Effects of Selective Site Pacing on Haemodynamic and Functional Recovery in Patients Requiring Permanent Right Ventricular Pacing

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by

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(International Standard Randomised Controlled Trial Registration Number: ISRCTN 67629267)

The single centre randomised trial aimed to assess whether right ventricular outflow tract (RVOT) compared to right ventricular apical (RVA) pacing is more beneficial at the medium term follow-up.

Fifty patients were randomised to either RVA (n=25) or RVOT (n=25) pacing. Baseline and 6 month follow-up investigations included: electrocardiogram, New York heart failure functional (NYHA) class, Minnesota Living with Heart Failure (MLWHF) score, Short Form-36 health survey (SF-36), echocardiogram, and a cardiopulmonary exercise test. The primary endpoint was peak oxygen consumption (PVO_2). Secondary endpoints were: NYHA class, MLWHF and SF-36 scores, LVEF, and dyssynchrony criteria.

There were no significant differences in changes in PVO_2 levels between the study groups. Similarly, QRS duration changes were not significantly different between the study groups. In contrast, MLWHF scores improved significantly in the RVOT group (32 ± 19) compared with the RVA group (21 ± 22), P=0.041. In addition, SF-36 health survey indicated better scores in RVOT patients in the following areas: (1) Physical Function, 36.6 ± 28.0 (RVOT) versus 11.2 ± 26.0 (RVA), P = 0.005; (2) Role Limitation due to Emotional Problem scores, 43.3 ± 9.7 (RVOT) versus 4.5 ± 11.6 (RVA arm), P = 0.016; (3) Vitality Energy Fatigue scores 26.3 ± 27.0 (RVOT) versus 7.2 ± 24.0 (RVA), P = 0.024. Echocardiogram data were not significantly different between the groups.

Within the limits of this study, RVOT pacing was not superior to RVA in terms of PVO_2 and echocardiogram parameters. However, RVOT pacing apparently offered a significant improvement in some health-related quality of life scores. Larger multi-centre randomised studies with a longer follow-up are now indicated.

List of Abbreviations

6MWT	6 minute walk test
AF	atrial fibrillation
AP	anteroposterior
BiV-P	biventricular pacing
CHB	complete heart block
CHF	chronic heart failure
CO	cardiac output
CPET	cardiopulmonary exercise test
CRT	cardiac resynchronisation therapy
CXR	chest X ray
DDD	dual chamber pacemaker
dP/dt	changes in pressure over time
ECG	electrocardiogram
HF	heart failure
ICD	implantable cardioverter defibrillator
IVD	interventricular delay
LAO	left anterior oblique
LBBB	left bundle branch block
LVEDD	left ventricular end-diastolic diameter
LVEF	left ventricular ejection fraction
MLWHF	Minnesota living with heart failure
NYHA	New York Heart Association Functional Class for Heart Failure
PA	postero-anterior
PVO_2	peak oxygen consumption (corrected for body mass)
QRSd	QRS complex duration
RAO	right anterior oblique
RBBB	right bundle branch block
RVA	right ventricular apex
RVA-P	right ventricular apical pacing
RVOT	right ventricular outflow tract
RVOT-P	right ventricular outflow tract pacing
RVS	right ventricular septum
SF-36	short form- 36 health survey
SSP	selective site pacing
SSS	sick sinus syndrome
VAT	ventilatory anaerobic threshold
VE	ventilatory equivalent
VTI	velocity time integral
VVI	single chamber ventricular pacemaker

Contents

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Author's Declaration

This thesis is the result of my own work. The material contained in the thesis has not been presented, nor is currently being presented, either wholly or in part for any other qualification. The research and clinical work were both carried out exclusively at the Liverpool Heart and Chest Hospital. All studies described in this thesis were either performed by me or in conjunction with other colleagues and other research personnel at Liverpool Heart and Chest Hospital.

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CHAPTER ONE

Introduction

Foreword

The right ventricular apex (RVA) has been the elective site for placing endocardial pacing leads since 1959 when Seymour Furman described the use of the transvenous route for pacemaker implantation (Furman & Schwedel 1959). Although, review of the X- ray following Furman's implant in fact demonstrates the lead to be within the basal septum. The RVA has subsequently been used because it is easily accessible, readily identified, and associated with a stable position and reliable chronic pacing parameters. It was recognised, however, that pacing from the RVA did not reproduce normal ventricular conduction or contraction. With the advent of reliable active fixation leads, alternative right ventricular sites became accessible and began to be explored. In this thesis introduction, the detrimental effects of RVA pacing will be outlined, the right ventricular outflow tract (RVOT) will be defined, and the evidence for selective site pacing (SSP) will be discussed.

1.1. Anatomy of the conduction system

1.1.1 Sinoatrial node

The sinoatrial (SA) node is a subepicardial structure located at the junction of the right atrium and superior vena cava. It has abundant autonomic innervation and a copious blood supply; it is often located within the adventitia of the large SA nodal artery, a proximal branch of the right coronary artery (55%), or the left circumflex coronary artery. Histologically, the SA node consists of a dense framework of collagen that contains a variety of cells, among them the large, centrally located P cells, which are thought to initiate impulses; transitional cells, intermediate in structure between P cells and regular atrial myocardial cells; and Purkinje-like fibre tracts, extending through the perinodal area and into the atrium.

