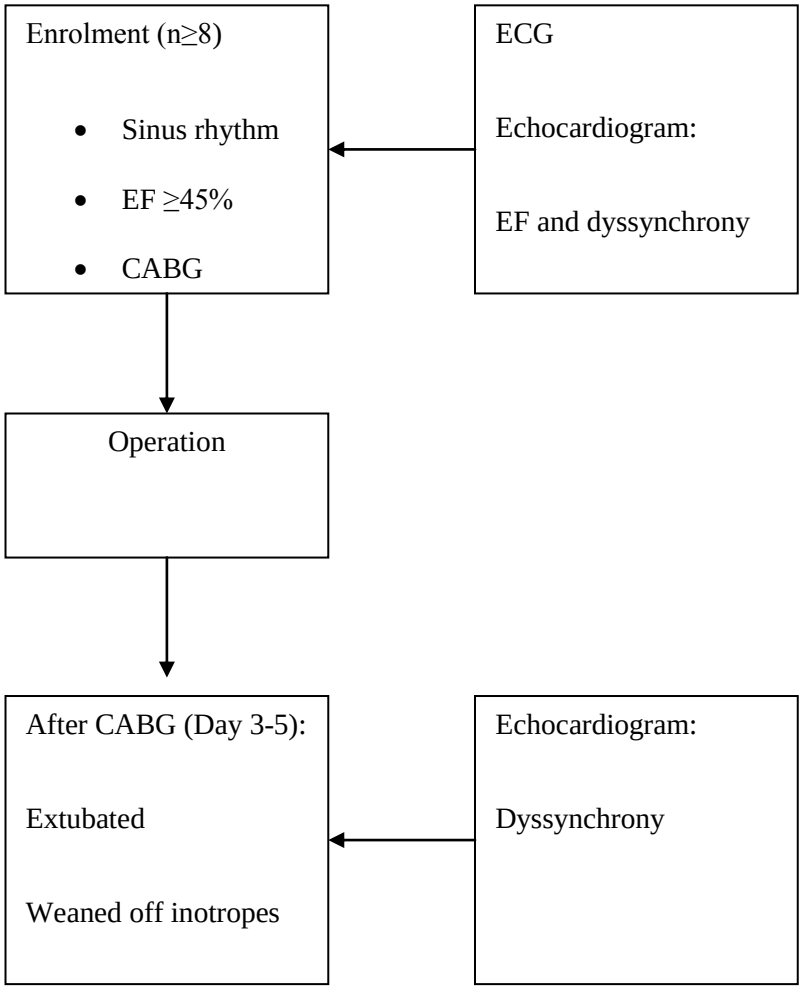
2.2.3 Statistical analysis

The echocardiogram protocol was repeated between day 3 and day 5 after surgery, after extubation and after the inotropes and vasoconstrictors had been discontinued. The interest focused on any changes in mechanical dyssynchrony: including E;E' ratio; inter-ventricular mechanical delay and septum to lateral wall delay using tissue Doppler. The changes in mechanical dyssynchrony in this group were compared to the changes in dyssynchrony in the main study, using an unpaired T test.

A paired t test was used to compare the pre and post operative measurements of mechanical dyssynchrony, and a $p<0.05$ was used for statistical significance. A sample size was estimated using published data on the inter-ventricular delay in hypertensive patients with preserved LV function, 21±19 ms (174). The calculation estimated that paired data from 8 patients would allow a 5% significance level and 80% power, to detect a 20 ms change in IVMD (175).

After the post-operative echocardiogram, the patients completed the study.

Figure 8: Flow diagram for control study.



2.3 Main study

Patients were invited to participate in this study if they were awaiting on-pump coronary revascularisation, valve surgery or both and they had a LV ejection fraction on echocardiography ≤35%. All patients were in sinus rhythm at the time of enrolment. The inclusion/exclusion criteria are documented in table 10.

Table 10: Inclusion/exclusion criteria–main study.

Inclusion criteria	**Exclusion criteria**
Age >18 years	Permanent pacemaker or defibrillator
Sinus rhythm	Infective endocarditis
Surgical revascularisation, valve surgery or both	Hypertrophic cardiomyopathy
	Off pump cardiac surgery
	Permanent atrial arrhythmia
	Renal failure (dialysis dependent)
	Emergency revascularisation.

After enrolment into the study, a 12-lead ECG was performed to confirm sinus rhythm and measure PR interval, QRS duration and morphology.

2.3.1 Echocardiography

After obtaining written consent to participate in this trial, I performed a transthoracic echocardiogram using the trial protocol described in table 11. The echocardiogram protocol was the same for the control study and the main trial. The echocardiogram was performed at least 24 hours before surgery. The echocardiogram

was repeated if the operation was performed 7 or more days after the original scan. Patients proceeded to the next phase of the trial if their EF remained <35%.

Table 11: Echocardiography protocol–main study

Echo window	**Modality**	**Measurement**
Parasternal long axis	MMode	LV internal dimensions
		LV wall thickness
		Septum to lateral wall delay
	Colour flow	Mitral regurgitation
Parasternal short axis	PW Doppler	RVOT- pulmonary pre-ejection interval (PPEI)
	CW Doppler	PA acceleration time
Apical 4 chamber	2D	LA and RA area
		LVEDV and LVESV
	MMode	Long axis displacement- RV lateral/ LV septal and lateral walls
	Colour flow	Mitral regurgitation
	PW Doppler	Mitral inflow
		LVOT- aortic pre-ejection interval (APEI)
		LVOT- VTI
	TDI	IVRT
		Medial and lateral E’
		Basal segments- peak velocity.
Apical 2 chamber	2D	LVEDV and LVESV
	TDI	Basal segments- peak velocity.
Apical 3 chamber	TDI	Basal segments- peak velocity.

All echocardiograms were performed using a 3.5 mHz transthoracic transducer and GE, Vivid 7, Horten, Norway, ultrasound scanner. The echocardiograms were

performed to evaluate LV systolic and diastolic function, valve function and cardiac dyssynchrony. Patients were scanned in the left lateral decubitus position.

From these measurements a Simpson's biplane ejection fraction and inter-ventricular mechanical delay were calculated. Patients with an EF >40% were excluded from the study. An inter-ventricular mechanical delay ≥40 ms was considered significant.

Tissue Doppler (TDI) 3-beat loops were acquired from the apical window to measure intra-ventricular mechanical delay between the basal septal and basal lateral walls. Gains, filters and sector width were optimised to improve frame rates. A time delay ≥65 ms between peak systolic velocities in the left ventricular septum and lateral wall was used as the threshold for intra-ventricular mechanical dyssynchrony, see figure 2.

At the discretion of the consultant cardiac surgeon or cardiologist, a dobutamine stress echocardiography study was performed to quantify functional reserve, and myocardial viability using a 3.5 mHz transthoracic transducer and a GE, Vivid 7, Horten, Norway, ultrasound scanner. Principal exclusions were a recent acute coronary syndrome or episode of decompensated heart failure (<30 days), valvular heart disease, or a prior viability assessment using another imaging modality.

Viability assessments were performed with ECG and blood pressure monitoring. Dobutamine was initially infused at a rate of 5 µg/kg/min and increased in steps to 10, 20, 30 and 40 µgrams every 3 minutes. Atropine 0.25 mg was added as a bolus, at intervals of 1 minute, up to a total dose of 1 mg to achieve a maximum target heart rate = [(220-age) x 0.85]. Viability was defined as 5 or more segments with abnormal

resting function but manifesting contractile reserve during dobutamine testing (176, 177).

The echocardiogram protocol was repeated on day 3 after surgery to measure changes in mechanical dyssynchrony: including E:E' ratio; inter-ventricular mechanical delay and septum to lateral wall delay using tissue Doppler.

I repeated the measurements of LV and RV pre-ejection intervals and basal septum to lateral wall delay using TDI, 5 minutes after completing the pre-operative echocardiogram. The reproducibilities of these measurements was compared to published data in the PROSPECT trial and a study by Thomas et al (95, 142), by calculating the co-efficient of variation, as described in the statistics section 2.4.6.

2.3.2 Laboratory investigations

Blood samples were obtained in the anaesthetic room prior to surgery, immediately after surgery and at 18 hours, 48 hours and 72 hours following the operation. Measurements included urea and electrolytes, troponin T, and N-terminal pro b-type natriuretic peptide (NT pro-BNP). Estimated glomerular filtration rate was calculated using the Cockroft-Gault formula:

$$\text{eGFR} = \frac{(140 - \text{Age}) \times \text{mass (kg)} \times \text{constant}}{\text{Creatinine } (\mu\text{mol/L})}$$

Constant: male=1.23 and female=1.04

For measurement of NT pro-BNP, blood samples were obtained and stored on ice. The sample was centrifuged for 15 minutes and the serum stored in 2 separate tubes at -80C. Once all the samples had been collected they were analysed in a core lab,

at St George's Hospital, London, using the IMMULITE™ 2500 analyser (Siemens, Los Angeles, USA).

2.3.3 Randomisation

After induction of anaesthesia, I randomised the patients into 2 groups, using a computer program- 'MINIMIMS' www.sghms.ac.uk/depts/phs/guide/randser.htm. This program performed a stratified randomisation to ensure both groups had approximately the same number of patients with similar characteristics. The variables taken into account included: LV size, ejection fraction and markers of dyssynchrony that may influence the post-operative response to BiV pacing. The variables are listed in table 12. Only the patient was blinded to the randomisation but not the investigator.

Group 1 was assigned to BiV pacing and group 2 to standard pacing. Standard pacing was atrial inhibited pacing (AAI) unless ventricular pacing was required for AV block, then atrial-synchronous right ventricular pacing (DDD-RV) was programmed. Pacing was continued until the primary endpoint was achieved or for 48 hours, whichever was the longest.

Table 12: A list of variables that were included into the stratified randomisation.

Parameter	**Reference**	
LV size	≤60 mm	>60 mm
QRS duration	≤120 ms	>120 ms
Euroscore	≤10	>10
Intra-aortic balloon pump	No	Yes
Valve surgery	No	Yes
Ejection fraction	≤20%	>20%

2.3.4 Operation

All patients received peri-operative heart rhythm monitoring, pulse oximetry, and a radial arterial line attached to a Vigileo™ (version 1.1) cardiac output monitor (FloTrac™ MHD8R, Edwards Lifesciences, Dominican Rep). A central line and a pulmonary arterial catheter (either 7.5F CCO: 139HF75P or 7F TD: 131 F7, Edwards Lifesciences, Irvine, USA) was inserted into the right internal jugular vein after intravenous induction of general anaesthesia.

The anaesthetic and cardio-pulmonary bypass (CPB) technique was standardised. After premedication with benzodiazepines, anaesthesia was induced with IV propofol (1-2 mg/kg) and fentanyl (10-20 µg/kg); muscle relaxation was achieved with rocuronium (1mg/kg), vecuronium (0.2mg/kg) or pancuronium bromide (0.1 - 0.2 mg/kg). The airway was intubated and mechanically ventilated with oxygen, air and

isoflurane 1-2%. Propofol and remifentanil infusion were used in addition to isoflurane for maintenance of anaesthesia.

Intravenous fluids (Hartmann's solution or gelofusin), vasopressors (metaraminol or phenylephrine) and inotropes (enoximone or milirone, dopamine, noradrenaline or adrenaline) were titrated according to patients' haemodynamic status. Prophylactic antibiotics (cefuroxime and teicloplanin) and antifibrinolytic agents such as tranexamic acid (2g) were administered prior to sternotomy.

Operative monitoring was identical in all patients. The extracorporeal circuit comprised of a Stockert™ roller pump (Shiley Inc, Irvine, CA), a Shiley S100™ membrane oxygenator, and polyvinylchloride tubes. Patients were given heparin just before the institution of CPB with 300 IU/kg, with additional dosing as necessary to maintain the activated clotting time greater than 480 seconds. Non-pulsatile extracorporeal circulation was initiated at flows of 2.4 to 2.6 L m^{-2} min^{-1}. Moderate systemic hypothermia (32 ^{0}C nasopharyngeal) was uniformly used. Cardiac arrest was achieved by infusion of 1 L of cold blood cardioplegic solution and topical slush. Repeated doses of cardioplegia were administered as required.

All distal anastomoses were performed during a single period of cross-clamping, and the proximal anastomoses to the aorta were completed during the re-warming period using a side-biting clamp. Extracorporeal circulation was terminated at a nasopharyngeal temperature of 37^{0}C. Heparin was neutralized after the end of CPB with protamine sulphate (1mg/100 IU heparin).

Before weaning from the cardio-pulmonary bypass circuit, temporary unipolar epicardial pacing wires were sutured to the roof of the right atrium, the right ventricular outflow tract and the postero-lateral free wall of the left ventricle (first obtuse marginal

territory) avoiding scar tissue. There were 6 temporary pacing wires, 3 active and 3 indifferent wires. The wires were attached via extension cables (APC Cardiovascular Ltd) to a temporary external triple chamber pacemaker (Osypka PACE 300™, Germany). A representative photograph and diagram of the positions of the electrodes in an individual patient in the trial are illustrated as figures 9 and 10.

Figure 9 : Position of temporary pacing wires (1=right atrium, 2=right ventricular outflow tract and 3=left ventricle, basal region of OM1). Two unipolar wires were attached at each site. (Consent-appendix A).

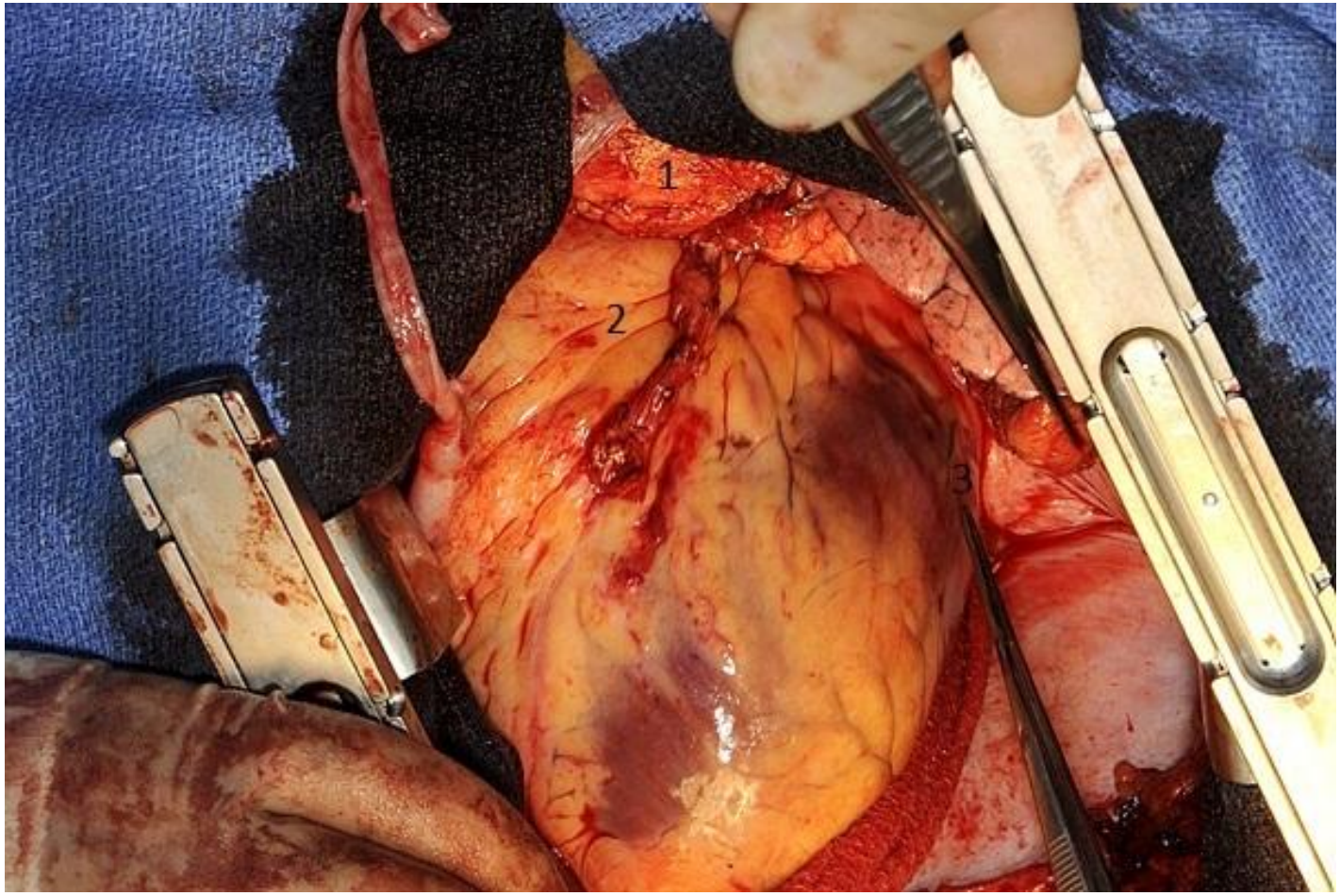
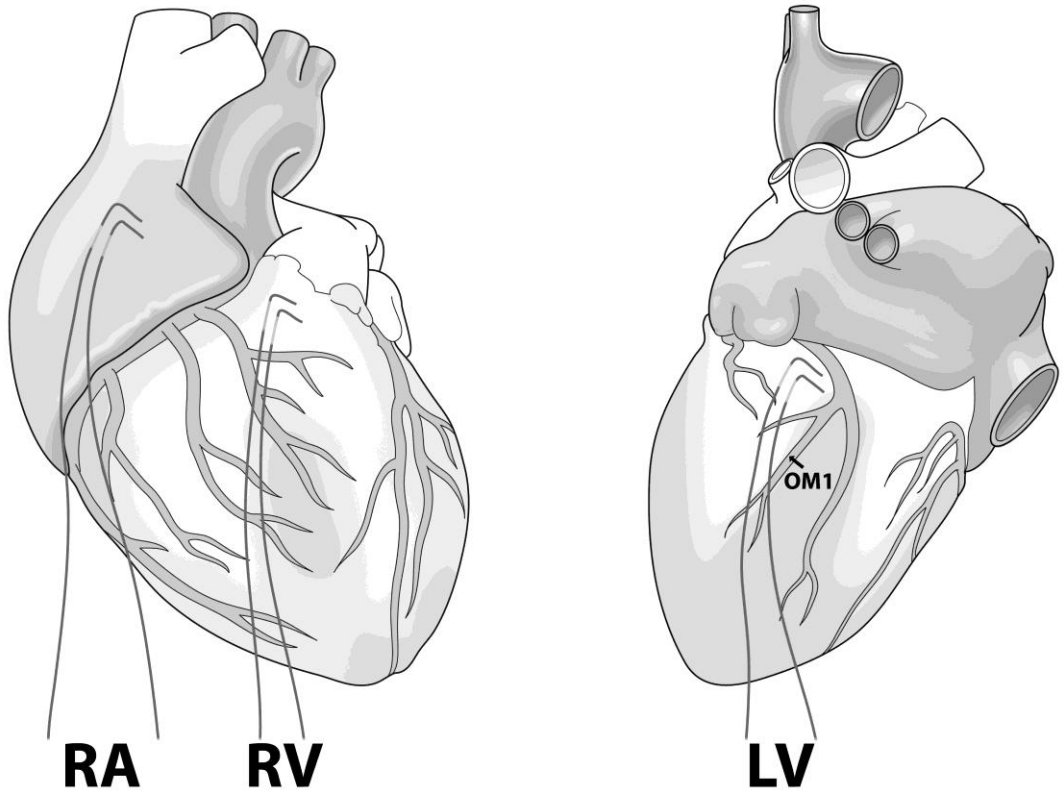


Figure 10: Position of temporary pacing wires-(RA=right atrium, RV=right ventricular outflow tract and LV= basal region of OM1).



Pacing was commenced prior to separation from the bypass circuit according to each patient's randomisation. Subjects in the biventricular pacing group (group 1) received DDD-BiV pacing, base rate 90 bpm, AV interval 120 msec, maximum tracking rate 110 bpm, VV interval -5 msec (the negative value indicates LV pre-activation). The standard pacing group (group2) received AAI pacing at base rate 90 bpm unless ventricular pacing was indicated for high grade AV block. In this situation DDD-RV pacing was programmed, base rate 90 bpm, AV interval 150 msec and maximum tracking rate 110 bpm. RV pacing was kept to a minimum.

Inotropes including enoximone or milrinone in combination with noradrenaline were administered according to haemodynamic requirements. The target ranges for haemodynamic parameters after surgery were:

- Mean arterial pressure 60-70 mm Hg
- Pulmonary capillary wedge pressure <18 mm Hg
- Cardiac index ≥2.0-2.5 L/min/m^2

2.3.5 Primary endpoint

The primary endpoint of the trial was the duration of level 3 care after cardiac surgery (178). Level 3 care was defined as the requirement for invasive mechanical ventilation, or multiple organ support, or multiple inotropes, or a single inotrope with an intra-aortic balloon pump. It was anticipated that for most patients, the transition from level 3 to level 2 care would occur after extubation from invasive ventilation and then after reducing the total number of IV infusions to either a single inotrope or vasoconstrictor. This is because a vasoconstrictor such as noradrenaline would

typically be prescribed in combination with a PDE III inhibitor to prevent post-operative hypotension.

An alternative scenario would be that a patient requiring haemodynamic support with a single IV infusion (either an inotrope or a vasoconstrictor) would reach the primary endpoint, after extubation from invasive ventilation. In patients for whom the inotropic agents or vasoconstrictors were restarted, the endpoint was taken to be the final transition from level 3 to level 2 care, before discharge from the intensive care unit.

I thought the transition from level 3 to level 2 care would be a more relevant endpoint than the total duration of ITU stay, which has been used in previous studies. The duration of ITU admission is limited by a number of confounding variables. This includes: the availability of beds on a step-down ward; the time of admission to ITU and the frequency of ward rounds to make plans for extubation from invasive ventilation and reducing the dose of IV inotropes and vasoconstrictors. These confounding variables can be removed by using this level of care model.

2.3.6 Sample size

Pokushalov et al (138), reported a 36% reduction in mean ITU admission with BiV pacing compared to standard pacing (no LV pacing) after surgery, (2.5 ± 0.5 days compared to 3.9 ± 0.6 days: $p < 0.001$ respectively). I anticipated that the duration of level 3 care would be shorter than the duration of ITU admission, perhaps with less variance, but we used these mean values and standard deviations for our power calculation.

Using the standard formula described by Campbell and Matchin (175):

$$\text{Sample size} = \frac{2 \times (Z_{1\alpha} + Z_{2\beta})^2 \times \sigma^2}{\delta^2}$$

σ = standard deviation of the population

δ = anticipated benefit from the intervention

$(Z_{1\alpha} + Z_{2\beta})$ = normal distribution of function

$(1-\beta) = 80\%$ and $\alpha = 5\%$.

From standard tables $(Z_{1\alpha} + Z_{2\beta})^2 = 7.85$

$$\text{Sample size} = \frac{2 \times (7.85) \times 0.6^2}{(0.15 \times 3.9)^2} = \frac{5.652}{0.342} = 16.5$$

In order to demonstrate a 15% reduction in the duration of level 3 care, with a power of 80% and with $p<0.05$ for a two-sided statistical significance, an estimated sample size of 34 patients was required.

2.3.7 Haemodynamic data

Haemodynamic data were collected using a pulmonary arterial catheter on admission to ITU and 6 hours and 18 hours after admission. This included measuring:

- Cardiac output/ index (L/min and L/min/m^2)
- Left ventricular stroke work index (g/m^2/beat)
- Mean arterial blood pressure (mm Hg)
- Pulmonary arterial pressures -systolic/diastolic/ mean (mm Hg)

- Pulmonary capillary wedge pressure (mm Hg)
- Systemic vascular resistance (dynes-sec/cm^{-5})

These measurements were taken in 5 different pacing modes:

- Biventricular pacing (DDD-BiV)
- Atrial inhibited pacing (AAI)
- Dual chamber right ventricular pacing (DDD-RV)
- Dual chamber left ventricular pacing (DDD-LV)
- Right ventricular pacing only (VVI)

The baseline pacing rate was 90 beats per minute but increased to 10 beats above intrinsic rate for the haemodynamic studies up to a maximum heart rate of 110 beats per minute. For BiV pacing the AV interval was set at 120 ms (VV interval = -5 ms, -ve indicating LV pre-activation) and 150 ms for DDD-RV and DDD-LV pacing with a target of 100% ventricular pacing. If intrinsic rhythm or fusion was observed, the AV interval was shortened by 10 msec until a paced ventricular rhythm was observed on the monitor.

Haemodynamic data were recorded 5 minutes after changing pacing mode. For thermodilution measurements, a minimum of 3 measurements were obtained. The data were assessed for accuracy by reviewing the thermodilution curves. If the cardiac output measurements lacked agreement (range ≥0.5 L/min) then 2 additional measurements were taken. The median value of the 5 readings was calculated. Cardiac output measurements ≥0.5 L/min from the median value were rejected as outlying results. For continuous cardiac output monitoring, the cardiac output was averaged for 3 cycles (1 cycle per minute).

At 18 hours, cardiac output measurements were also taken using the FloTrac device (arterial wave-form contour analysis) for AV and VV optimisation. The Flotrac device was used as it allowed a rapid assessment of cardiac output and reduced the volume of saline administered via the PA catheter by 500 ml. Cardiac output was measured for a range of AV intervals from 80-200 ms in 20 ms intervals and VV range -40 to +40 ms in 20 ms intervals.

The optimal AV and VV intervals were programmed for the BiV pacing group (group 1). After each set of haemodynamic studies, the base rate of pacing was reduced to 90 beats per minute and the AV interval was reset to 150 ms in the DDD-RV group (group 2).

2.3.8 Haemodynamic comparison PA v FloTrac

All patients in the main trial received a PA catheter. The device was inserted into the SVC in the anaesthetic room before surgery and then advanced into the PA in the cardiac intensive care unit. In addition, all patients received a radial arterial line. A FloTrac sensor (MHD8, Edwards Lifesciences, Irvine, CA, USA) was attached to the radial arterial line in all patients except those with intra-aortic balloon pumps. The FloTrac sensor (3rd generation) was attached to a Vigileo monitor (V1.1, Edwards Life sciences, Irvine, CA, USA) to calculate cardiac output using arterial waveform analysis.

Simultaneous measurements of cardiac output were taken using either a thermodilution or continuous cardiac output PA catheter (either 7.5F CCO: 139HF75P or 7F TD: 131 F7, Edwards Lifesciences, Irvine, USA) used in the main trial. Measurements of cardiac output were taken at baseline, 6 hours, and 18 hours after surgery in 5 different pacing configurations (AAI, VVI, DDD-RV, BiV and DDD-LV)

as previously described. The infusion rates of inotropes and vasopressors were kept constant while performing haemodynamic measurements. For thermodilution, a minimum of 3 measurements was taken 5 minutes after changing pacing mode to ensure consistent results were obtained. Outlying results were discarded as described in section 2.3.7.

The results obtained were compared using linear regression (Pearson co-efficient). A Bland-Altman plot and an agreement of methods was assessed as recommended by Critchley and Critchley (164). The agreement of methods was assessed by calculating the percentage error for the cardiac output measurements obtained using the PA catheters and FloTrac system.

To calculate the percentage error:

1. Calculate the mean cardiac output obtained from the PA catheter and Flotrac device.
2. The bias (μ) of the Flotrac device is the difference between the CO measured using the Flotrac device and the mean cardiac output.
3. The standard deviation of the individual bias measurements is then used to calculate 95% confidence intervals (= μ ± 2xSD).
4. The percentage error is calculated (= ± 2xSD/mean cardiac output of both methods).

The standard error of measurement using a thermodilution PA catheter is reported to be 10-20%. Therefore, limits of agreement between the PA catheter and FloTrac device can be established if the percentage error is less than 30%:

Percentage error = Square root ($20^2 + 20^2$) = 28.3% (approximately 30%).

2.3.9 Feasibility study

The surgical databases at the University Hospital of Wales (UHW), Cardiff, and Morriston Hospital, Swansea, were analysed for the number of patients in sinus rhythm with severe LV dysfunction (EF ≤30%), who had cardiac surgery in 2005. At UHW, 14 subjects in sinus rhythm with severe LV systolic dysfunction (EF ≤30%) had cardiac surgery. At Morriston Hospital, 45 subjects fulfilled these criteria.

Each year approximately 60 subjects would be potential candidates for the post-operative BiV pacing trial. If 50% of available subjects consented to the study and the dropout rate was 30%, then 41 subjects should complete the study over 2-years. This would satisfy the sample size calculation (n=34). Patients were therefore recruited from both surgical centres.

2.4 Statistical methods

I performed all the analyses using the intention-to-treat principle. Baseline characteristics were averaged and displayed as arithmetic means with standard deviations for continuous variables. Counts and percentages for categorical variables were compared using a two-sample t-test, a chi-squared test or Fisher's exact test. All the data were analysed using IBM SPSS version 18, statistical software.

2.4.1 Primary endpoint

A time-to-event analysis was performed for the duration of level 3 care, as the data were not normally distributed. The distribution of the data was assessed using a histogram. The primary endpoint was displayed using a Kaplan-Meier plot. A log-rank

test was performed to assess for statistical significance between the two pacing groups. A Cox-regression analysis was used to calculate hazard ratios and 95% confidence intervals. Linear regression analysis was performed to investigate the relationship between baseline characteristics including electrical and mechanical dyssynchrony with respect to the primary endpoint. The methods used to assess the primary endpoint were reviewed and approved by Mr Hills, Department of Medical Statistics, Cardiff University during the open-access study day 2012.

2.4.2 Haemodynamic monitoring

The haemodynamic data were compared between pacing groups: at baseline, 6 hours and 18 hours after admission to cardiac ITU using a repeated measures ANOVA test for within-subjects effects. A p value <0.05 implied significance. The relationship between groups was further investigated with a two-sided, paired Student t test. Comparisons were made for cardiac output and cardiac index, LV stoke work index, mean arterial pressure (MAP), pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP). The principal comparisons were between BiV v AAI pacing and BiV v DDD-RV pacing.

A Bonferroni correction was applied to allow for multiple comparisons between the groups with a p value ≤ 0.25 implying statistical significance. A linear regression analysis was also performed to investigate the significance of baseline dyssynchrony in predicting an acute haemodynamic response to BiV pacing. The nominal v optimal AV and VV pacing intervals were compared using a paired Student t test.

The correlation between the measurements of cardiac output using the PA catheter and the FloTrac device was assessed using a Pearson correlation co-efficient (r)

and systematic bias was reported using a Bland-Altman analysis. A p value <0.05 implied statistical significance.

2.4.3 Haemodynamic support

The total duration (hours) of inotropic support and the total dose per Kg of each infusion were calculated for both groups of patients. The results were expressed as means with standard deviations. After assessing for normal distribution, an unpaired 2-sided Student t test was used to assess for significance between the two groups, a p value <0.05 implied statistical significance.

2.4.4 Biochemical tests

Blood samples were taken in the operating theatre: before induction; on admission to cardiac intensive care unit; and at 18 hours, 48 hours and 72 hours after admission for serum creatinine, troponin T and NT-pro-BNP. Estimated glomerular filtration rate was calculated using the Cockroft-Gault formula. The requirement for post-operative haemofiltration was also recorded.

Continuous variables between the 2 groups was analysed using an unpaired t test. For NT-pro-BNP, a non-parametric test was used; the Wilcoxon Signed Rank Test because the values were not normally distributed. A p value <0.05 implied statistical significance.

2.4.5 Arrhythmias

Patient telemetry was used during the ITU and HDU admission. A 48-hour Holter monitor was attached to each patient on arrival to ITU. I reviewed the tapes in the physiology department.

All atrial and ventricular arrhythmias were recorded if they lasted over 30 seconds. A Chi squared test was used to compare the number of arrhythmic episodes in each group, a p value <0.05 implied statistical significance.

2.4.6 Echocardiography

The transthoracic echocardiograms were performed before the operation and on post-operative day-3 using the echocardiogram protocol described in table 11. Changes in diastolic function (E:E' ratio), inter-ventricular mechanical delay and LV septum to lateral wall delay using tissue Doppler were compared before and after surgery using a paired t test. A p value <0.05 implied statistical significance.

2.4.7 Reproducibility

An intra-observer co-efficient of variation (CV %) was calculated for the measurements of mechanical dyssynchrony, including aortic and pulmonary pre-ejection intervals and LV septum to lateral wall delay using tissue Doppler. The co-efficient was calculated using the formula:

CV= (SD2/arithmetic mean of measurements) x 100

SD2= the standard deviation of residuals (measurement 1- measurement 2).

2.5 Safety data

Post-operative re-sternotomy for bleeding along with any complication related to a temporary pacing wire or pulmonary arterial catheter was reported to the sponsor and ethics committee. Total mortality was recorded up to the end of the trial at 30-days.

Chapter 3- Results

3.1 Control study

Between May 2011 and January 2012, 13 subjects provided written consent to participate in the control study. 10 patients completed the protocol. Two patients declined the second post-operative echocardiogram and one patient was discharged before the study could be performed. The baseline characteristics are illustrated in table 13**.** This group of patients were at low risk of surgical complications with a Euroscore 1 of 4.0±2.6 and QRS duration was 84.5±6.5ms. All patients had a QRS duration less than 120 ms and only one patient had a PR interval above 200 ms (285 ms).

All patients had on-pump coronary artery bypass surgery and received an internal mammary graft and 2±0.5 vein grafts. No valve replacements or repairs were performed. The mean cardio-pulmonary bypass time and aortic cross clamp time were 95.3±17.5 and 70.3±24.7 minutes respectively.

Baseline echocardiography showed preserved LV systolic function with a mean EF 54.3±6.0%. There was no evidence of baseline mechanical dyssynchrony: inter-ventricular mechanical delay <40 ms and intra-ventricular mechanical delay <65 ms**,** for all patients**.** There was a 23% reduction in diastolic filling time after cardiac surgery (70.8±7.6 ms v 54.8±31.8 ms; p=0.02, before v after surgery) but no change in inter or intra-ventricular mechanical delay or isovolumic relaxation time. All patients developed a paradoxical motion of the inter-ventricular septum after cardiac surgery**;** see figure 11 and table 14.

Therefore, after on-pump cardiac surgery, patients with preserved LV systolic function only developed subtle changes in diastolic and systolic function.

Figure 11: Tissue tracking of the basal septum and posterior wall after bypass surgery, illustrating a paradoxical motion of the ventricular septum. Yellow marker indicates septal wall motion and green marker posterior wall motion.

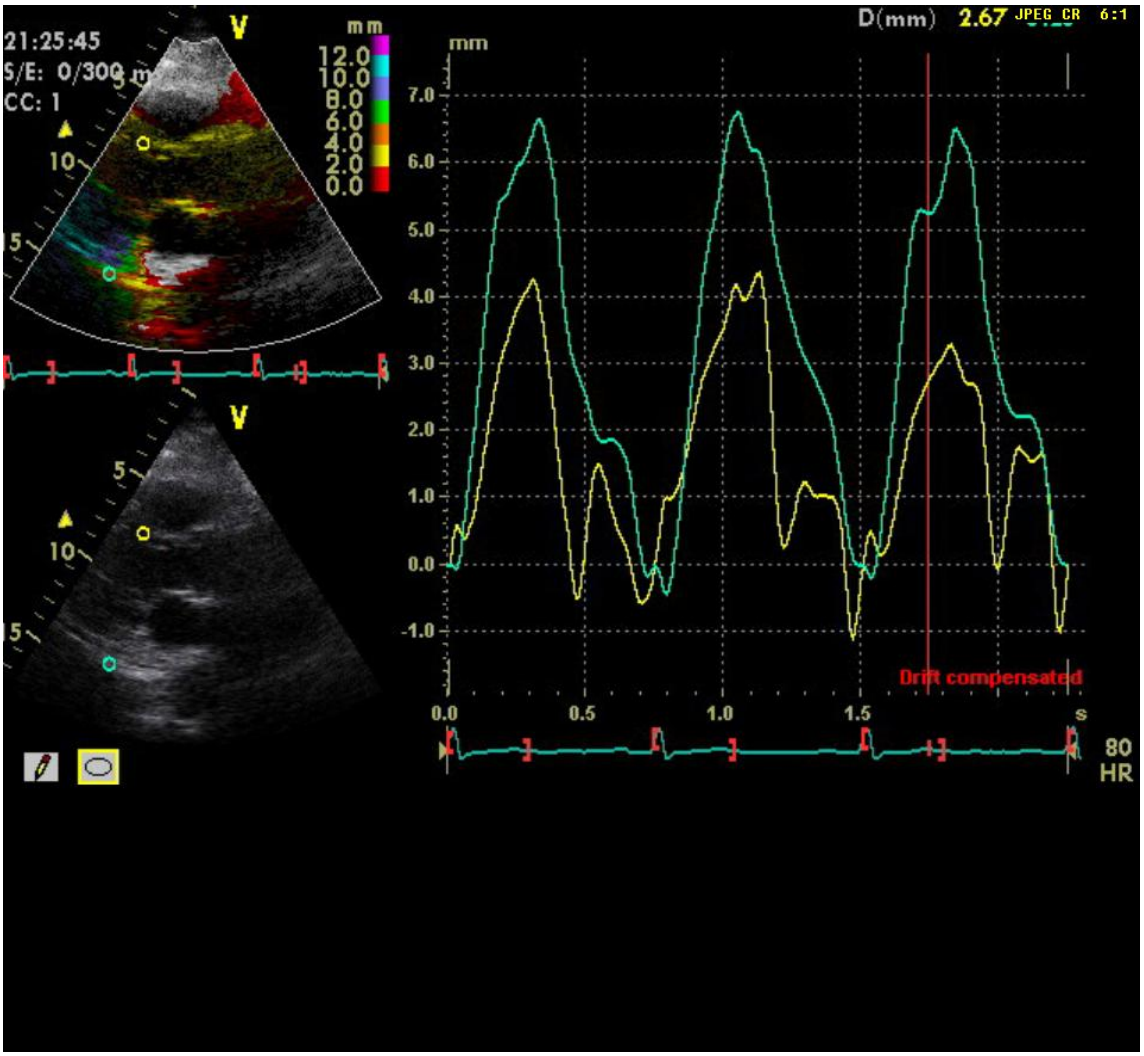


Table 13: Baseline characteristics–control study.

Parameter	**Reference (n=10)**
Age	65.6±10.7
Male gender (%)	70
Euroscore 1	4.0±2.6
Smoker (n)	3
Hypercholesterolaemia (n)	8
Diabetic (n)	1
Hypertensive (n)	8
Aspirin (n)	7
Beta Blocker (n)	7
ACE inhibitor (n)	8
Statin (n)	10
ECG: sinus rhythm (n)	10
PR interval (ms)	174±44.3
QRS duration (ms)	84.5±6.5
Paroxysmal AF (n)	0

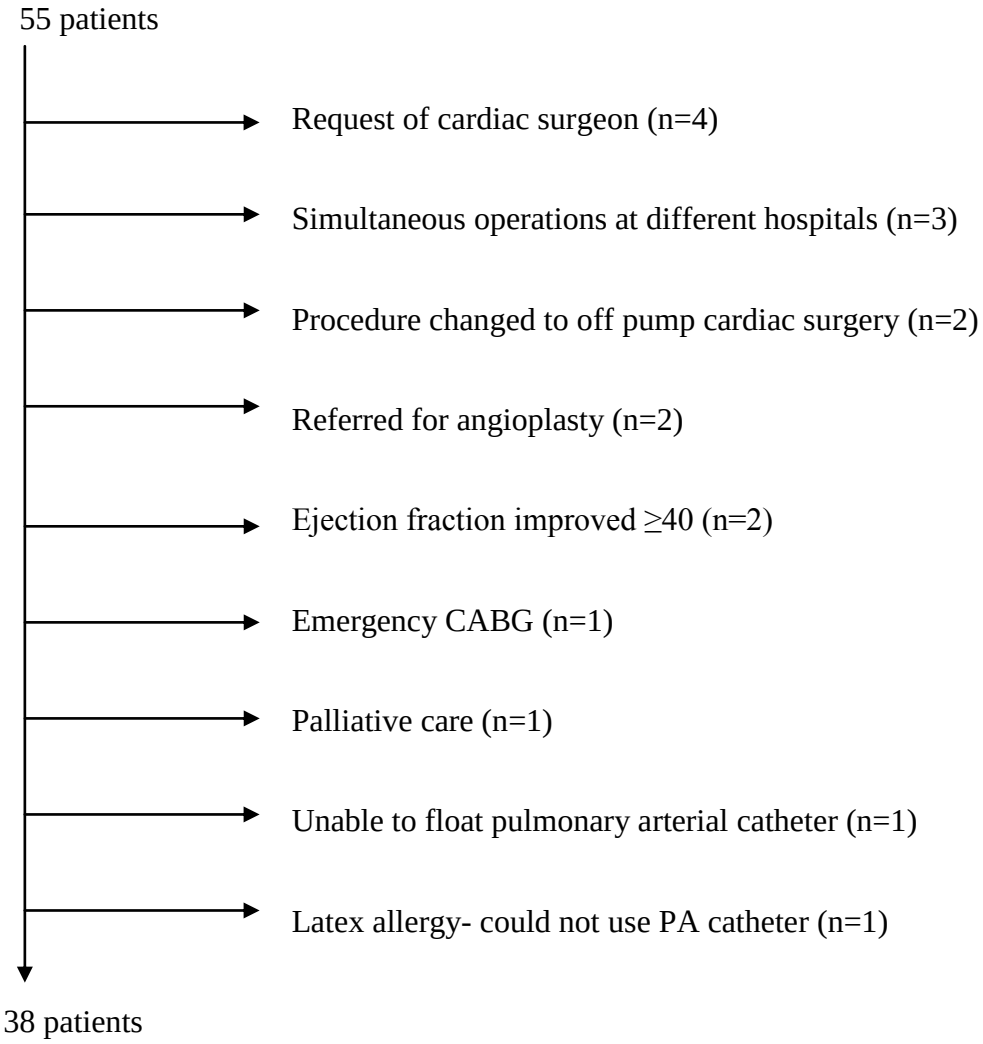
Table 14: Echocardiographic measurements before and after on-pump surgery.

Parameter	**Before surgery**	**After surgery**	**p value**
LV end diastolic dimension (cm)	4.8±0.5	4.4±0.6	0.06
Pulmonary pre-ejection interval (ms)	83.3±11.2	77.8±15.3	0.34
Aortic pre-ejection interval (ms)	87.5±10.8	85.8±14.3	0.80
Inter-ventricular mechanical delay (ms)	4.2±10.9	8.0±18.0	0.44
Diastolic filling time (ms)	70.8±7.6	54.8±16.3	0.02
Pulmonary acceleration time (ms)	98.0±12.2	91.5±31.8	0.50
Left atrial area (cm^2)	17.7±3.5		
Right atrial area (cm^2)	14.3±2.7		
Mitral valve E wave (m/s)	0.7±0.1	0.75±0.1	0.70
Mitral valve A wave (m/s)	0.8±0.1	0.72±0.1	0.14
E:A ratio	0.9±0.3	1.0±0.3	0.11
E:E' ratio	7.1±1.6	8.1±3.2	0.35
Isovolumic relaxation time (ms)	102.3±19.4	89.2±17.0	0.17
End-diastolic volume (ml)	101.1±26.3		
End-systolic volume (ml)	47.1±17.6		
Ejection fraction (%)	54±6.0		
Intra-ventricular mechanical delay (ms)	49.1±35.0	41.6±32.0	0.40

3.2 Main study

Between January 2010 and July 2012, 55 patients with severe LV systolic dysfunction gave written consent to participate in the post operative BiV pacing trial. 38 subjects completed the trial protocol and 17 subjects exited the study (figure 12). Four patients were removed at the request of the surgical team because of planned intervention to the tricuspid valve.

Figure 12: Flowchart for patients excluded from the trial.



3.2.1 Pre-operative data

The baseline demographics for the 38 patients who completed the trial are illustrated in table 15. The 2 groups were well matched. For all participants, the mean age was 67.4 ±11.4 years and 79% were male. 31/38 (82%) had NYHA class II or III heart failure. The majority of patients 32/38 (85%) had a prior myocardial infarction and 13/38 (34%) had an acute coronary syndrome within 30-days before surgery.

All patients were in sinus rhythm on the pre-operative ECG with an ejection fraction ≤ 35% before surgery. 9 patients had previously documented episodes of atrial fibrillation. None of the patients entering into the trial required haemodialysis. 28/38 (74%) of patients had a Chronic Kidney Disease (CKD) score 1 or 2 with an estimated glomerular filtration rate ≥60 ml/min/1.73m^2. Pre-operative beta blockers were continued prior to surgery but ACE-I were discontinued in 11/20 (55%) patients.

The baseline ECG confirmed 7/38 (18%) patients had first degree AV block (PR interval ≥ 200ms) and 10/38 (26%) had a QRS duration ≥120 ms and left bundle branch block.

Table 15: Clinical characteristics of the patients enrolled into the main trial.

Demographic	**Biventricular pacing (n=19) Group 1.**	**Standard pacing (n=19) Group 2**	**p**
Age (years)	69.2 ±9.3	65.5 ±12.7	0.32
Male (%)	79	79	1.0
NYHA score	2.5 ±0.7	2.4 ±0.9	0.18
CCS score	1.9 ±0.9	1.8 ±0.8	0.71
Euroscore 1	8.3 ±3.1	7.0 ±2.8	0.18
ACE-I (%)	58	47	0.52
Beta blocker (%)	63	84	0.14
Diabetic (%)	10	37	0.06
Paroxysmal AF (%)	5	16	0.33
Prior CVE (%)	20	11	0.34
Prior MI (%)	80	89	0.37
CKD score	2.2 ±0.9	1.9 ±0.6	0.28
LVEF (%)	26.1 ±5.4	28.0 ±7.3	0.38
PR interval (ms)	176 ±30	174 ±28	0.87
QRS duration (ms)	113.3 ±29.3	115.2 ±24.4	0.84
LBBB (%)	24	29	0.40
LMS (≥50%), (n)	2	6	0.11
Prox LAD (≥70%), (n)	9	11	0.52

3.2.2 Echocardiographic data

Table 16 contains the pre-operative transthoracic echocardiographic measurements and calculations. The stratified randomisation produced two well matched groups for LV dimensions, systolic function and markers of mechanical dyssynchrony. 4/38 (11%) patients had an ejection fraction <20% and 8/38 (21%) had raised LV end-diastolic filling pressures (E/E' ≥15). 11/38 (29%) patients had severe LV dilatation (end-diastolic volume; ≥202 ml for males and ≥131 ml for females) (179).

10/38 (26%) of patients had an intra-ventricular mechanical delay ≥65ms (difference in time to peak basal septum and lateral wall velocities) and 26% had an inter-ventricular mechanical delay ≥40 ms, (difference in time of onset of pulmonary and aortic ejection period). Overall, prior to surgery, 61% of patients had evidence of either electrical or mechanical dyssynchrony.

Dobutamine stress echocardiography (DSE) was only performed in 2/38 (5%) patients. 2/38 (5%) patients had a PET viability scan and subsequently had surgical revascularisation. In total, 4/38 (10%) patients had a viability assessment before surgery. The other reasons for not performing a viability test included concomitant valvular heart disease in 10/38 (26%) patients and 3 patients had unstable angina before surgery. Left main stem stenosis >50% or proximal left anterior descending artery stenosis >70% excluded 9 patients from having a DSE. 9 patients received an intra-aortic balloon pump, which was another contra-indication to viability assessment.

Table 16: Data from transthoracic echocardiogram before cardiac surgery.

Demographic	**Group 1 (n=19)**	**Group 2 (n=19)**	**p**
LVEDD (cm)	5.7±0.8	5.4±1.4	0.46
End-diastolic volume (ml)	173.9±66.5	161.0±39.2	0.47
End-systolic volume (ml)	132.6±65.2	115.6±29.0	0.30
Ejection fraction (%)	26.1±5.4	28.0±7.3	0.38
LA area (cm^2)	20.8±5.6	20.1±5.9	0.70
RA area (cm^2)	16.0±6.8	14.5±4.6	0.43
Mitral inflow: E wave velocity (m/s)	0.77±0.32	0.86±0.33	0.41
Mitral inflow: A wave velocity (m/s)	0.72±0.34	0.75±0.24	0.79
Mitral inflow: E:A ratio	1.60±1.26	1.44±0.97	0.67
Mitral inflow: E deceleration time (ms)	235.8±89.1	222.2±105.2	0.67
TDI: E' (cm/s)	7.1±0.02	7.3±0.04	0.81
Ratio E:E'	12.6±7.6	13.0±9.1	0.90
Isovolumic relaxation time (ms)	100.6±37.7	128.3±41.2	0.20
LV: lateral annulus excursion (cm)	0.74±0.35	0.90±0.30	0.19
LV: medial annulus excursion (cm)	0.61±0.15	0.79±0.33	0.06
RV: tricuspid annulus excursion (cm)	2.1±0.38	1.94±0.60	0.35
Pulmonary pre-ejection interval (ms)	96.8±24.6	82.0±22.2	0.07
Aortic pre-ejection interval (ms)	105.2±23.2	109.3±40.4	0.70
Inter-ventricular mechanical delay (ms)	19.7±22.2	26.4±39.6	0.53
Inter-ventricular mechanical delay ≥40ms (n)	6	4	0.46
TDI: septum-lateral wall delay/ (n≥65ms)	6	4	0.46

3.2.3 Operation

All 38 patients had on-pump cardiac surgery. 33/38 (87%) had revascularisation, and 15/38 (39%) had valve surgery. There were no differences between the groups with respect to the number of bypass grafts created, the use of arterial conduits or the duration of cardio-pulmonary bypass or aortic cross clamp time. All patients received cold blood cardioplegia via anterograde catheters with 2/38 (5%) receiving both anterograde and retrograde cardioplegia, see table 17.

Table 17: Revascularisation and valve surgery performed during the trial.

Demographic	**Group 1 (n=19) BiV pacing**	**Group 2 (n=19) Standard pacing**	**p**
CABG (n)	12	11	0.74
CABG and Valve (n)	4	6	0.46
Valve only (n)	3	2	0.63
Valves replaced:			NS
Aortic only	5	6	
Mitral only	0	2	
Both (aortic and mitral)	1	0	
IABP (n)	5	4	0.70
Internal mammary graft (n)	13	15	0.46
CPB time (min)	127.1±41.4	144.2±45.9	0.25
Aortic clamp (min)	86.2±33.6	89.5±27.6	0.43

All patients received 6 temporary pacing wires (3 active and 3 indifferent wires) prior to separation from the cardio-pulmonary bypass circuit. The active wires were attached to the right atrial appendage, the right ventricular out-flow tract and the basal posterolateral LV wall in 37/38 (97%) cases. In one patient, the LV wire had to be placed in a more anterior location because of scar tissue in the region of the first obtuse marginal artery. The average duration of BiV pacing was 22.7±8.8 hours in group 1.

BiV pacing was successfully initiated on separation from the bypass circuit in all 19 patients in group 1. Phrenic nerve stimulation was observed in 3/19 (16%) of patients. In two patients this complication was resolved by reducing the LV pacing voltage to prevent phrenic nerve stimulation while preserving BiV capture. In one patient, BiV pacing was terminated after extubation because of phrenic nerve stimulation.

3.2.4 Mechanical dyssynchrony

Mechanical dyssynchrony did not significantly change after on-pump cardiac surgery in patients with impaired LV function, see table 18. The analysis included measurements of systolic dyssynchrony (inter and intra-ventricular mechanical delay) and diastolic function (E:E') described in section 2.3.1. The post-operative measurements were obtained after discharge from the intensive care unit and after completing the pacing studies. None of the patients required ventricular pacing during the post-operative echocardiogram.

Table 18: Changes in mechanical dyssynchrony before and after cardiac surgery– impaired LV systolic function (EF≤ 35%).

Marker of Dyssynchrony	**Pre-Op**	**Post-Op**	**P**
Pulmonary pre-ejection (ms)	87.8±27.1	85.3±32.5	0.74
Aortic pre-ejection (ms)	109.2±32.7	112.7±39.7	0.62
Inter-ventricular mechanical interval (ms)	23.7±39.3	27.4±28.7	0.64
E:E' ratio	13.7±10.1	12.6±4.9	0.60
TDI- LV septum to lateral wall delay (ms)	55.6±21	62.6±41	0.90

However, comparing the pre-operative data in patients with impaired LV systolic function to the control group, aortic pre-ejection period but not inter-ventricular mechanical delay and the ratio of E:E' were prolonged in the impaired LV systolic function group, see table 19. Aortic pre-ejection was prolonged by 25% longer and E:E' almost doubled in the impaired LV systolic function group compared to the control sample of patients.

The wide standard deviation and limited sample size may explain why the difference in inter-ventricular mechanical interval did not reach statistical significance. The intra-ventricular mechanical delay did not change in the impaired LV group after surgery and baseline measurements were similar in the control and impaired LV groups.

Table 19: Mechanical dyssynchrony before cardiac surgery in patient with impaired v preserved LV systolic function.

Marker of Dyssynchrony	**Impaired LV (EF≤35%)**	**Preserved LV (EF≥45%)**	**p**
Pulmonary pre-ejection (ms)	87.8±27.1	83.3±11.2	0.29
Aortic pre-ejection (ms)	109.2±32.7	87.5±10.8	0.04
Inter-ventricular mechanical interval (ms)	23.7±39.3	4.2±10.9	0.24
E:E' ratio	13.7±10.1	7.1±1.6	0.04
TDI- LV septum to lateral wall delay (ms)	55.6±21	49.1±35	0.84

The final observation was that all patients developed a paradoxical motion of the ventricular septum after bypass surgery. This was also noted in the control study. In all cases after surgery; the pericardium was left open, see figure 11.

3.2.5 Duration of level 3 care

The duration of level 3 care was not normally distributed (figure 13). The median duration of level 3 care was 22.0 (IQR: 16.0-66.5) hours and 37.5 (IQR: 16.3-55.0) hours in group 1 and 2 respectively (log-rank p=0.58, 95% CI: 0.43-1.61), see figures 13 and 14.

One subject in group 1 had a premature discontinuation of BiV pacing due to phrenic nerve stimulation and one patient in group 2 received BiV pacing at the request of the attending consultant. Only one subject in group 1 had transient second degree

heart block after aortic valve surgery. No patients required a permanent pacing system for heart block before discharge from hospital.

30 patients reached the primary endpoint after extubation followed by reducing the number of infusions to either a single inotrope or vasoconstrictor. 8 (21%) patients only required a single infusion after surgery, and therefore reached the primary endpoint after extubation from invasive ventilation.

Figure 13: Histogram for the duration of level 3 care for all patients.

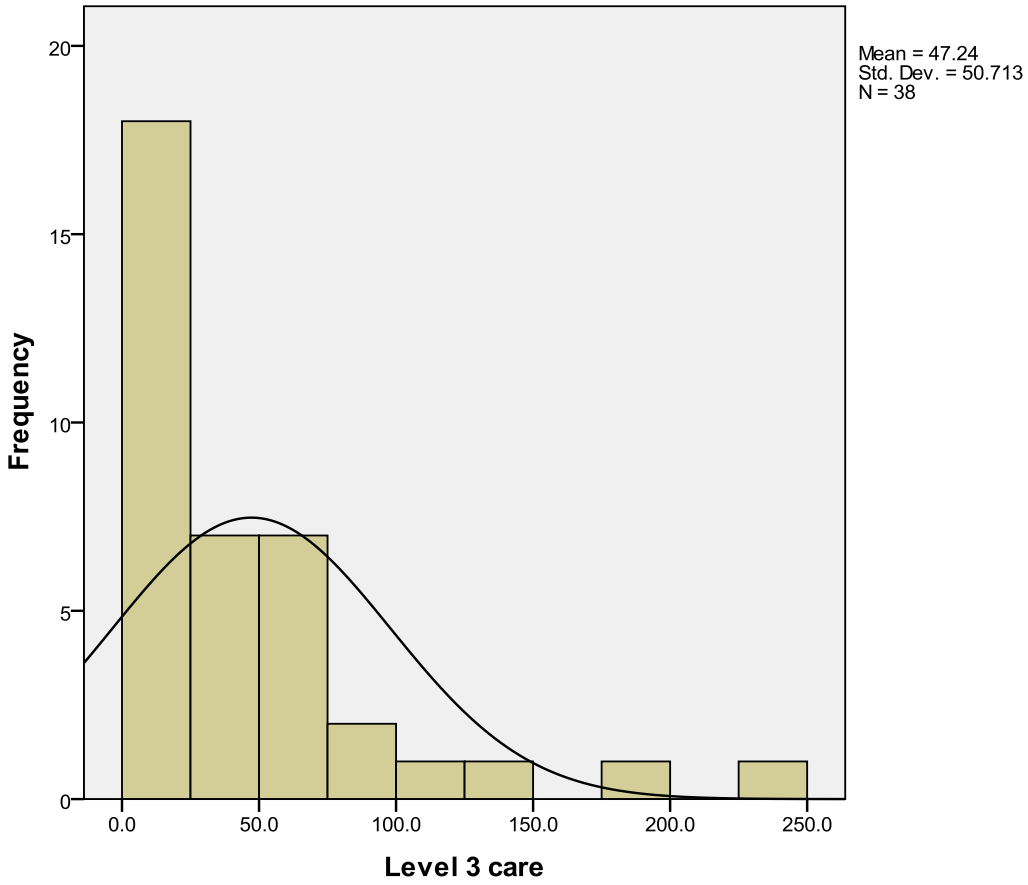
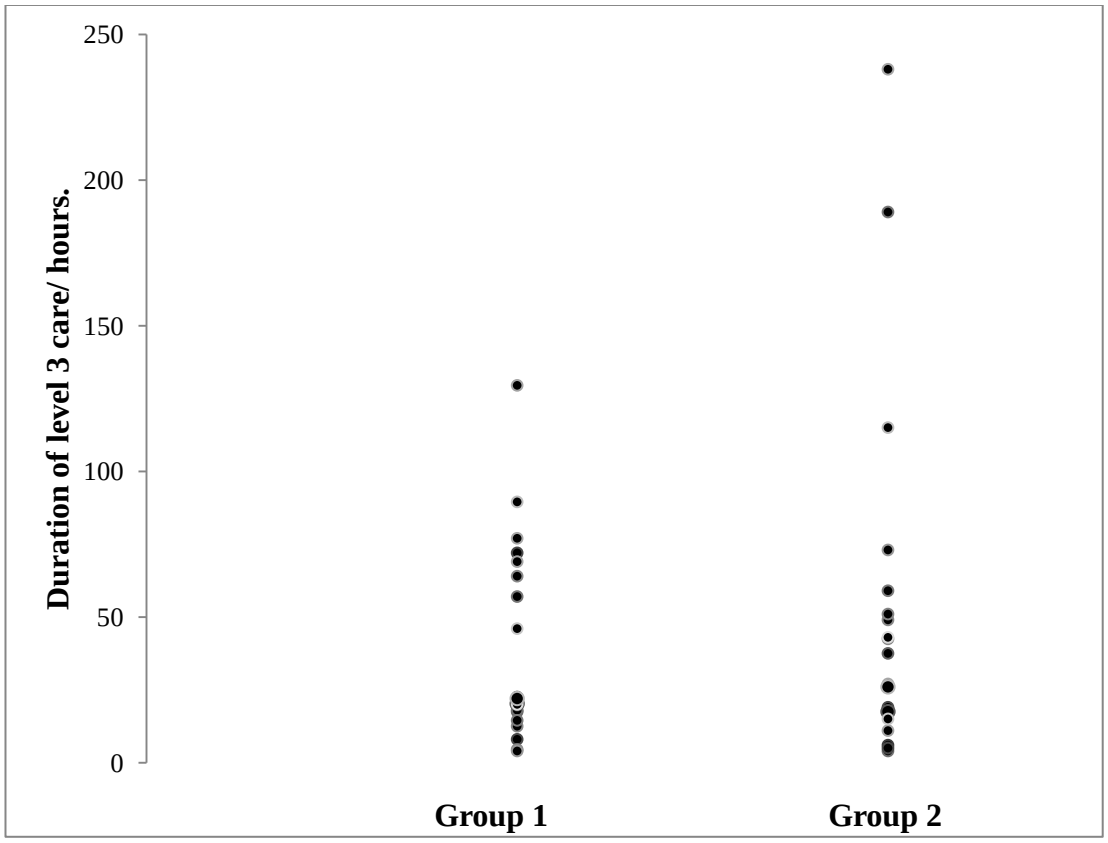


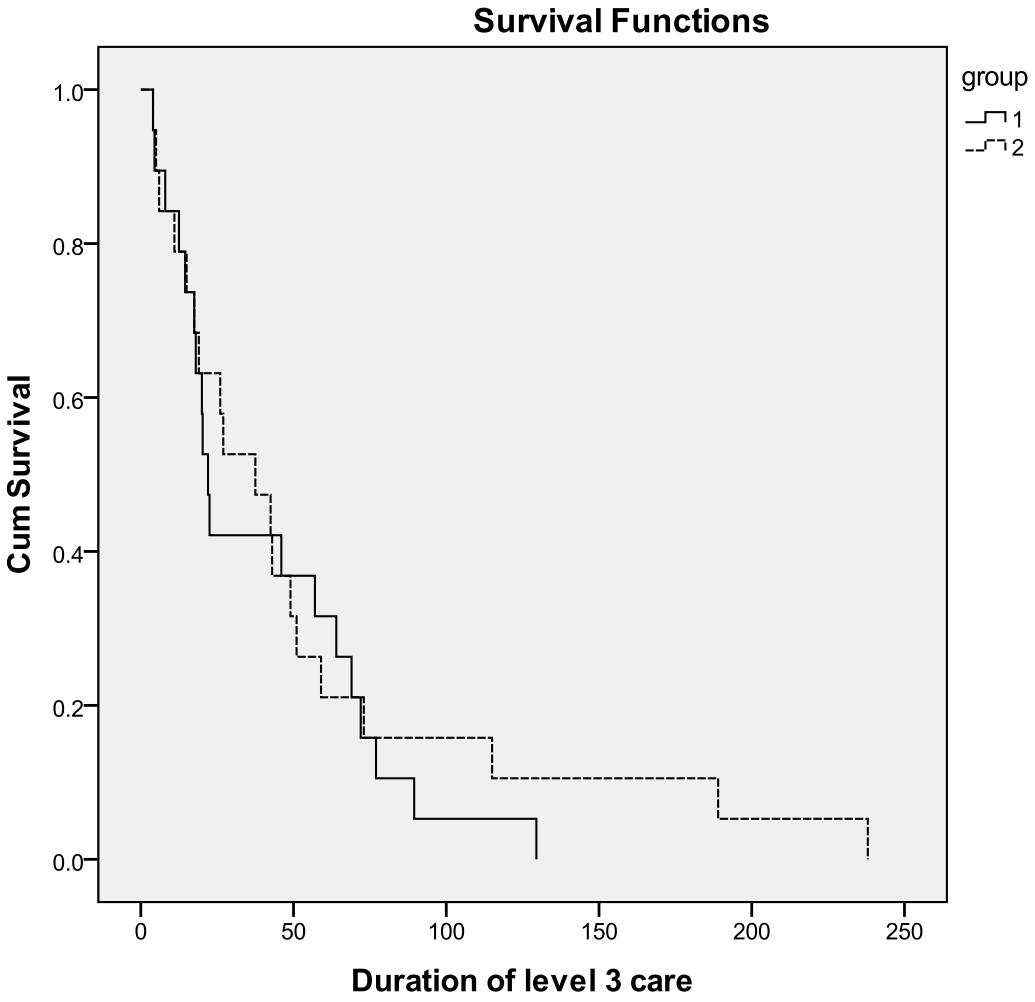
Figure 14: Duration of level 3 care in the two treatment groups-individual plots.



Two patients in group 2 had a prolonged duration of level 3 care: one patient had post-operative cardiac tamponade requiring re-sternotomy and removal of clots with subsequent haemofiltration, and the other required prolonged inotropic support with 2 infusions for 238 hours despite being extubated at 10 hours.

One patient in group 1 developed atrial fibrillation and required 129.5 hours of level 3 care and haemofiltration. Excluding these outliers would reduce the duration of level 3 care to 21.1 (IQR: 15.3-62.3) hours in group 1 and 27.0 (IQR: 15.0-49.0) hours in group 2 (log-rank p=0.95).

Figure 15: ‘Time-to-event’ Kaplan-Meier plot for the primary endpoint/hours (p=0.58; 95% CI 0.43-1.61).



There was no association between the baseline QRS duration or the presence of electro-mechanical dyssynchrony and the duration of level 3 care, see figures 16-21.

Figure 16: Relationship between QRS duration and duration of level 3 care. Pearson's correlation co-efficient r=0.25, (p=0.14).

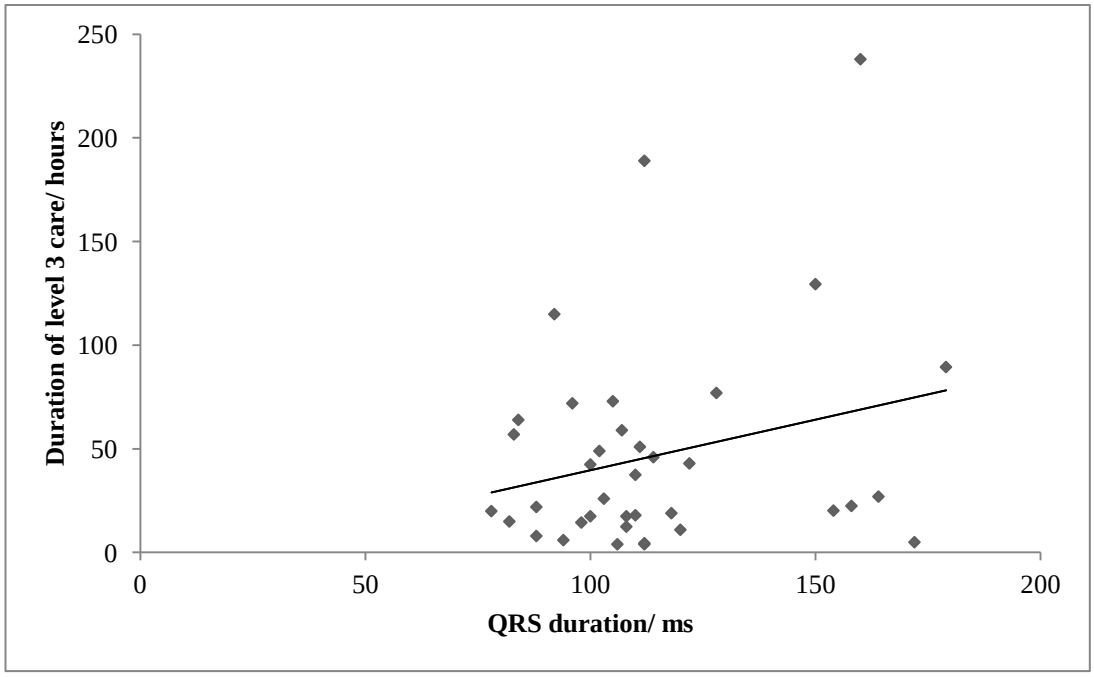


Figure 17: Group 1- Relationship between QRS duration and duration of level 3 care. Pearson's correlation co-efficient r=0.38, (p=0.12).

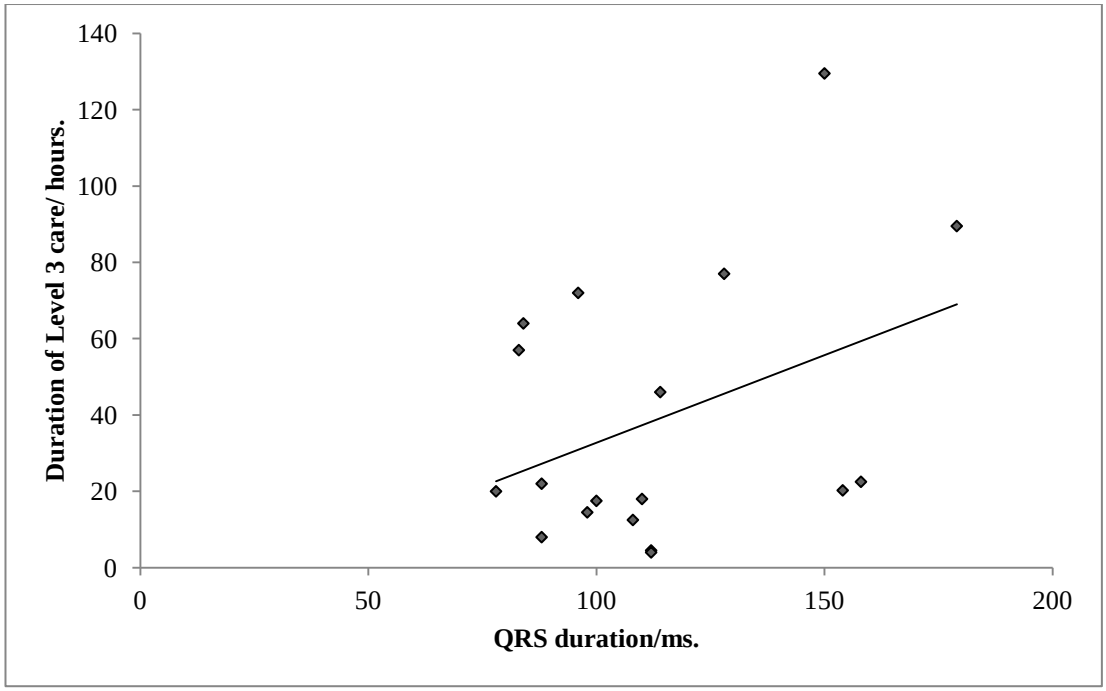
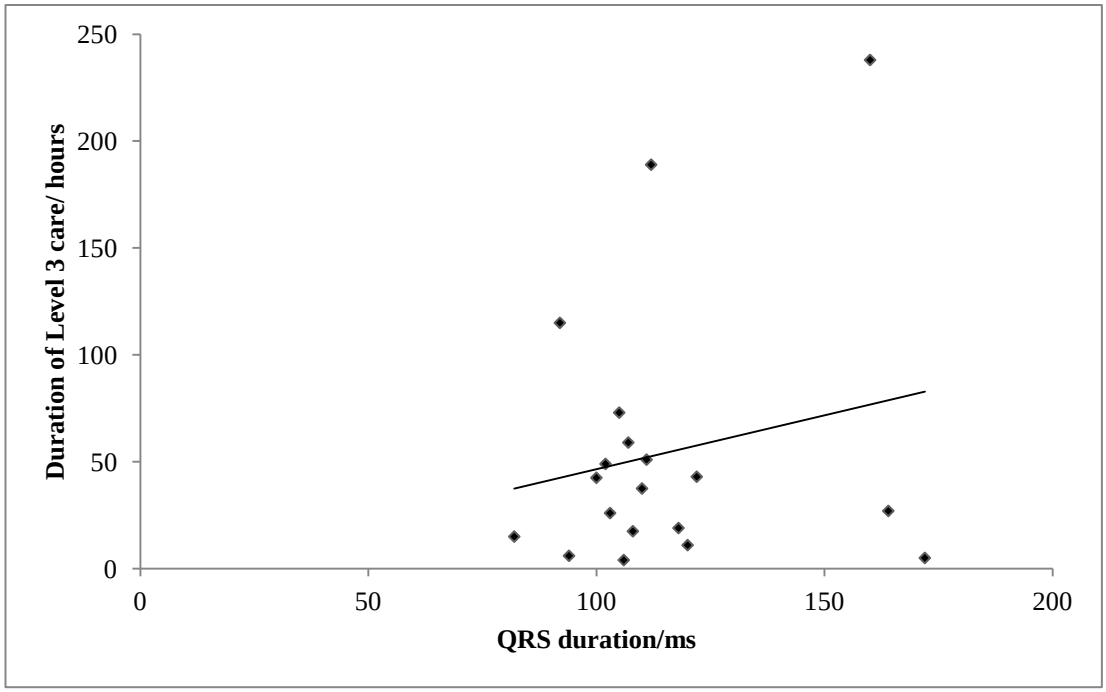
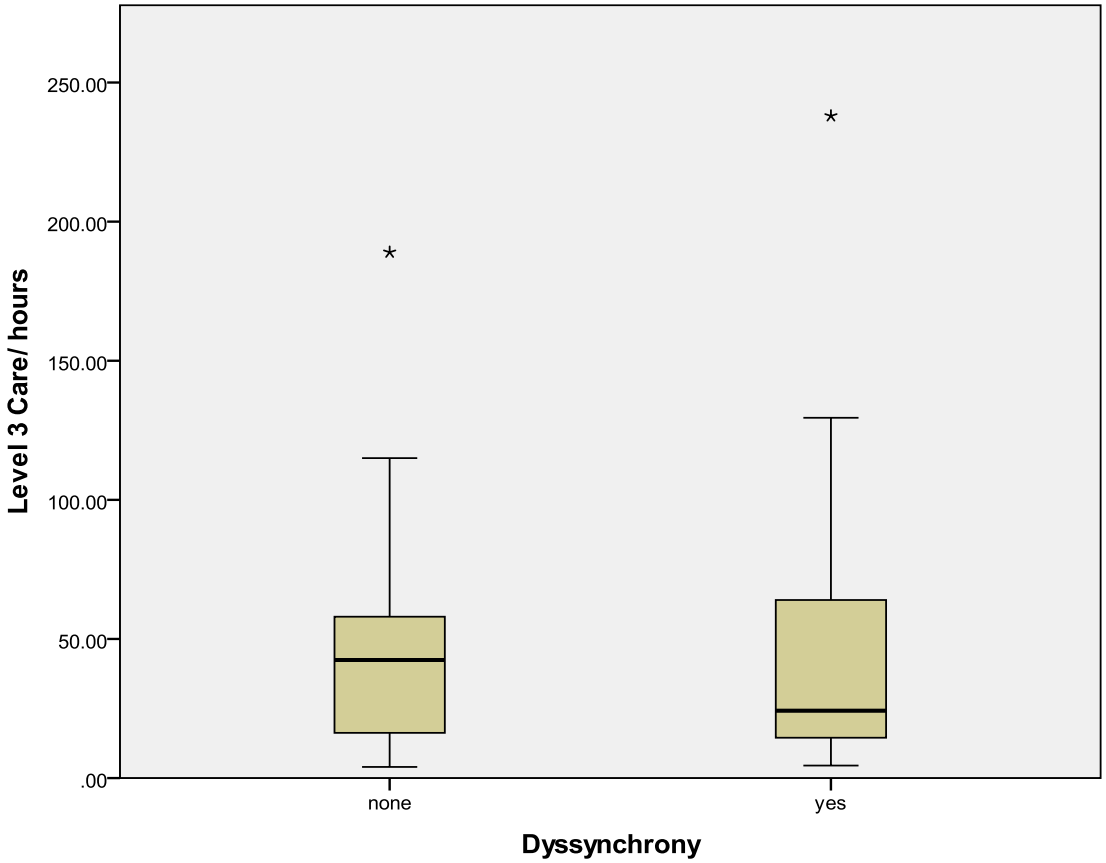


Figure 18: Group 2- Relationship between QRS duration and duration of level 3 care. Pearson's correlation co-efficient r=0.20, (p=0.42).



Using Cox regression analysis, the duration of level 3 care was not associated with: the QRS duration (p=0.14, 95% CI: 0.98-1.00): the presence of dyssynchrony (p=0.85, 95% CI: 0.49-1.81): pacing group assignment (p=0.53, 95% CI 0.39-1.63) or heart valve surgery (p=0.43, 95% CI: 0.66-2.64). However, only 10 patients had a QRS duration greater than 120 ms and a larger sample size would have been desirable to exclude a type II statistical error.

Figure 19: Relationship between baseline dyssynchrony and duration of level 3 care.



Median duration of level 3 care 42.5(IQR: 16.3-58.0) hours v 46.3 (IQR: 15.3-58.8) hours for no dyssynchrony v baseline dyssynchrony respectively.

Figure 20: Duration of level 3 care (hour) in patients without baseline dyssynchrony. Group 1, 21.0 (IQR: 16.6-48.8) hours v Group 2, 49.0 (IQR: 16.3-66.0) hours.

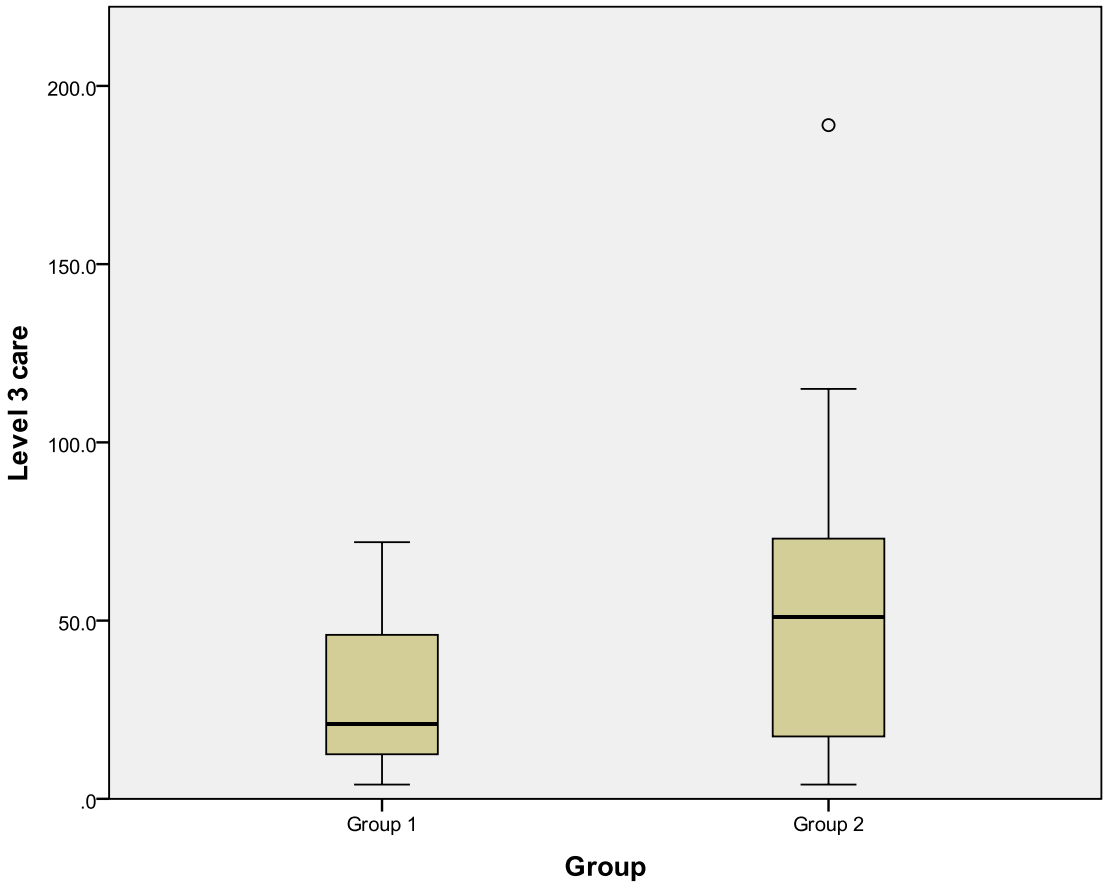
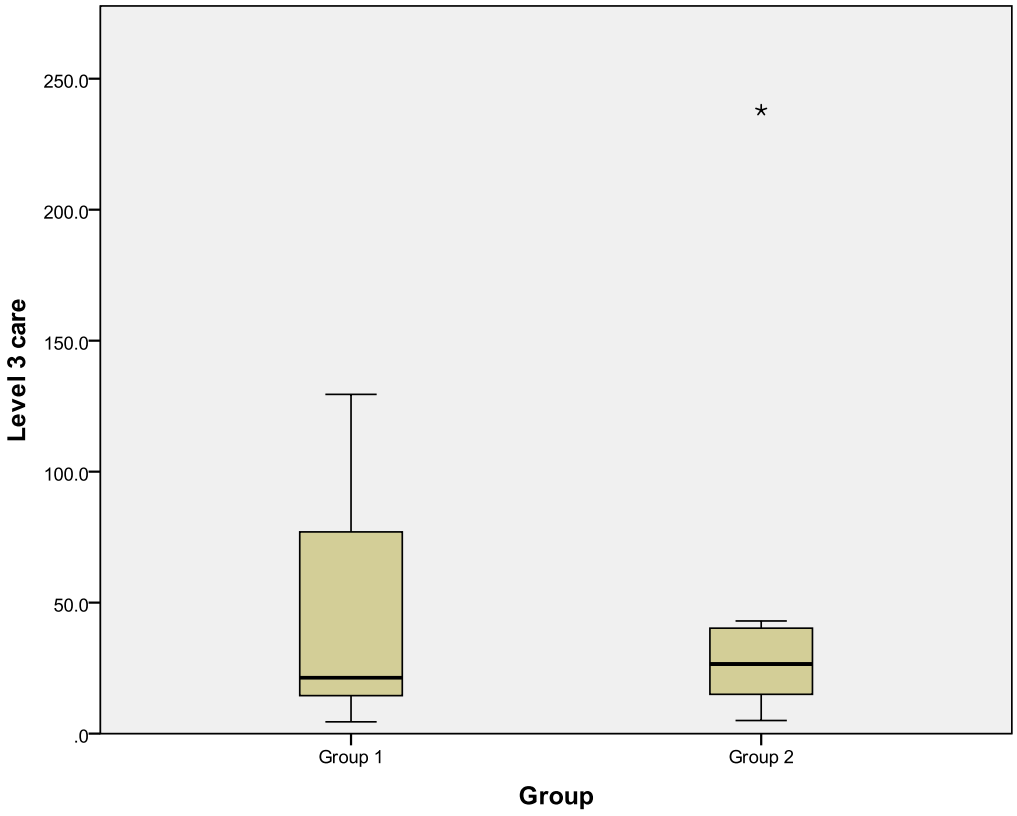


Figure 21: Duration of level 3 care (hour) in patients with baseline dyssynchrony. Group 1, 24.4 (IQR: 15.3-73.8) hours v Group 2, 26.5 (IQR: 17.0-38.9) hours.



3.2.6 Haemodynamic data

Haemodynamic data were collected on admission to cardiac ITU and at 6 and 18 hours thereafter, see table 20. This included: cardiac output (CO), cardiac index (CI), LV stroke work index (LVSWI), mean arterial blood pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressures (PAP), systemic vascular resistance index (SVRI) and pulmonary capillary wedge pressure (PCWP).

Using the repeated measures statistic (ANOVA) the pacing modes were compared for significant differences in cardiac output at all 3 time points. The F scores were 26.8, 17.5 and 26.0 at baseline, 6-hours and 18 hours respectively and $p < 0.001$ for all comparisons. The groups were then further analysed to identify the superior modes of pacing using a paired T test with a Bonferroni correction.

At baseline (time=0) and 6 hours after the operation, cardiac output and index were similar for all pacing modes except right ventricular-only (VVI) pacing which was inferior to all other pacing modes due to loss of AV synchrony ($p<0.001$), see table 20. Cardiac output was 16-19% lower with right ventricular-only (VVI) pacing compared to the other pacing modes ($p<0.001$).

However, at 18 hours BiV pacing was superior to all other pacing modes ($p=0.02$ compared to atrial-inhibited (AAI); $p<0.001$ compared to right ventricular-only (VVI); $p=0.001$ compared to dual chamber-RV and $p=0.003$ compared to dual chamber-LV), see figures 22-23. BiV pacing increased cardiac output by 7% compared to atrial-inhibited (AAI), dual chamber-RV and dual chamber-LV pacing mode.

BiV pacing also increased cardiac index by at least 10% at 18 hours, ($p=0.02$ compared to atrial-inhibited (AAI) pacing and $p<0.001$ for all other pacing modes). LV stroke work index was similar for all pacing modes at baseline and 6 hours with the

exception of right ventricular-only (VVI) pacing ($p < 0.001$ for all comparisons). At 18 hours, BiV pacing improved LV stroke work index by 12% compared to dual chamber-RV ($p<0.001$); by 39% compared to right ventricular-only (VVI) ($p<0.001$); and by 9% compared to dual chamber-LV ($p=0.02$). There was no significant improvement in LV stroke work index with BiV pacing compared to atrial-inhibited (AAI) pacing mode ($p=0.15$). BiV pacing did not influence mean arterial pressure, pulmonary arterial pressure or pulmonary capillary wedge pressure at 18 hours, with the exception of right ventricular-only (VVI) pacing. Right ventricular-only (VVI) pacing decreased cardiac output by 16-19%, cardiac index by 15-20% and LV stroke work index by 31-39% ($p < 0.001$ for all comparisons).

Table 20: Haemodynamic data obtained from PA catheters (mean values ±SD).

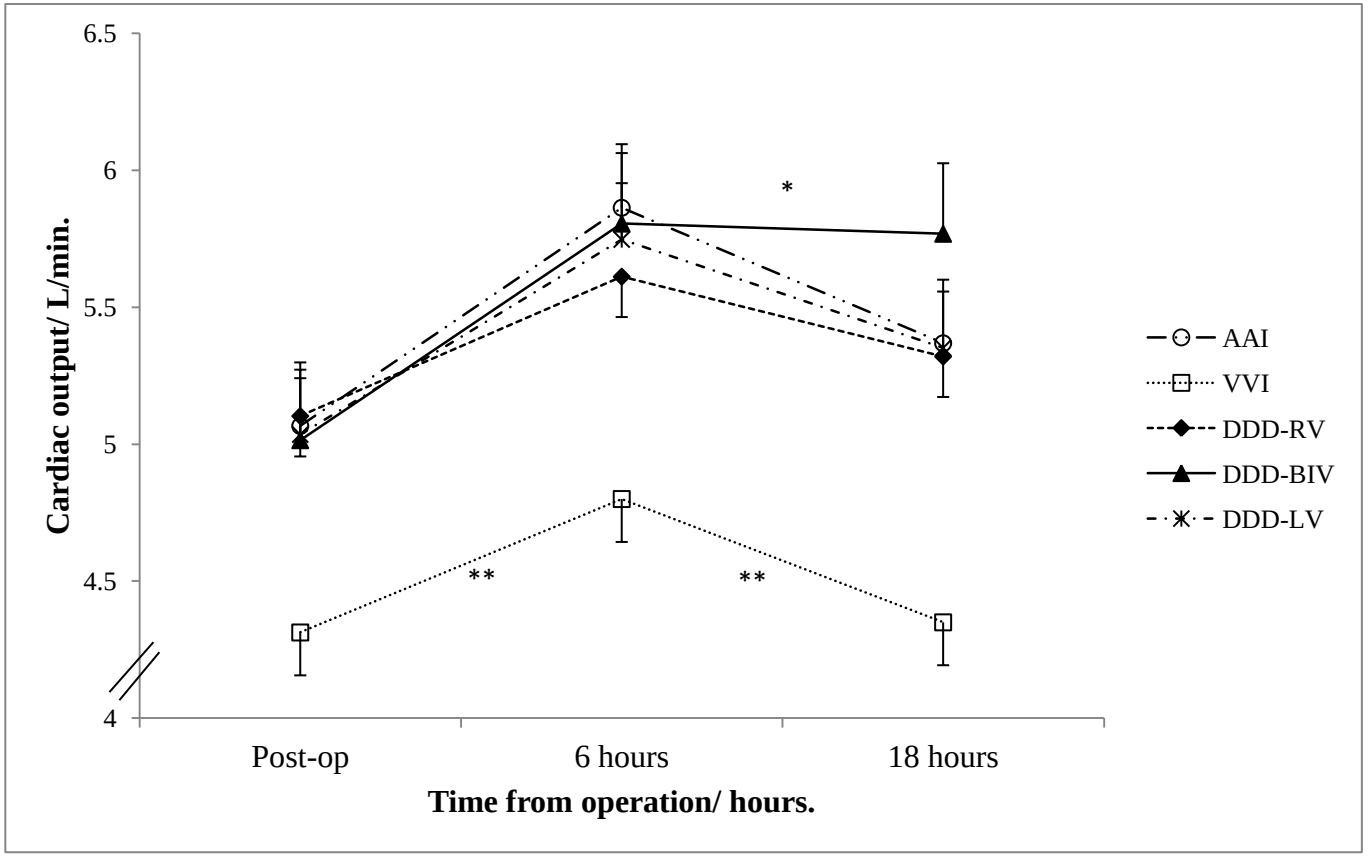
Measurement	Time	AAI	VVI (RV)	DDD-RV	DDD-BiV	DDD-LV
Cardiac output	0	5.1±1.9	4.3±1.8†	5.1±1.8	5.0±1.8	5.0±2.0
(L/min)	6	5.9±1.6	4.8±1.7†	5.6±1.7	5.8±1.6	5.7±1.6
	18	5.4±1.1	4.4±1.1†	5.3±1.1	5.8±1.2*	5.4±1.2
Cardiac index	0	2.7±0.9	2.3±0.8†	2.7±0.8	2.7±0.9	2.7±1.0
($L/min/m^2$)	6	3.1±0.8	2.5±0.8†	3.0±0.7	3.0±0.7	3.0±0.7
	18	2.8±0.6	2.3±0.6†	2.8±0.6	3.1±0.7*	2.8±0.7
LVSWI	0	26.6±12.8	18.4±5.4†	24.6±7.4	24.1±8.2	23.6±8.9
($g/m/m^2$)	6	25.9±6.7	19.0±6.6†	24.2±6.6	24.1±6.2	24.3±6.5
	18	26.3±7.3	17.3±5.3†	24.7±6.4	28.2±7.2**δ**	25.7±7.6
MAP	0	73.6±10.0	60.0±10.8†	73.6±10.1	72.7±8.6	72.3±10.6
(mm Hg)	6	73.4±8.4	65.3±13.6†	71.3±9.6	70.8±9.3	73.9±10.3
	18	73.4±11.1	63.3±9.2†	73.5±9.6	75.9±8.2	73.9±8.5
CVP	0	9.6±4.4	11.1±5.4	11.1±4.5	9.7±4.3	9.9±4.1
(cm)	6	11.7±3.9	11.2±3.5	10.7±4.3	10.8±4.9	10.8±4.5
	18	10.4±3.7	11.6±3.8	11.1±4.2	10.8±3.7	10.8±4.1
PAP	0	22.4±6.4	22.1±6.1	24.1±6.4	23.5±6.0	22.1±5.7
(mm Hg)	6	26.3±7.0	23.5±8.4	25.4±7.1	26.3±7.3	25.0±7.3
	18	21.3±6.9	22.2±6.1	22.5±6.8	22.1±6.8	21.3±5.7
SVRI	0	2235±563	2294±858	2166±882	2066±772	2292±1097
(dyne $s/cm^{-5}/m^{-2}$)	6	1702±583	2107±1033	1749±761	1688±574	1735±746
	18	1754±563	1962±681	1786±449	1714±654	1863±589
PCWP	0	10.8±4.7	10.4±5.3	10.1±4.6	11.1±4.7	10.8±4.5
(mm Hg)	6	13.3±6.3	12.4±7.3	12.7±6.7	13.6±6.6	12.8±6.5
	18	11.7±3.9	11.1±3.6	12.0±3.4	12.0±3.6	11.8±3.4

Key: † $p < 0.001$ compared to other pacing modes.

* $p < 0.05$ compared to other pacing modes.

δ $p < 0.05$ compared to other pacing modes except AAI pacing (p=NS).

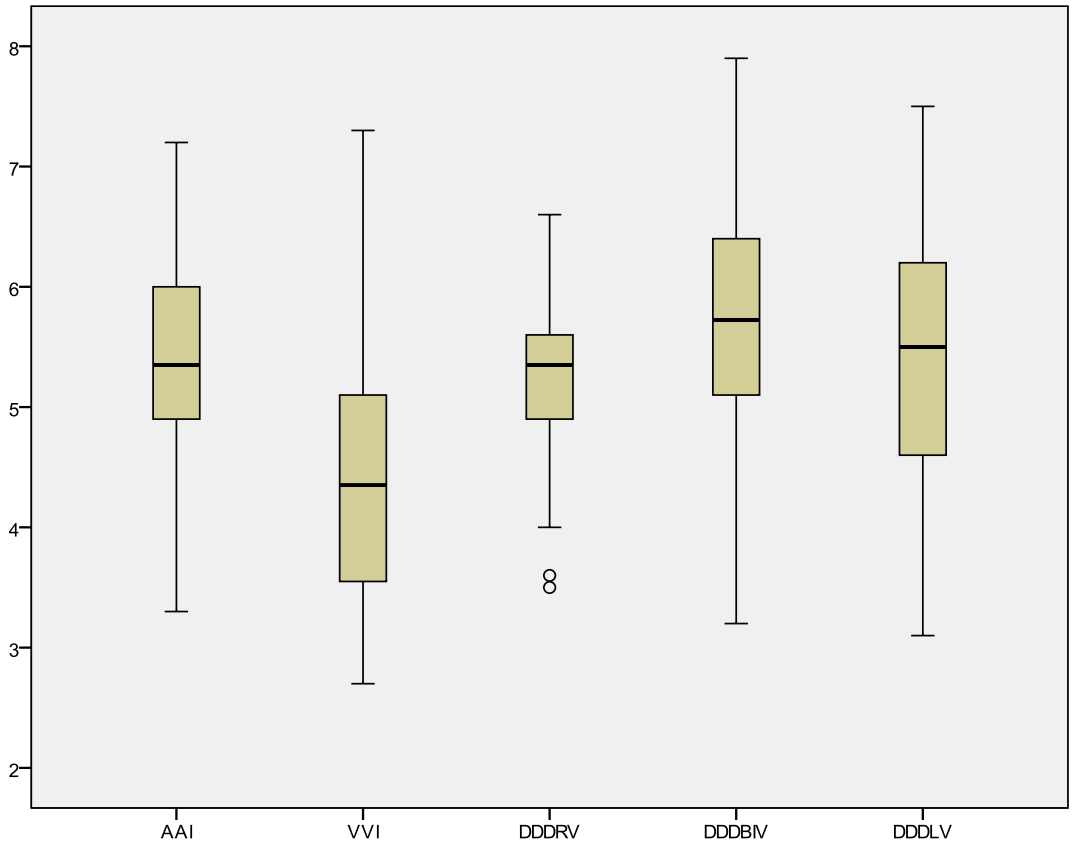
Figure 22: Cardiac output (L/min ±SEM) in the 5 different pacing modes.



Key: *= p<0.05 for all pacing modes compared to BiV mode.

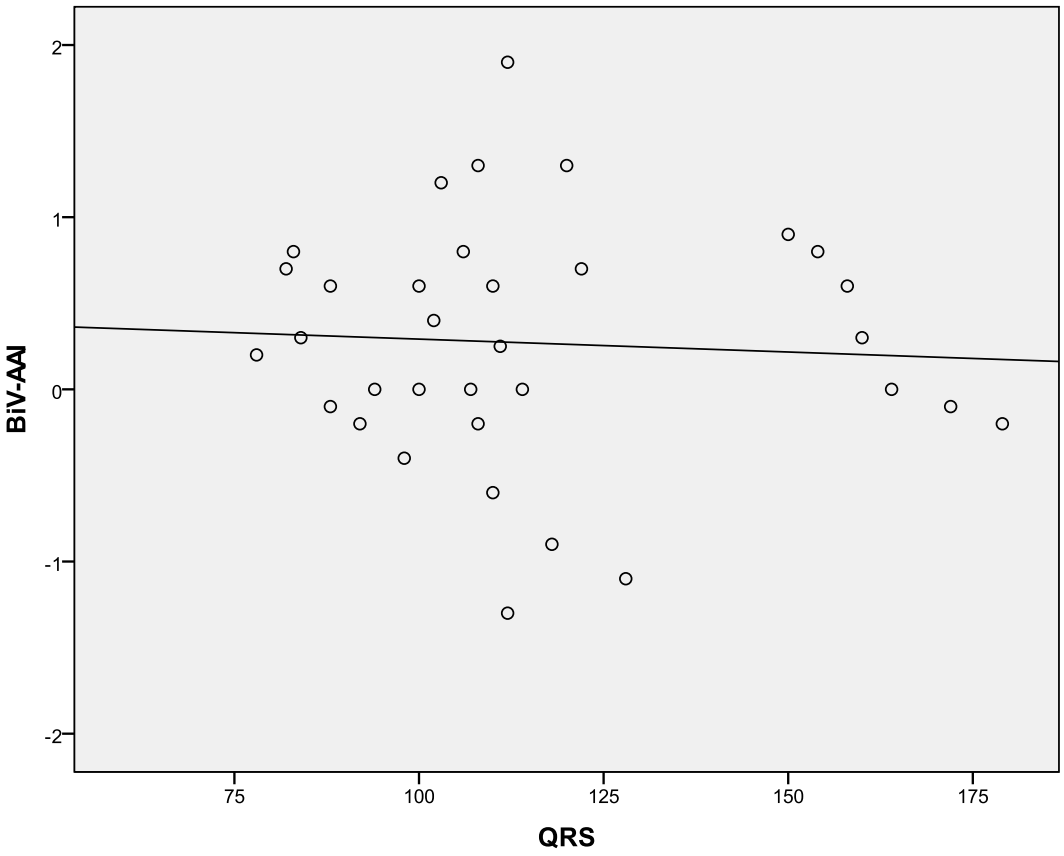
**=p<0.001 for all pacing modes compared to VVI mode

Figure 23: Comparison of cardiac outputs (L/min ±SD) using 5 pacing modes at 18 hours. p=0.02 v AAI; p<0.001 v VVI; p=0.001 v DDD-RV and p=0.003 v DDD-LV compared to BiV pacing).



The net augmentation of cardiac output (BiV-AAI) at 18 hours was analysed for baseline characteristics that may predict a favourable response to BiV pacing. The data were analysed using a linear regression model with 95% confidence intervals. The baseline characteristics analysed included: QRS duration, valve surgery and electro-mechanical dyssynchrony. Figure 24 indicates that there is no link between the augmentation of cardiac output and baseline QRS duration (p=0.97; 95% CI -0.15 to 0.15).

Figure 24: The relationship between QRS duration and augmentation of cardiac output at 18 hours (p=0.965: 95% CI -0.15 to 0.15).



Likewise, valve surgery (p=0.61; 95% CI -0.64 to 1.06), mechanical dyssynchrony (p=0.486; 95% CI -0.59 to 1.20) and electro-mechanical dyssynchrony (p=0.64; 95% CI -0.98 to 0.61) did not predict a favourable response to BiV pacing compared to AAI pacing at 18 hours, see figures 25-27.

Figure 25: The relationship between valve surgery and augmentation of cardiac output at 18 hours, (p=0.61; 95% CI -0.64 to 1.06).

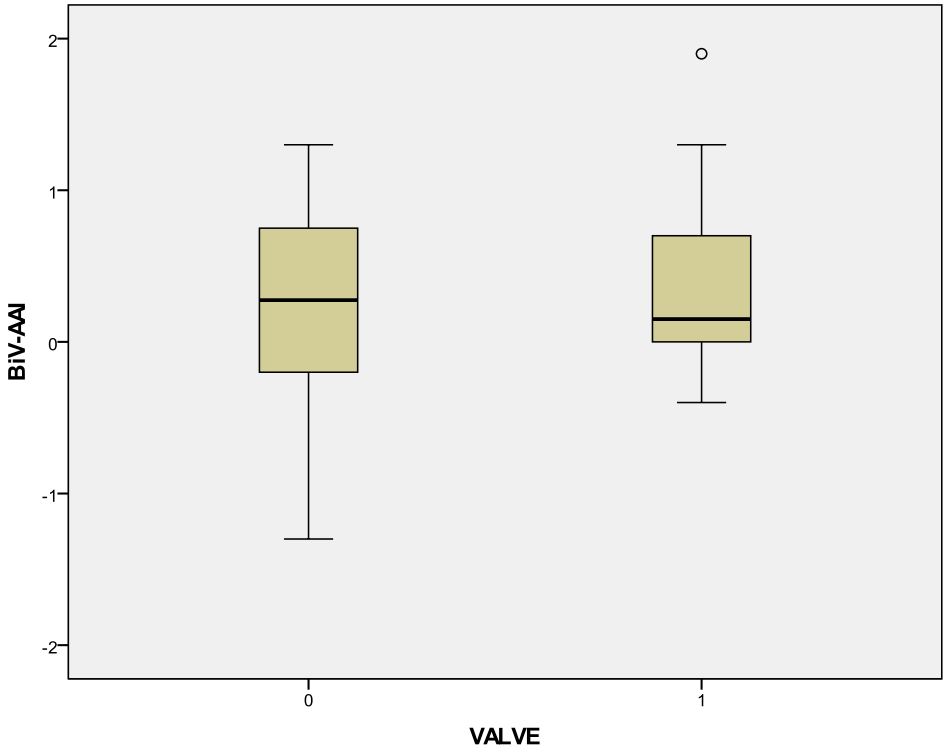


Figure 26: The relationship between mechanical dyssynchrony and augmentation of cardiac output at 18 hours, (p=0.486; 95% CI -0.59 to 1.20).

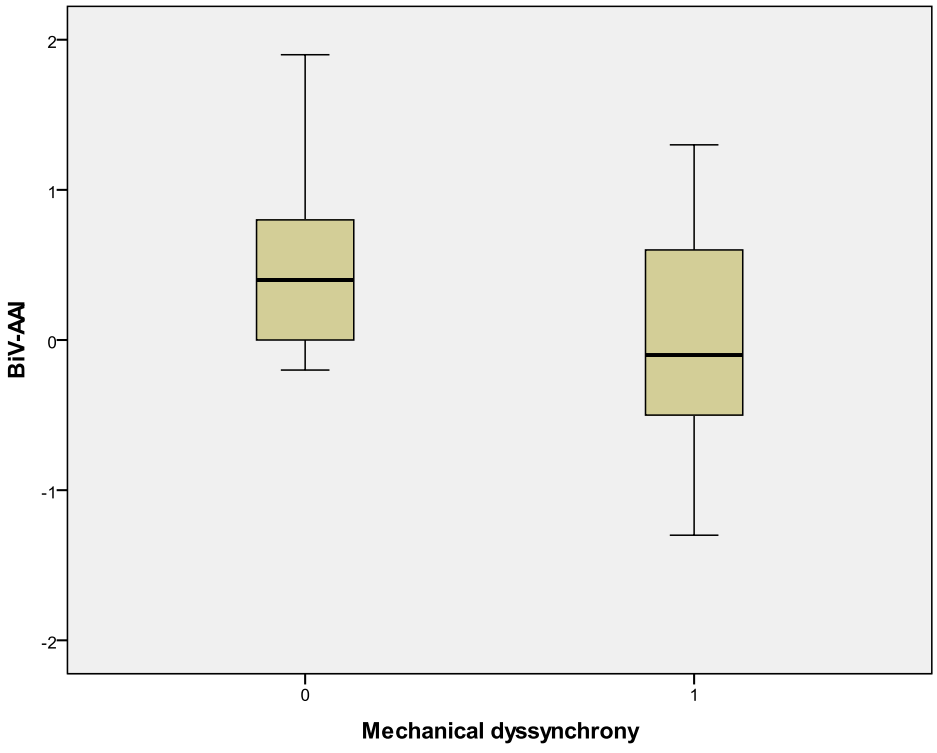
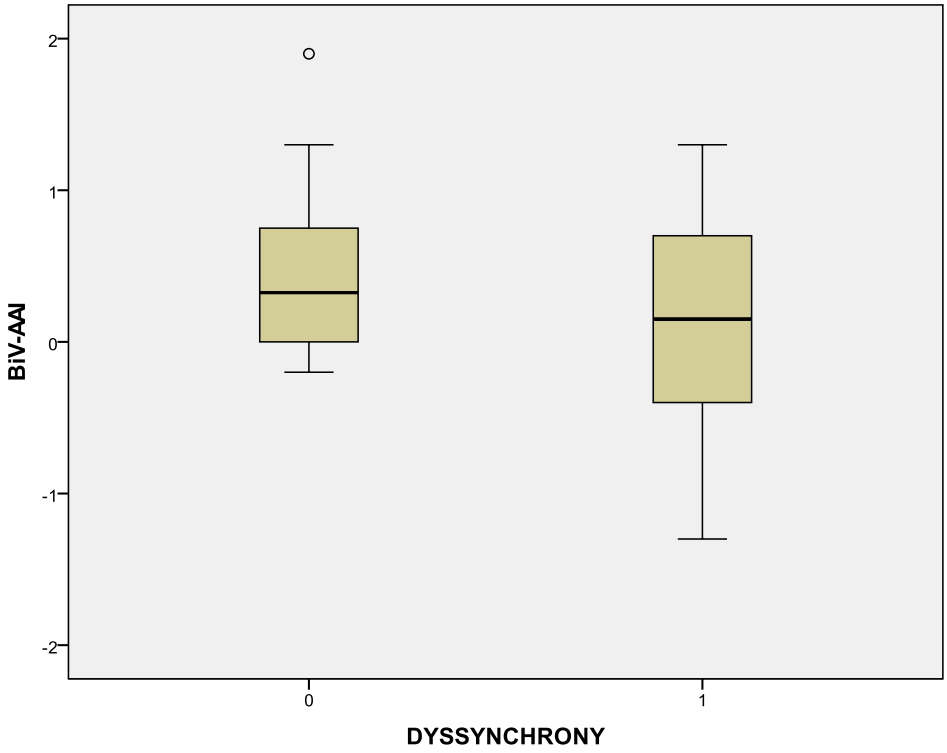


Figure 27: The relationship between baseline dyssynchrony and augmentation of cardiac output at 18 hours, (p=0.64; 95% CI -0.98 to 0.61).

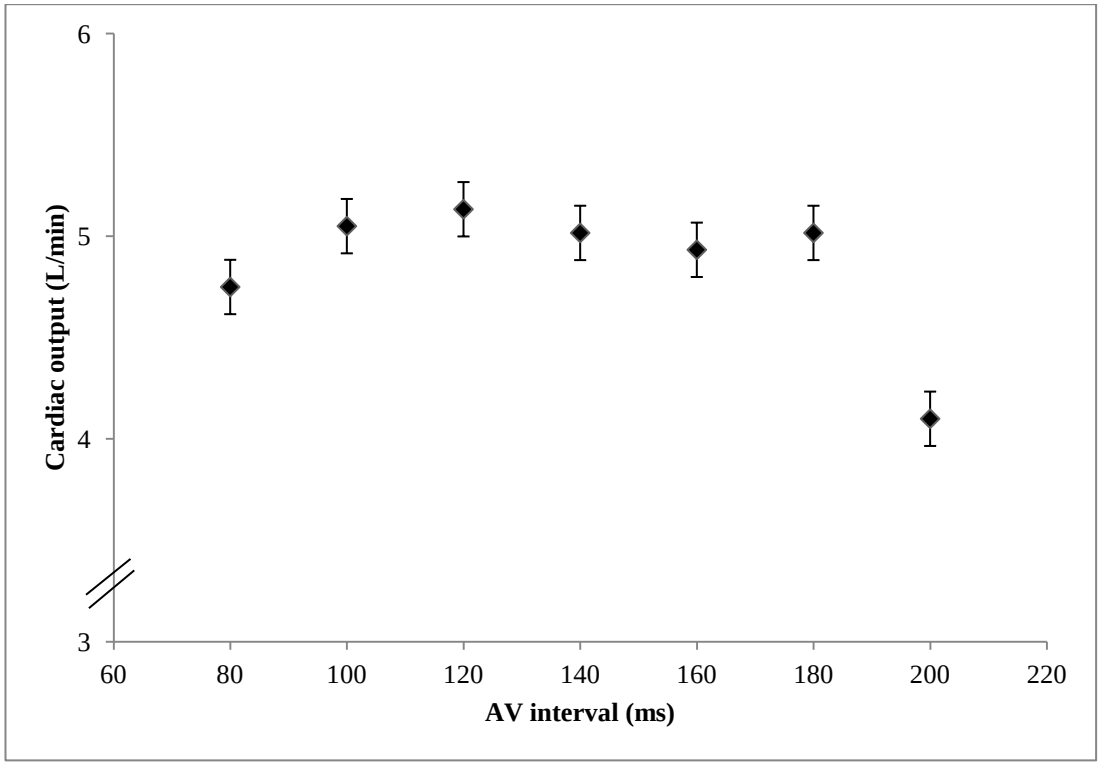


3.2.7 Optimisation of pacing intervals at 18 hours

3.2.7.1 AV optimisation

Cardiac output was measured using a FloTrac device for 7 different AV intervals ranging from 80ms to 200 ms using 20 ms increments with simultaneous VV pacing, see figure 28. The nominal setting was an AV interval of 120 ms.

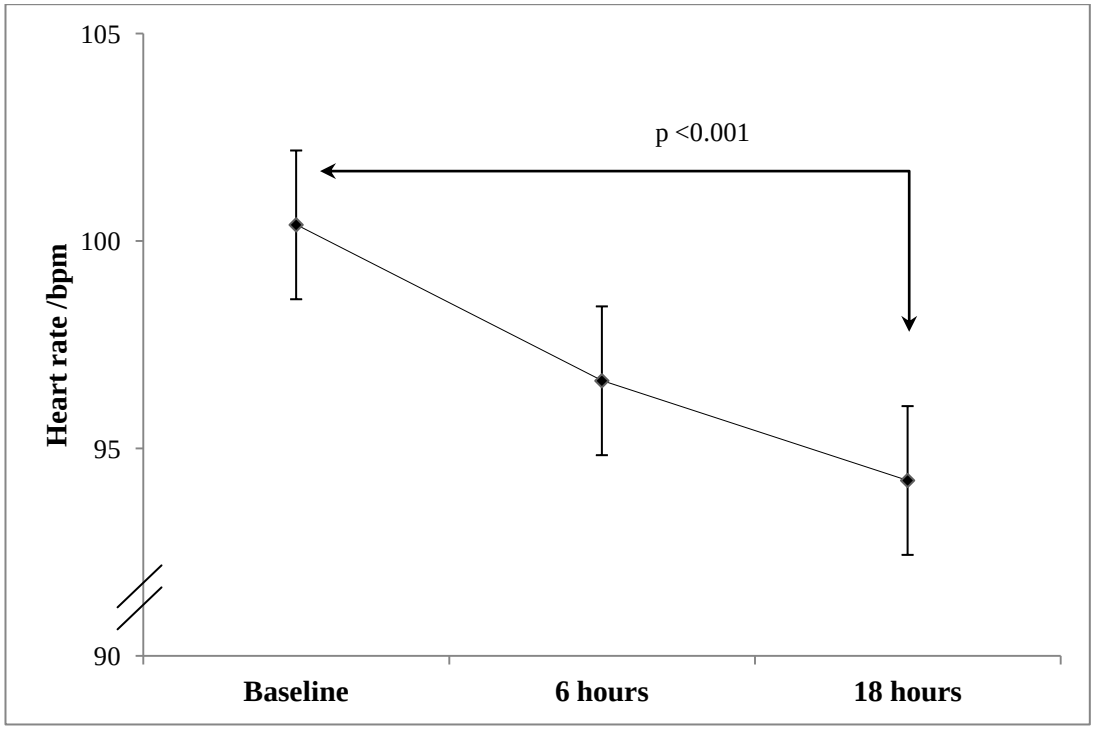
Figure 28: Cardiac output measured at different AV intervals (nominal setting AVI= 120ms). Mean values with standard error of the mean.



A paired T test did not indicate that any that any individual AV delay was superior to the norminal setting ($p>0.05$). Overall, the nominal setting produced the greatest cardiac output and was the optimal AV interval for 40% of patients. The optimal range of AV intervals was from 80-140 ms. A further analysis comparing the individual optimal v nominal AV interval did not increase cardiac output (5.3±0.7 L/min v 5.1±0.7 L/min, $p=0.19$ respectively).

The patients enrolled in this study had a PR interval <200 ms with the exception of one individual. After surgery and in the presence of inotropes, AV conduction may be enhanced, reducing the range of AV intervals available for BiV pacing. The elevated heart rate after surgery also had a dynamic effect on reducing diastole, which again limited the options of AV optimisation, see figure 29.

Figure 29: Heart rate during the trial, at baseline after surgery and 6 and 18-hours. Mean ±SEM.

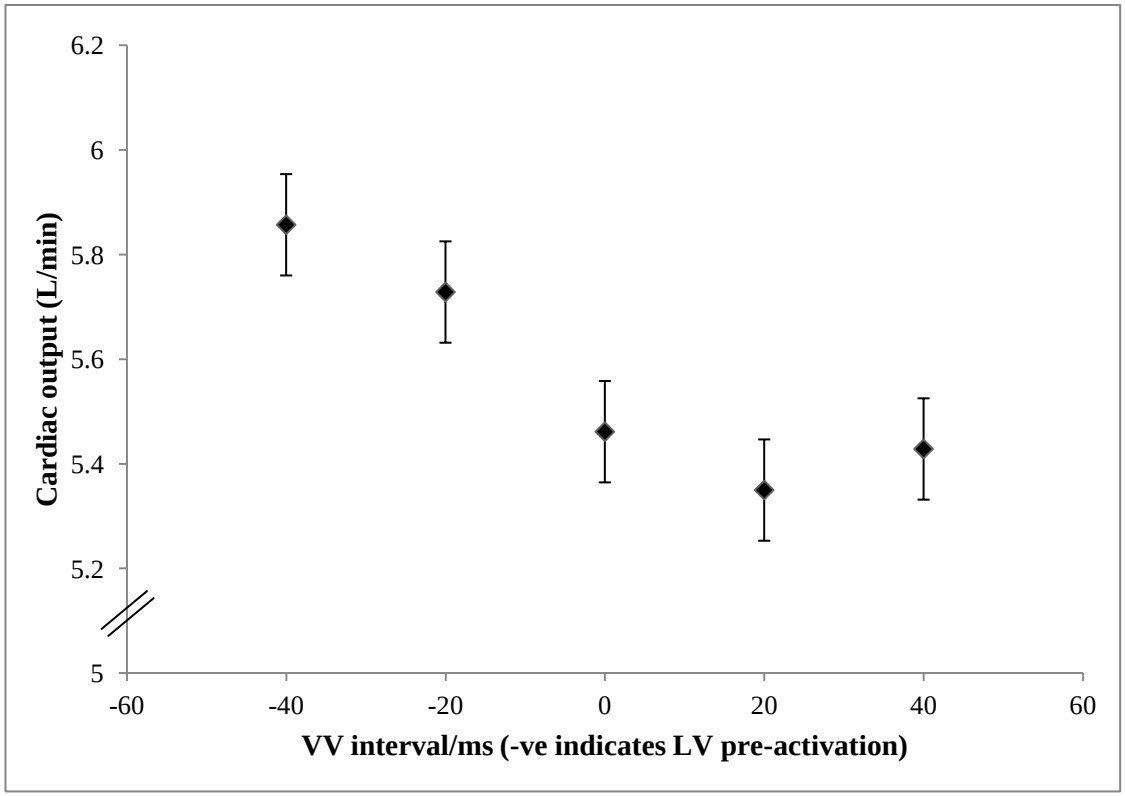


In this study, only 4 subjects were able to receive BiV pacing with an AV interval up to 200ms because of fusion with the intrinsic QRS complex.

3.2.7.2 VV optimisation

Optimisation of VV intervals were conducted over a range from -40 to +40 ms in 20 ms increments (-ve indicating LV pre-activation). The AV interval was set at 120 ms, to prevent fusion with the intrinsic QRS complexes. LV pre-activation by 40 ms yielded the greatest augmentation of cardiac output but this did not reach statistical significance compared to the nominal setting of simultaneous LV and RV pacing (VV=0), see figure 30.

Figure 30: Cardiac output measured at different VV intervals (nominal setting VV= 0ms). Mean values with standard error of the mean.



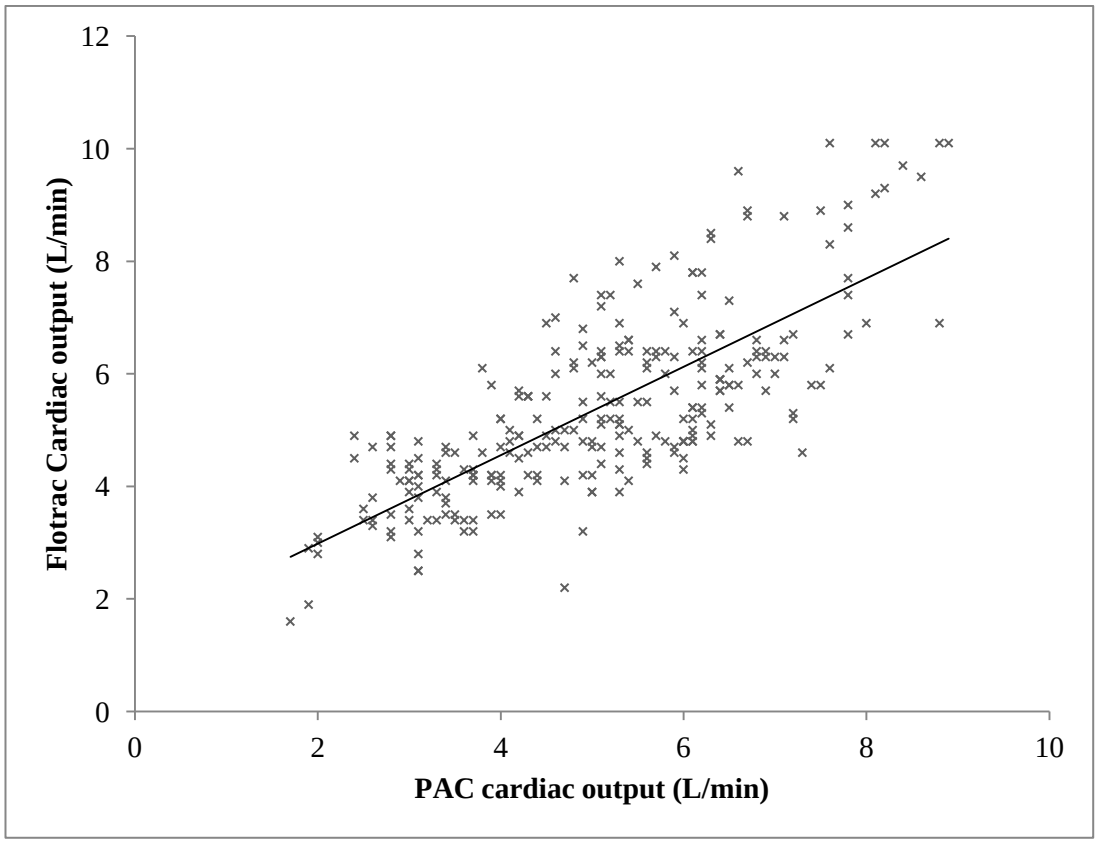
However, the optimal VV interval did produce a small but significant improvement in cardiac output compared to the nominal setting. Optimisation of the VV interval produced a 4% increase in cardiac output, (5.7±1.6 v 5.5±1.7 L/min respectively; p=0.005). 77% of patients benefited from LV pre-activation. The optimal setting was LV pre-activation by 20 ms for 62% of patients.

3.2.8 Comparison of PA catheter and FloTrac

271 measurements of cardiac output were collected simultaneously from a PA catheter and the FloTrac device, during the haemodynamic studies at baseline, 6 hours and 18 hours after surgery. Measurements were collected from 24 patients. The principal exclusion was the peri-operative insertion of an intra-aortic balloon pump

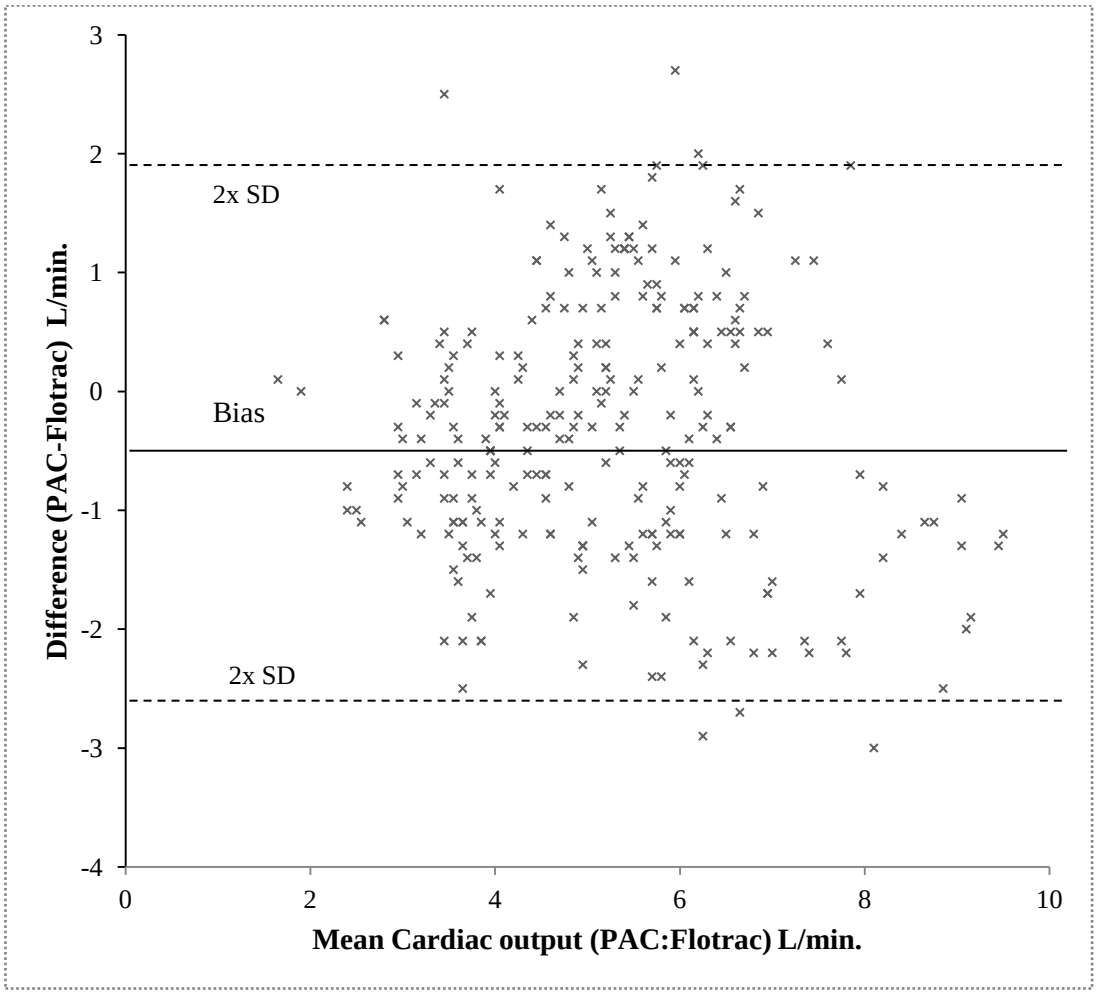
(n=9), which is incompatible with the FloTrac sensor. The data is illustrated in figure 31. A fair correlation is observed between the two devices with a Pearson's correlation co-efficient r=0.75 ($p<0.001$).

Figure 31: Linear correlation between measurements of cardiac output obtained from a PA catheter and FloTrac sensor. Pearson's correlation co-efficient r=0.75 ($p<0.001$).



A second analysis was then conducted using the Bland-Altman method. The bias between the two methods was - 0.33 L/min, with the FloTrac device tending to over-estimate the cardiac output compared to the PA catheter. The precision of the FloTrac sensor (combined standard deviation) was 1.1 L/min, see figure 32.

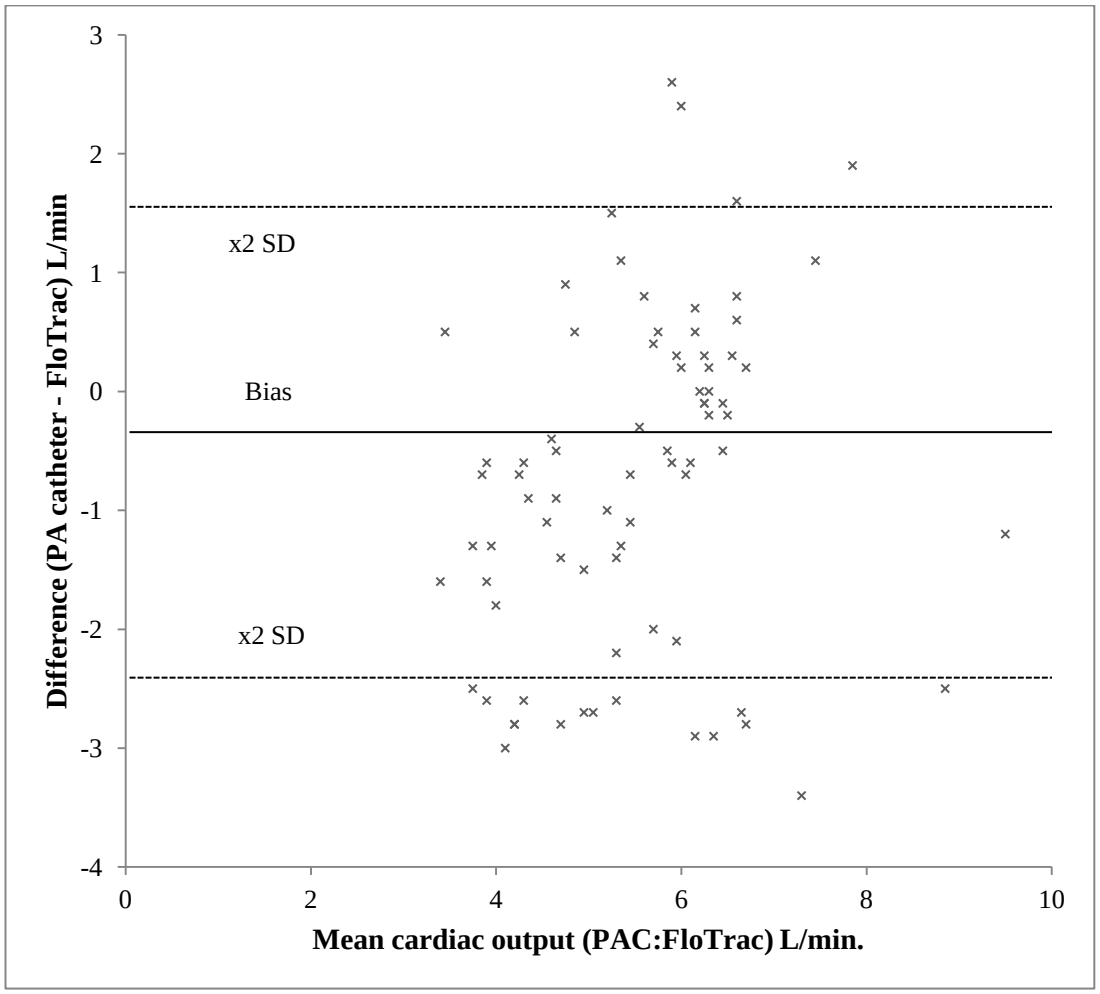
Figure 32: Bland-Altman analysis of cardiac output measured using a PA catheter compared to the FloTrac sensor. Bias=-0.33 L/min ±2.2 L/min, 95% confidence interval (±2SD).



The percentage error was 42.5% using the method described by Critchley and Critchley and was outside of the acceptable threshold of 28.3% (164).

Another analysis was performed using only measurements obtained from thermodilution catheters (n=77 measurements). Using the same method, the bias was -0.76 L/min with the FloTrac device recording a higher output compared to the PA catheters. The precision was 1.2 L/min and the co-efficient of variation was still outside the recommended reference range at 43.0%, see figure 33.

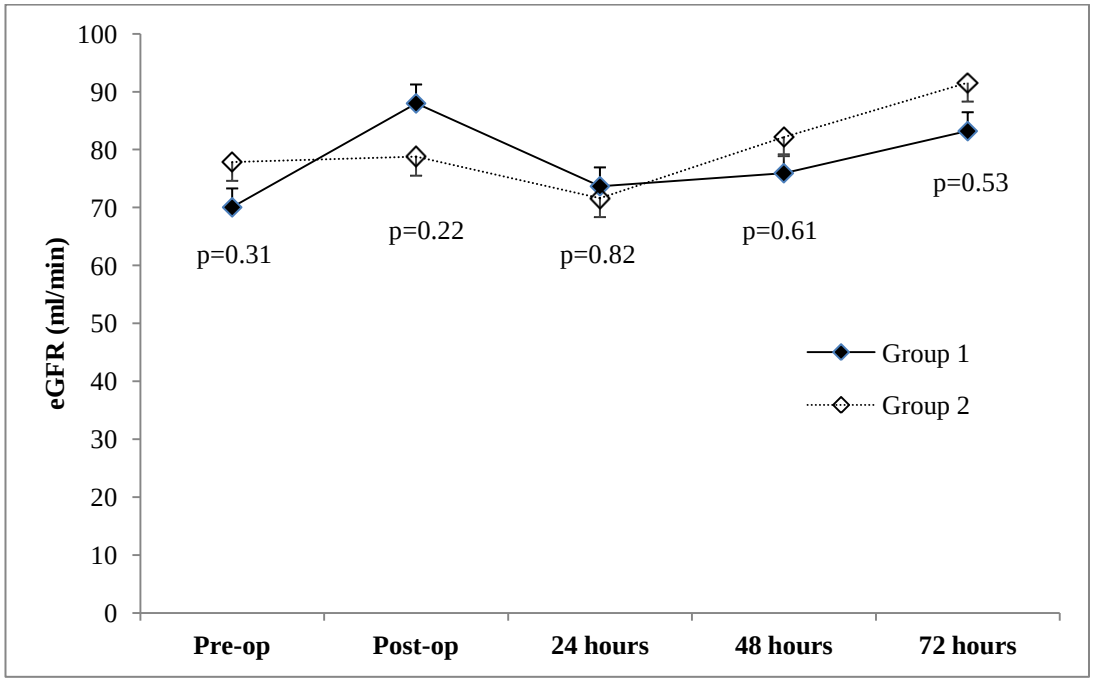
Figure 33: Bland-Altman analysis of cardiac output measured using thermodilution PA catheters compared to the FloTrac sensor. Bias=-0.76 L/min ±2.4 L/min, 95% confidence interval (±2SD).



3.2.9 Renal function

Estimated glomerular filtration rate (eGFR) was measured before surgery and on admission to cardiac ITU and at 24 hours, 48 hours and 72 hours after the operation. Baseline chronic kidney disease score (CKD) was similar in both groups: 2.2±0.9 and 1.9±0.6, p=0.28 in groups 1 and 2 respectively. One patient in group 1 and 2 patients in group 2 required haemofiltration in the cardiac ITU, (p=0.55). Renal function was similar in both groups throughout the trial, see figure 34.

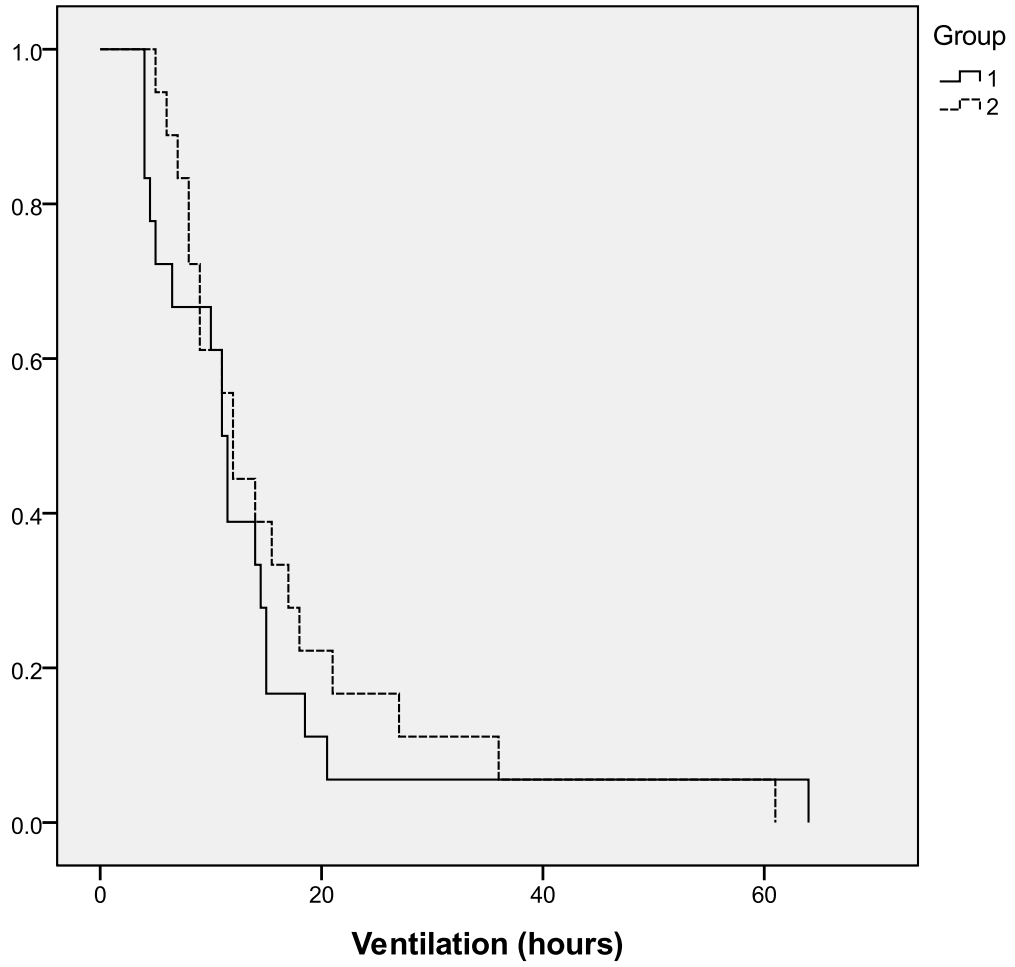
Figure 34: Renal function (eGFR) before and after cardiac surgery (mean±SEM).



3.2.10 Ventilation

The duration of ventilation was similar in both groups, survival analysis (log rank) p=0.85, see figure 35. The majority of patients were extubated within 24 hours. The patient who required emergency re-sternotomy for tamponade required 110 hours of ventilation and one other patient in the BiV group was slow to wean and required 64 hours of ventilation. Mean duration of ventilation was 12.9±13.6 hours v 17.9±24.9 hours in group 1 v 2 respectively.

Figure 35: Kaplan-Meier curve for the duration of ventilation in both treatment groups- log rank p=0.85.



3.2.11 Inotrope infusions

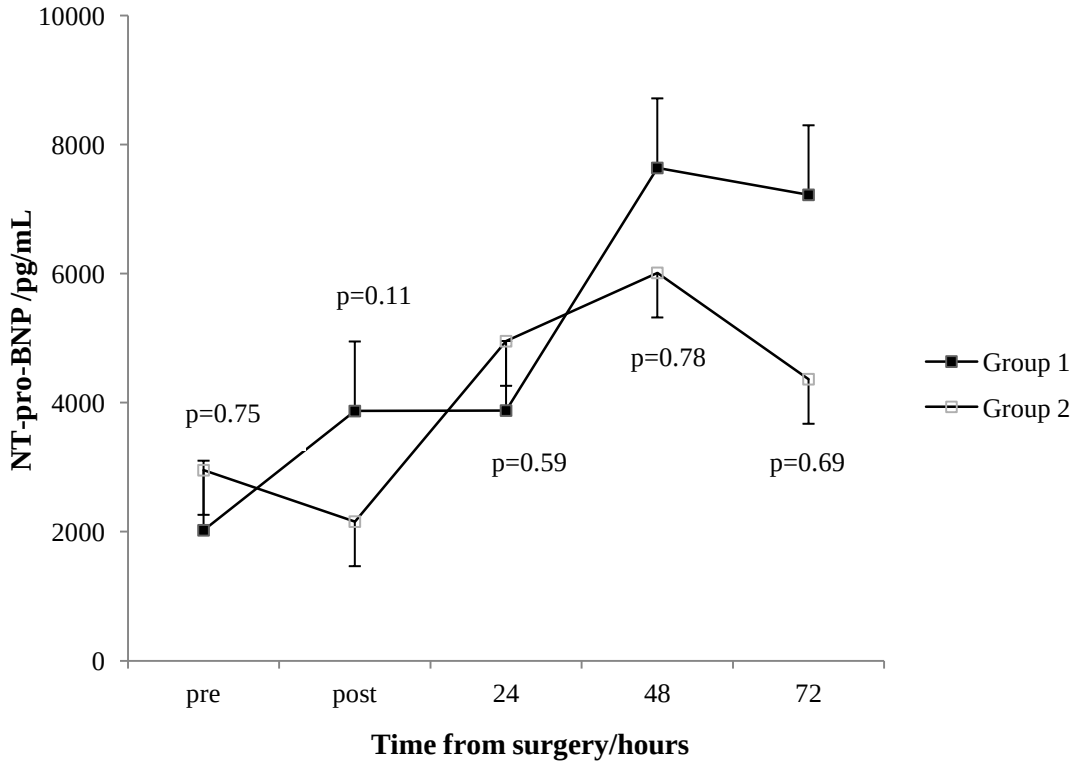
Both enoximone and milrinone were used after cardiac surgery. The average duration of using a phosphodiesterase inhibitor was similar in groups 1 and 2, 37.5±31.2 hours v 56.5±60.3 hours respectively (p=0.24). Likewise, biventricular pacing did not influence the duration of noradrenaline, 53.1±36.9 hours v 53.4±62.5 hours respectively (p=0.98). Correcting the total dose for body mass did not affect the outcome (group 1 v group 2): enoximone- 3.5±1.8 mg/kg v 5.0±3.2 mg/kg (p=0.25); milrinone- 0.6±0.6

mg/kg v 0.6±0.36 mg/kg (p=0.99) and noradrenaline- 0.3±0.5 mg/kg v 0.3±0.4 mg/kg (p=0.97).

3.2.12 NT-pro-Brain Natriuretic Peptide

Plasma was collected at baseline, after bypass surgery and at 24hours, 48 hours and 72 hours after the operation. The baseline measurement of NT-pro-BNP was similar in both groups: group 1 v 2 (2023±6083 pg/ml v 2950±4205 pg/ml; p=0.75 respectively). The change in NT-pro-BNP was analysed in both groups (figure 36). Overall, biventricular pacing did not affect NT-pro-BNP compared to standard post-operative pacing.

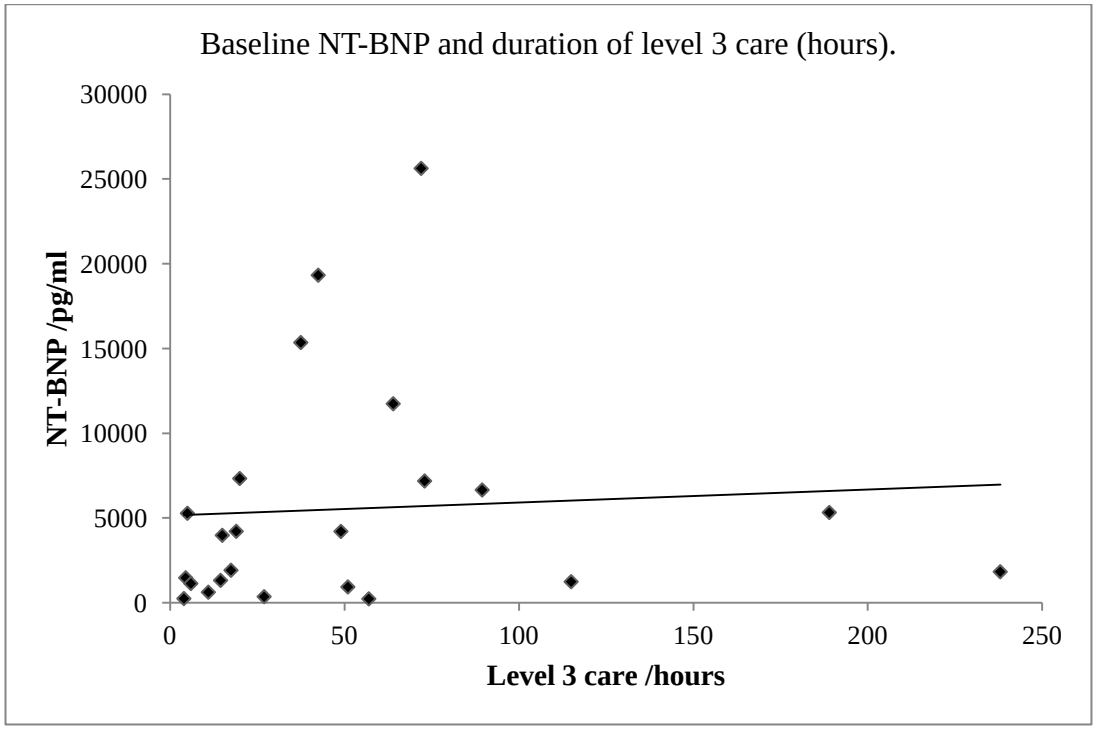
Figure 36: Change in NT-pro-BNP compared to baseline measurements in both treatment groups.



(Median values analysed using Wilcoxon Signed Rank Test).

Likewise, there is no clear correlation between baseline NT-pro-BNP and the duration of level 3 care for both groups, see figure 37.

Figure 37: Relationship between baseline NT-pro-BNP and the duration of level 3 care- Pearson's ranking co-efficient=0.07.



3.2.13 Cardiac biomarkers

Cardiac troponin T (ng/ml) was measured at the same time as NT-pro-BNP. Biventricular pacing did not reduce post-operative TnT levels compared to standard pacing methods, see table 21.

Table 21: Post-operative troponin T in both pacing groups.

Time	Troponin T(ng/ml)		
	Group 1	Group 2	p
Pre-op	0.05 ±0.01	0.21 ±0.66	0.26
Post-op	0.70 ±0.48	0.82 ±0.79	0.66
24 hours	0.60 ±0.28	0.84 ±0.70	0.28
48 hours	0.37 ±0.21	0.46 ±0.51	0.59
72 hours	0.29 ±0.20	0.63 ±0.70	0.13

3.2.14 Complications (arrhythmias and re-operations)

After cardiac surgery, 16 patients developed atrial fibrillation (8 cases in both groups). The arrhythmias were observed after 24 hours and did not affect the pacing protocols. 6 patients were chemically cardioverted with amiodarone (4 patients in group 1 and 2 patients in group 2) and one patient in each group required an electrical cardioversion. There were no documented cases of ventricular arrhythmias after surgery. Only one patient had transient second degree heart block (Mobitz type II) after aortic valve surgery but no patients required permanent bradycardia pacing.

One patient required a re-opening of the sternum after surgery for cardiac tamponade and removal of blood clots with subsequent haemofiltration. This was not related to the temporary pacing wires implanted during surgery. A second patient developed an unstable sternum that required re-wiring on day 10 after the original operation. This patient had been discharged from the ITU and this adverse event did not affect the primary endpoint. Two patients had a stroke and in total 3 patients required haemofiltration including the patient who required the emergency re-sternotomy.

3.2.15 Reproducibility

Intra-observer reproducibility was calculated for RV and LV pre-ejection intervals and TDI measurements of intra-ventricular mechanical delay, (time delay to peak velocity in the basal septum and basal lateral wall). For 10 patients, these measurements were repeated and analysed using a co-efficient of variability model. The results were compared to published data (95, 142), see table 22.

Table 22: Co-efficient of variation (%) for echocardiogram markers of dyssynchrony used in this study compared to data published in previous studies.

Measurement	**This study**	**Thomas**	**Chung**
RV pre-ejection interval /ms	13.9 %		
LV pre-ejection interal/ms	12.4%		3.7%
TDI- septum to lateral wall/ms	30.7%	62.5%	

Intra-ventricular mechanical dyssynchrony was the least reproducible measurement of mechanical dyssynchrony, compared to RV and LV pre-ejection intervals. The low reproducibility of this measurement has previously been reported in studies analysing the clinical utility of mechanical dyssynchrony (142). The reproducibility of these markers limits their clinical application. In this study, baseline mechanical dyssychrony did not influence the primary endpoint (duration of level3 care after surgery) or predict a haemodynamic response to BiV pacing.

Chapter 4- Discussion

4.1 Control study

The patients in this control study had preserved LV systolic dysfunction and no baseline evidence of dyssynchrony using QRS duration or markers of mechanical dyssynchrony. After on-pump cardiac surgery, the diastolic filling time was reduced by 23% and all patients developed paradoxical motion of the inter-ventricular septum.

Although only minor changes in mechanical dyssynchrony were observed on the post-operative echocardiogram, dyssynchrony was not assessed in the immediate post-operative period. During this period, inotropes and the deleterious effects of RV pacing may have resulted in LV inefficiency and BiV pacing rather than dual chamber RV pacing may have been beneficial.

This study was designed to give an insight into mechanical events after on-pump bypass surgery. Patients with preserved LV function and without baseline dyssynchrony were selected, to see if dyssynchrony developed after cardiopulmonary bypass. This would have important implications and support the hypothesis that BiV pacing may be beneficial post-bypass, even in patients without baseline dyssynchrony.

The sample size was limited in this study and on reflection a larger sample of patients would have offered reassurance that a type 2 error had not been observed. This study was designed and approved as a major amendment to the main trial and timescale limited recruitment into this trial. The data collected from the post-operative echocardiogram was also limited. The recent sternotomy limited the image quality and patient co-operation with a detailed imaging protocol. The echocardiographic protocol was therefore adapted to focus on mechanical dyssynchrony, which was obtained in all patients who agreed to the post-operative scan.

Despite these limitations, analysis of the data for the impaired LV study supported the finding of the control study. In the main study, there were no major changes in mechanical dyssynchrony after cardiopulmonary bypass. However, the post-operative echocardiogram was performed after stopping the temporary pacing and inotropes, which are potential causes of dyssynchrony.

On reflection, a TOE would have allowed assessment of peri-operative dyssynchrony using the different pacing modes. However, in the early post-operative period (<6 hours), acute resynchronisation with BiV pacing did not increase cardiac output compared to atrial-inhibited or dual chamber pacing.

4.2 Main study

4.2.1 Recruitment

This research trial was successfully completed over an 18 month period. Initially patients were recruited from the Cardiac Centre at the University Hospital of Wales, Cardiff. The initial recruitment was limited and to achieve the required sample size, patients were also recruited from the Cardiac Centre at Morriston Hospital, Swansea.

There were several reasons why recruitment was limited at the start of the trial. This included limited numbers of patients with heart failure receiving cardiac surgery, technical problems with operating equipment/sterile packs and the availability of 'off-pump' bypass surgery. In total, 74 patients were invited into this trial, 6 patients declined participation, 6 patients had off-pump surgery and 7 patients did not have an operation. 55 patients provided written consent and 38 patients completed the trial.

The recruitment rate was approximately 50% (38/74) and lower than our anticipated rate of 65-70%. The logistics of trying to attend operations at two sites limited recruitment. 3 patients provided consent and were subsequently not included in the final analysis and a further 6 were not enrolled because of conflicts in the operation schedule.

4.2.2 Echocardiography and dyssynchrony

A transthoracic echocardiogram was performed on all patients entering the research trial. However, only 2 patients received a dobutamine stress echocardiogram for viability, which was part of the original trial protocol, and 2 patients had a PET scan. There were several reasons for the limited number of dobutamine scans including: patients with unstable coronary artery disease (n=3); concomitant valvular heart disease (n=15); left main or proximal LAD disease (n=9) and pre-operative intra-aortic balloon pump (n=5). The STICH sub-study also reported difficulty in performing viability studies with only 601/1212 patients receiving an assessment which included 280 dobutamine stress echocardiograms (177). In our trial, the attending Consultant Cardiac Surgeon and/or Cardiologist made the final clinical judgement on whether a viability assessment was required before surgery.

Despite the limitation of performing dobutamine stress echocardiography, all patients received a transthoracic echocardiogram before and after surgery. 15 patients were found to have mechanical dyssynchrony on the pre-operative echocardiogram. The haemodynamic data showed no association between baseline dyssynchrony and response to BiV pacing. There are several explanations for this result. Firstly, the total sample size was limited and 74% of patients had QRS duration <120 ms. Secondly,

after surgery all patients may develop mechanical dyssynchrony from RV pacing or alterations in loading conditions that would not necessarily respond to BiV pacing. Thirdly, the study by Chung et al (95) reported that no single echocardiographic marker of dyssynchrony was sufficiently robust to predict a response to BiV pacing to be used in routine clinical practice.

Although Chung's study was published in 2008, a more recent publication in 2013 studying radial strain and TDI time delay in regional deformation, also failed to predict a response to BiV pacing (ECHO-CRT) (108). Patients received optimal medical therapy and had QRS duration <130 ms. This study was prematurely terminated at 19 months follow up on the grounds of futility and there was an association between BiV pacing and an increase in mortality.

In summary, the data to support BiV pacing in patients with QRS duration <120 ms is limited to small, single-centre studies and it has not been found to be beneficial in multi-centre, randomised, control trials. The data from BiV studies after cardiac surgery would also suggest that QRS duration >120 ms is required to observe a haemodynamic response to BiV pacing (129, 137). A prolonged QRS duration (>120 ms) is also required for post-operative permanent BiV pacing to observe LV remodelling and reduced mortality (138).

4.2.3 Surgical protocol

This study was conducted at two cardiac centres and 9 cardiac surgeons enrolled patients into this trial. Despite variations in surgical and anaesthetic practice, all patients had on-pump bypass surgery and received 6 pacing wires as defined in the protocol. My initial plan was to recruit patients from only 1 centre to reduce

confounding factors but two centres were required to achieve the desired sample size. On reflection, recruiting patients scheduled for revascularisation only and not valve operations may have been desirable. However, patients are more likely to require pacing after aortic valve surgery and therefore, this group of patients merited investigation.

There were subtle variations in the choice of post-operative inotropes but in general, all patients received a phosphodiesterase inhibitor in combination with noradrenaline. Thermodilution catheters were used at the University Hospital of Wales, Cardiff but the cardiac centre at Morriston Hospital used the continuous cardiac output PA catheter. Unfortunately, clinical governance issues prevented standardising the PA catheter. However, the same Flotrac/Vigelio system was used in both centres.

4.2.4 Primary endpoint

The duration of level 3 was used as the primary endpoint. Although other studies have reported the total duration of ITU stay, we thought that the duration of level 3 care was a more robust and clinically relevant endpoint. It is based on a patient's requirement for multi-organ support and invasive ventilation. The duration of level 3 care has a clear definition and is not influenced by logistical issues including the availability of beds on step down units or portering services.

For the majority of patients 30/38 (80%), the primary endpoint was achieved after extubation and then successful weaning to a single inotrope or vasopressor. For eight patients, the primary endpoint was reached after extubation. This small cohort of patients had baseline hypertension and therefore minimal requirements for a vasoconstrictor to be combined with a phosphodiesterase inhibitor. There was a skewed

distribution with the majority of patients reaching the endpoint within 48 hours but a small number of patients required prolonged multi-organ support. This included one patient requiring an emergency re-sternotomy for tamponade with subsequent acute renal failure requiring haemofiltration, one patient who required prolonged inotropic support and haemofiltration and one without haemofiltration.

The results from this trial are similar to the findings reported by Eberhardt (130) and Evonich (132) with biventricular pacing having no net effect on the duration of ITU admission compared to other pacing modes.

The trial by Pokushalov (138) did report a 1.4 day reduction in ITU stay with biventricular pacing compared to standard post-operative pacing. However, the duration of ITU stay was longer in Pokushalov's study (CRT group: 2.5±0.5 days v no CRT: 3.9±0.6 days; $p<0.001$) compared to this trial, 22.0 hours (IQR: 16.0-66.5 hours) and 37.5 hours (IQR: 16.3-55.0 hours) in group 1 and 2 respectively (log-rank $p=0.58$) and the trials by Eberhardt (130) and Evonich (132). This may be due to variations in the description of the primary endpoint. However, there were no haemodynamic studies to explain the significant reduction in ITU admission with biventricular pacing in Pokushalov's trial.

4.2.5 Haemodynamic data

Haemodynamic data were collected from all patients that were enrolled into this study. Only one patient was excluded from the trial because we were unable to float a PA catheter. There were no complications related to the insertion of a PA catheter or the additional pacing wires. The initial haemodynamic studies showed that biventricular pacing was not superior to the other pacing methods with the exception of

VVI pacing. However, at 18 hours biventricular pacing was found to be superior to all other pacing modes. There are several potential explanations for this finding.

Firstly biventricular pacing is usually performed in patients taking optimal doses of heart failure medications including beta blockers. However after cardiac surgery, beta blockers are temporarily discontinued. In addition, patients are prescribed inotropes, which counteract the beneficial effect of beta-blockade and also increase heart rate. Finally, immediately after surgery patients are hypovolaemic, hypothermic and ventilated. These factors may reduce the clinical benefit of biventricular pacing compared to the other pacing modes.

At 18 hours, the majority of patients were extubated and the dose of inotropes was minimal. There was also a net reduction in heart rate at 18 hours compared to baseline (baseline: 100.4±15.9 b.p.m v 18 hours: 94.2±9.5 b.p.m; $p<0.001$). This may explain why biventricular pacing was observed to be beneficial only at 18 hours compared to other standard pacing modes, figure 29.

In context, in the absence of diabetes, pre-operative arrhythmia and heart block on separation from cardio-pulmonary bypass, only 2.6% require temporary pacing after cardiac surgery (123). However, the risk of a serious complication from temporary pacing wires is low (0.04%). In this high-risk surgical cohort, atrial synchronous pacing should be considered because of the significant reduction in cardiac output (>20%) with VVI pacing. If prolonged ventricular pacing is likely because of pre-operative HIS/Purkinje fibre disease or the nature of the operation (180, 181), then temporary BiV pacing should be considered.

4.2.6 Optimisation of pacing intervals

Pacing intervals were optimised at 18 hours using a FloTrac haemodynamic monitor. These measurements were taken after performing a full set of haemodynamic measurements in 5 different pacing modes at 18 hours using a PA catheter and a FloTrac device.

The FloTrac monitor was used because it rapidly recorded acute changes in cardiac output. The disadvantage of using a PA catheter was the time required to perform 3-5 separate haemodynamic measurements of cardiac output using thermodilution or the time required for the continuous cardiac output monitor to calibrate after each change in an AV or VV interval. 12 separate measurements of cardiac output were required per patient for the AV and VV optimisation protocol.

The limitation of using a FloTrac device was that all patients with an intra-aortic balloon pump were excluded from the optimisation study. The FloTrac device cannot be calibrated in patients with aortic counter-pulsation. Therefore, 9 patients were excluded from the optimisation protocol. Optimisation of the VV interval was feasible in all patients. Left ventricular pre-activation was found to be beneficial compared to nominal settings. The optimal VV interval produced a 4% augmentation of cardiac output ($p=0.005$). Although statistically significant, the clinical utility of this small improvement in cardiac output is open to interpretation.

AV optimisation was limited because most patients had a normal PR interval on their resting ECG. This limited the range of AV delays that would allow biventricular pacing, without fusion with intrinsic rhythm. Only two patients could be paced with an AV interval of 200 ms. The data suggest that an AV interval of 120 ms is optimal and there is an acute decrement in cardiac output with an AV interval <100 ms

or >180 ms. However this did not reach statistical significance. This may impart be explained by the limited sample size.

4.2.7 FloTrac system

The arterial wave form analysis device (FloTrac, Edwards Lifesciences) was easy to use and rapidly reported acute changes in cardiac output, for example when VVI pacing was assessed during the haemodynamic studies. One of the major disadvantages of this technology is that the device is incompatible with intra-aortic balloon pumps, which are frequently used in high risk patients.

The Bland-Altman analysis revealed a small bias between the PA catheter and the FloTrac device (0.33 L/min) but a wide 95% confidence interval ±2.2 L/min. The percentage error (42.5%) was also in excess of the acceptable limit of <30%. The poor correlation between these two methods of assessing cardiac output, along with the limitations of the FloTrac device suggests that the PA catheter remains a better option for monitoring high-risk patients in ITU after surgery.

However, it is important to highlight that PA catheters carry a 1-2% risk of significant complications including pulmonary artery or tricuspid valve injury (161). In addition, the continuous cardiac output catheter is slow to respond to acute changes in cardiac output and the thermodilution method of assessing cardiac output is less reliable immediately after surgery, in the context of systemic hypothermia (161). In routine clinical practice, the risks and benefits of invasive haemodynamic monitoring need to be carefully considered on an individual basis.

An alternative method of assessing cardiac output and volume status after cardiac surgery is the transoesophageal Doppler. Previous studies have reported that

peri-operative Doppler guided volume replacement reduces the length of hospital admission by 2.5 days (18%) (p=0.02) and reduces the incidence of gut mucosal hypoperfusion by 8-fold (182, 183). However, this technology has only been investigated in elective cardiac patients with preserved function and not in patients with severe LV dysfunction. This technology has a good safety record with minimal risk of complications (184). Future studies should consider evaluating this technology to optimise fluid status and inotropes in the cardiac ITU. This device may also be helpful to optimise the AV and VV pacing intervals and is compatible with an intra-aortic balloon pump.

4.2.8 Limitations

Recruiting patients into this trial was challenging because of the requirement for additional pacing wires and a PA catheter. 38 patients completed this trial, which represents the third largest published study of temporary biventricular pacing after cardiac surgery. The largest study (n=178) did not publish acute haemodynamic data. The primary endpoint was survival at 18 months between patients receiving biventricular pacing compare to a control group.

The average duration of biventricular pacing in group 1 was 22.7±8.8 hours, which on average was 12.3±28.4 hours less than the duration of level 3 care (p=0.07). The temporary biventricular pacing was frequently discontinued on the morning after surgery at the request of the attending surgeon, when the patient had a minimal requirement for inotropes. Although the patients were haemodynamically stable, they had not reached the primary endpoint. It is possible that continuation of biventricular pacing may have altered the primary endpoint. However, it is unlikely that continuation

of biventricular pacing beyond this point would have changed the clinical outcome after the operation.

It is also difficult to comment on whether a prolonged duration of temporary biventricular pacing would have reduced the incidence of post post-operative atrial fibrillation. 8 patients in the biventricular pacing group developed atrial fibrillation, the peak of which was observed on post-operative day 2-3.

The duration of AV/VV optimised pacing was limited to 4.8±8.8 hours before discontinuation of biventricular pacing. It is possible that a longer duration of optimised biventricular pacing may have been beneficial with respect to the primary endpoint. However the beneficial effects of biventricular pacing were only evident at 18 hours and not at baseline or 6 hours. Finally, performing the optimisation protocol was time-consuming. It would have been difficult to keep inotropic concentrations constant, to allow for an accurate comparison cardiac output at baseline or 6 hours. At 18 hours most patients were extubated and prescribed low concentrations of inotropes, which made performing an optimisation protocol feasible.

Chapter 5- Summary

5.1 Conclusions

The main findings of this thesis are:

- Patients with preserved LV function (EF >45%) have minimal evidence of mechanical dyssynchrony. After on-pump cardiac surgery, only subtle changes are observed, including a 23% reduction in diastolic filling time and a paradoxical motion of the inter-ventricular septum- section 3.1.
- Intra and inter-ventricular mechanical delay were not adversely affected by on-pump cardiac surgery in patients with severe LV systolic dysfunction- section 4.2.2.
- Temporary biventricular pacing is feasible and safe after cardiac surgery. The most common side-effect is phrenic nerve stimulation which was noted in 16% (3/19) patients and can usually be resolved by reprogramming the LV pacing voltage- section 3.2.14.
- Despite the routine use of pacing wires after cardiac surgery, only 1 patient developed transient second degree AV block, after an aortic valve replacement- section 3.2.14.
- The primary endpoint, 'duration of level 3 care' was not influenced by temporary BiV pacing. Previous trials have reported similar results even with 96 hours of BiV pacing (130, 132)- section 3.2.5.
- Baseline mechanical dyssynchrony did not predict a response to temporary BiV pacing in patients with severe LV systolic impairment- section 3.2.6.
- Temporary BiV pacing improved cardiac output at 18 hours but not at baseline or 6 hours after surgery compared to all other pacing modes with the exception of VVI pacing. This may in part be explained by a reduction in heart rate at 18

hours compared to baseline measurements; 6.2 b.p.m reduction observed at 18-hours v baseline ($p < 0.001$)- section 3.2.6.

- VVI pacing uncoupled AV synchrony and was detrimental to haemodynamic function compared to all other pacing modes in this trial, reducing cardiac output by up to 19%- section 3.2.6.
- VV optimisation increased cardiac output by 4% but this small increment may be of limited clinical value. 77% of patients benefitted from LV pre-activation but no individual setting was found to be superior to the nominal setting (RV=LV)- section 3.2.7.
- AV optimisation was not beneficial but all except one patient had a normal PR interval (<200ms) on the pre-operative ECG- section 3.2.1.
- BiV pacing did not influence: the duration of ventilation or inotropes; the total dose of inotropes; or post-operative markers of myocardial injury including troponin T (TnT) and NT pro-brain natriuretic peptide (NT-pro-BNP)- sections 3.2.10 to 3.2.13.
- Equal numbers of arrhythmic events were observed in both treatment groups (BiV v standard pacing). The episodes of atrial fibrillation occurred after discontinuation of the temporary BiV pacing- section 3.2.14.
- All patients survived to 30-days after surgery and were successfully discharged from hospital. Two patients had a cerebro-vascular event. One patient required an emergency re-sternotomy for bleeding, which significantly prolonged there duration of level 3 care- section 3.2.14.
- There were no adverse events from using PA catheters or LV pacing wires in this trial. Only one set of LV wires was implanted outside the region of the first

obtuse marginal branch of the circumflex artery because of LV scar tissue- sections 3.2.3 and 3.2.14.

- The PA catheters were usually removed on post-operative day 1 to allow the patient to sit out of bed. This limited the time frame to collect haemodynamic data to less than 24 hours- section 3.2.6.
- The duration of BiV pacing was 12.3±28.4 hours less than the duration of level 3 care in group 1, (p=0.08). BiV pacing was only prematurely discontinued at the request of the surgical team. In most cases, the inotropic requirements were minimal when the BiV pacing was stopped and this is unlikely to influence the transition from level 3 to level 2 care- section 3.2.5.
- The FloTrac/Vigelio system uses pulse-contour analysis to calculate cardiac output from the radial arterial tracing. This method is simple to use and rapidly reports acute changes in cardiac output but the percentage error was 42.5% and outside an acceptable limit of agreement with the PA catheter- reference <28.3% (164)- section 3.2.8.
- Future studies should target patients with broad QRS durations, and consider pacing at the site of latest LV activation. Future research should also investigate the effects of post-operative BiV pacing in patients with atrial fibrillation.

5.2 Future directions

This was a challenging and yet rewarding research project. Recruitment was slow at the start of this study. There were many reasons including: the limited number of patients with severe LV dysfunction having cardiac surgery; the prevalence of AF in this population and logistical issues, including our supply of temporary BiV pacing boxes. The addition of a second surgical centre and a second pacing box undoubtedly

helped with recruitment. The total number of patients recruited into this study exceeded the estimated sample size.

5.2.1 Dyssynchrony

Unfortunately, BiV pacing did not influence the duration of level 3 care in this study. The largest study of BiV pacing after cardiac surgery reported that permanent epicardial BiV pacing after surgical revascularisation reduced mortality by 16% compared to CABG-only (138). This study recruited patients with a QRS duration >120 ms or mechanical dyssychrony, including: inter-ventricular mechanical delay >40 ms; aortic pre-ejection delay >140 ms or intra-ventricular dyssychrony using TDI. Most patients had a prolonged QRS duration, the mean duration was 139±28ms.

The trial by Straka et al, included patients with QRS >150 ms or 120-149 ms with dyssynchrony on 3D TOE (129). LV lead position was targeted to the site of latest LV activation and the AV and VV pacing intervals were optimised using TOE. BiV pacing increased mean arterial pressure by 5% and cardiac output by 24% compared to dual-chamber RV pacing (129).

These data suggest that patients with a QRS duration >120 ms are more likely to benefit from post-operative BiV pacing rather than taking all patients with severe LV dysfunction. This should guide patient selection for future studies of BiV pacing after cardiac surgery. The data to recommend 3D transoesphageal echocardiography to guide LV lead positioning is limited but the provisional results appear promising. Further studies to confirm this hypothesis would be welcome.

Pre-operative mechanical dyssychrony with a QRS duration <120 ms does not appear to influence the post-operative response to BiV pacing. Selecting patients based on QRS duration appears to be the best strategy.

5.2.2 Post-operative AV block

The number of patients developing second or third degree AV block after surgery was limited to one patient. Overall, the proportion of patients requiring post-operative pacing is 9%, but the loss of AV synchrony with VVI pacing reduces cardiac output by up to 20% (123).

Therefore, patients with severe LV dysfunction should receive atrial pacing wires. If patients are likely to require post-operative ventricular pacing, BiV pacing would be the preferable option. Patients are more likely to require post-operative ventricular pacing after aortic valve surgery or if AV block is present on separation from the cardio-pulmonary bypass circuit.

5.2.3 Atrial fibrillation

This study followed the pattern of the randomised control trials of BiV pacing by recruiting patients in sinus rhythm. However, in the heart failure population up to 30% of patients have AF and this sub-group of patients remains under researched. The study by Eberhardt et al, included 12% (n=11) of patients in AF before surgery but this sub-group was too small for sub-analysis (130).

Patients with paroxysmal AF may spend up to 90% of the time in sinus rhythm and permanent BiV pacing may reduce the number and duration of these arrhythmic

episodes and promote atrial remodelling (185). However, there is no clear evidence that post-operative BiV pacing reduces the incidence of atrial arrhythmias. This is an area that would merit further research.

A meta-analysis of heart failure patients in atrial fibrillation who received BiV pacing, reported that BiV pacing improved heart failure symptoms and LV remodelling (186). NHYA score improved on average by one point on the NHYA scale and EF by 10% compared to baseline. However, heart rate control is important in this group of patients to ensure a high percentage of BiV pacing and AV node ablation may improve clinical response to BiV pacing v no ablation (RR 0.4; 95% CI 0.28-0.58; $p<0.001$) (187, 188). Therefore, the elevated heart rate after cardiac surgery may suggest that BiV pacing is unlikely to improve cardiac output compared to intrinsic rhythm. However, in patients with post-operative AV block, BiV pacing may be beneficial and this merits investigation.

A further consideration is whether the group of patients who receive pulmonary vein isolation/AF ablation during surgery may benefit from BiV pacing to maintain sinus rhythm. This may be considered in heart failure patients with prolonged QRS durations but there is evidence to suggest that bi-atrial pacing may reduce AF after cardiac surgery.

A study of 220 patients, who had a MAZE procedure with or without valve surgery, over-drive bi-atrial pacing reduced incidence of post-operative AF by 3-fold compared to right atrial pacing or no atrial pacing ($p <0.01$) (189). A study of patients with no prior history of AF reported that bi-atrial pacing reduced the occurrence of AF after CABG by 3-fold, compared to left or right atrial, or no atrial pacing ($p <0.05$) (190). Bi-atrial pacing in combination with BiV pacing may prevent post-operative AF

and optimise cardiac output, but requesting up to 8 temporary pacing wires after surgery may be ‘a bridge too far’, even for a pacing enthusiast!

5.2.4 Haemodynamics

The requirement for inotropic support is at its highest in the early post-operative phase. The study by Lalu et al, illustrated a nadir in LV stroke work index at 3 hours after surgery, that eventually improved by 12 hours (figure 1) (43). Paradoxically, the beneficial effects of BiV pacing were not observed until 18 hours after surgery and the mean duration of inotropic support was 48.2±48.3 hours. Therefore, inotropes and intra-aortic balloon counter-pulsation are required to support cardiac output during this critical period.

The trial by Eberhardt et al, reported no reduction in ITU admission or increase in cardiac output with BiV pacing compared to conventional pacing modes, after 96 hours of post-operative BiV pacing (130). Therefore, the shorter duration of BiV pacing is this study is unlikely to have influenced the primary endpoint. The duration of post-operative pacing should be based on the requirements for bradycardia pacing rather than haemodynamic support. There was no evidence that post-operative BiV pacing reduced myocardial injury (TNT/NT-pro-BNP) or protected against acute kidney injury compared to conventional pacing in Eberhardt’s study or my study.

These statements are based on the current published literature of post-operative BiV pacing, which principally enrolled patients with narrow QRS complexes (<120 ms). There is limited data from Straka et al, that BiV pacing may increase cardiac output after surgery in patients with QRS durations >120 ms. Future studies should

focus on the haemodynamic effects of temporary BiV pacing in patients with prolonged QRS durations (>120 ms).

5.2.5 Pacing intervals

Optimisation of the AV and VV pacing intervals was performed at 18 hours after surgery. It was technically difficult to perform AV optimisation because of the elevated resting heart rate and the limited range of AV intervals available for optimisation. VV optimisation did yield a small (4%) increase in cardiac output. In routine practice, optimisation of these pacing intervals is unlikely to alter clinical outcome with respect to the duration of ITU admission or inotropic support. This process is time consuming and can take up to 1 hour to perform.

Only one other study has reported data on AV/VV optimisation after cardiac surgery. Wang et al, reported that optimised BiV pacing increased cardiac output by 13% ($p=0.003$) compared to atrial-inhibited pacing in 11 patients, QRS 116±19ms and EF <35% (157). Further studies are required to confirm these findings.

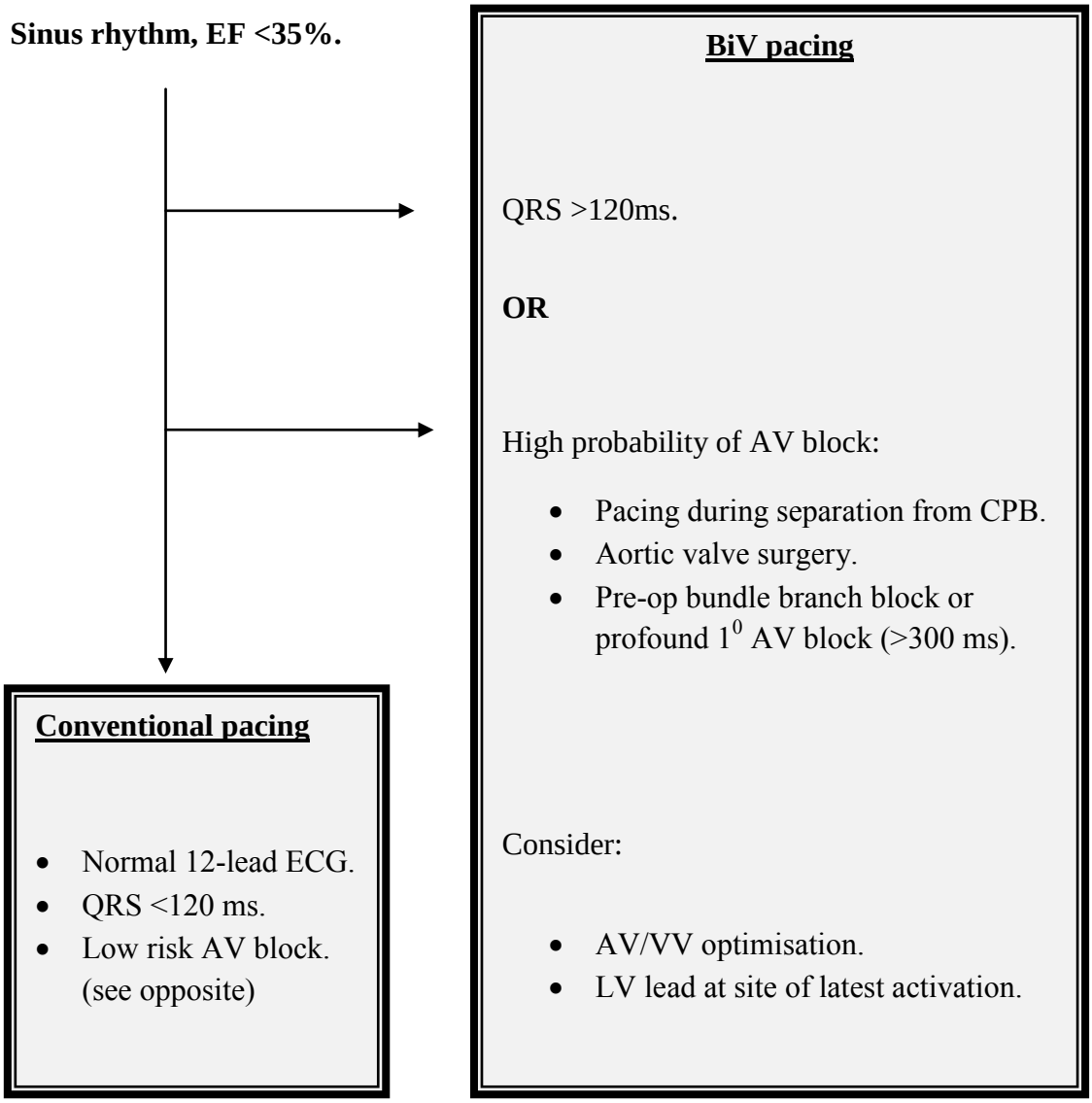
Optimisation of pacing intervals may be considered for patients who require post-operative pacing, extending beyond the first 24 hours after surgery. There are limited data to suggest that optimised BiV pacing may improve cardiac output compared to nominal BiV settings.

5.3 Pacing algorithm

After reading the literature and conducting this trial, I would suggest the following algorithm for post-operative BiV pacing, illustrated in figure 38.

Haemodynamic studies should be performed at 18 hours to confirm augmentation of cardiac output with BiV pacing compared to conventional pacing modes. At this stage, AV/VV optimisation may be considered: if patients have escalating requirements for inotropic agents or are likely to require prolonged BiV pacing as a bridge to permanent device implantation.

Figure 38: Algorithm for post-operative BiV pacing.



5.4 Final Summary

Biventricular pacing is an established heart failure treatment for patients with severe LV dysfunction (EF <35%) and prolonged QRS durations (QRS >120 ms). The beneficial haemodynamic effects of temporary biventricular pacing after cardiac surgery are minimal in patients with narrow QRS complexes (QRS <120 ms). I only observed a small (7%) increase in cardiac output with biventricular pacing compared to dual chamber-RV and atrial inhibited pacing at 18 hours. For biventricular pacing to be beneficial after surgery, this increment needed to be observed in the first 6 hours after the operation.

Biventricular pacing could be considered in patients with severe LV impairment and QRS duration >120 ms, especially if prolonged pacing is anticipated after cardiac surgery. A nominal AV interval of 120 ms is usually programmed but optimisation may produce a further small increment in cardiac output. The optimal AV delay is variable and needs to be defined for each patient although this is a time consuming process.

For the majority of patients the standard right atrial and right ventricular leads will suffice to treat post-operative AV block which is an uncommon event after isolated coronary artery bypass surgery.

Appendix A

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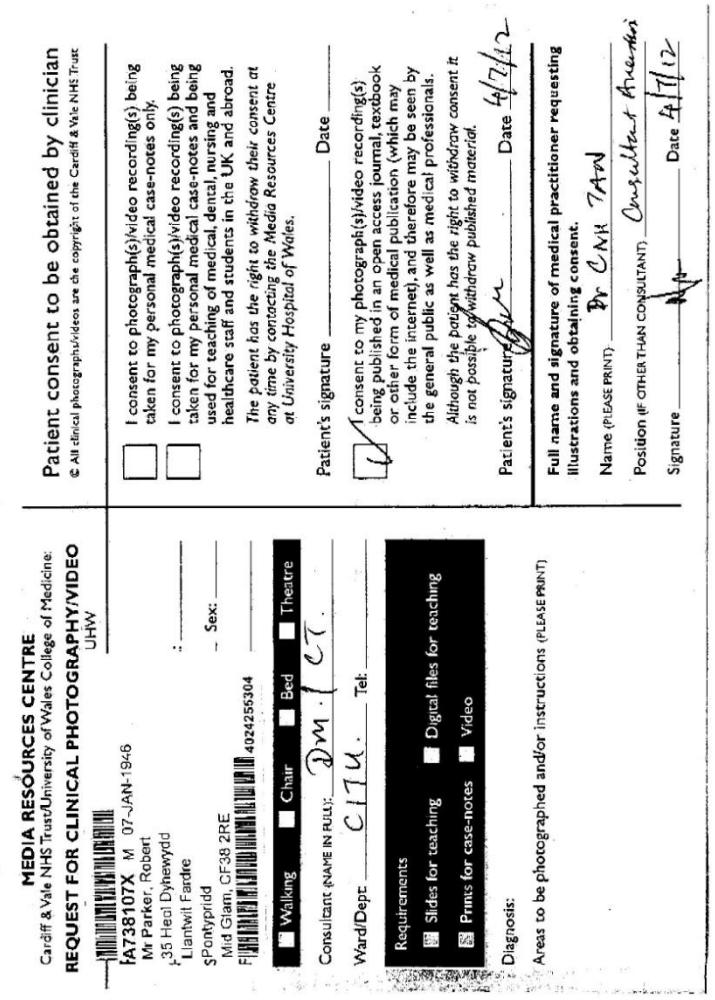

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Consultant (NAME IN FULL): DM. Pict.

Ward/Dept: CITU. Tel:

Requirements
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Prints for case-notes Video

Diagnosis:

Areas to be photographed and/or instructions (PLEASE PRINT)

Patient consent to be obtained by clinician
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Although the patient has the right to withdraw consent it is not possible to withdraw published material.

Patient's signature _____ Date 4/7/12

Full name and signature of medical practitioner requesting illustrations and obtaining consent.

Name (PLEASE PRINT): Dr CNH TAYLOR

Position (IF OTHER THAN CONSULTANT) Consultant Anaesthetist

Signature _____ Date 4/7/12

Consent form for figure 9.

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