1.1.2 Atrioventricular node

The atrioventricular (AV) node is a small subendocardial structure within the interatrial septum located at the convergence of the specialised conduction tracts that course through the atria. Like the SA node, the atrioventricular node has extensive autonomic innervation and an abundant blood supply from the large atrioventricular nodal artery, a branch of the right coronary artery in 90% of cases, and also from septal branches of the left anterior descending coronary artery. Histologic examination of the AVN reveals a variety of cells embedded in a loose collagenous network including P cells (although not nearly as many as in the SA node), atrial transitional cells, ordinary myocardial cells, and Purkinje cells.

1.1.3 His bundle

Purkinje fibres emerging from the area of the distal atrioventricular node converge gradually to form the His bundle, a narrow tubular structure that runs through the membranous septum to the crest of the muscular septum, where it divides into the bundle branches. The His bundle has relatively sparse autonomic innervation, although its blood supply is quite ample, emanating from both the AV nodal artery and septal branches of the left anterior descending artery. Longitudinal strands of Purkinje fibres, divided into separate parallel compartments by a collagenous skeleton, can be discerned by histologic examination of the His bundle. Relatively sparse P cells can also be identified, embedded within the collagen.

1.1.4 Bundle branches

The bundle branch system is an enormously complex network of interlacing Purkinje fibres that varies greatly among individuals. It generally starts as one or more large fibre bands that split and fan out across the ventricles until they finally terminate in a Purkinje network that interfaces with the myocardium. In some cases, the bundle branches clearly conform to a trifascicular or quadrifascicular system. In other cases, however, detailed dissection of the conduction system has failed to delineate separate fascicles. The right bundle is usually a single, discrete structure that extends down the right side of the interventricular septum to the base of the anterior papillary muscle, where it divides into three or more branches. The left bundle more commonly originates as a very broad band of interlacing fibres that spread out over the left ventricle, sometimes in two or three distinct fibre tracts. There is relatively little autonomic

innervation of the bundle branch system, but the blood supply is extensive, with most areas receiving branches from both the right and left coronary systems.

1.2 Physiological background

1.2.1 The normal physiology of the conduction system and ventricular activation

The SA node has the highest rate of spontaneous depolarisation (automaticity) in the specialised conduction system, and under ordinary circumstances, it is the major generator of impulses. Its unique location astride the large SA nodal artery provides an ideal milieu for continuous monitoring and instantaneous adjustment of heart rate to meet the changing metabolic needs of the body. The SA node is connected to the AV node by several specialised fibre tracts, the function of which has not been fully elucidated. The AV node appears to have three major functions: It delays the passing impulse for approximately 0.04 seconds under normal circumstances, permitting complete atrial emptying with appropriate loading of the ventricle; it serves as a subsidiary impulse generator, as its concentration of P cells is second only to that of the SA node; and it acts as a type of filter, limiting ventricular rates in the event of an atrial tachyarrhythmia. His bundle arises from the convergence of Purkinje fibres from the AV node, although the exact point at which the AV node ends and the His bundle begins has not been delineated either anatomically or electrically. The separation of the His bundle into longitudinally distinct compartments by the collagenous framework allows for longitudinal dissociation of electrical impulses. Thus, a localised lesion below the bifurcation of the His bundle (into the bundle branches) may cause a specific conduction defect (e.g., left anterior fascicular

block). The bundle branches arise as a direct continuation of the His bundle fibres. Disease within any aspect of the His bundle branch system may cause conduction defects that can affect AV synchrony or prevent synchronous right and left ventricular activation. The electrical activation wavefronts first exit to the LV endocardial cavity at the lower interventricular septum and then propagate in an apicobasal direction because the initial portion of the His-Purkinje system is electrically insulated from the surrounding contractile ventricular myocardium. As a result, the mechanical contraction begins at the apex and progresses upward to eject blood into the aorta. The high conduction velocity of cardiac electrical impulses through the His-Purkinje conduction system (3-4 m/s) ensures rapid and synchronised depolarisation of ventricular myocardium that is essential for effective blood pumping. As demonstrated in the perfused isolated human heart (Durrer et al. 1970), the electrical activation of the LV starts synchronously (within 5 milliseconds) at 3 endocardial areas (the anterior paraseptal wall, the left surface of the mid-interventricular septum, and the posterior paraseptal wall about one third the distance from apex to base) and envelops nearly the whole LV endocardial cavity 30 milliseconds after the onset of ventricular activation, except the latest activated regions at the inferior and/or posterobasal area. Electrical activation of the whole left ventricle completes within 80 milliseconds. A similar LV electrical activation sequence has also been observed in patients undergoing endocardial catheter mapping (Cassidy et al. 1984). This normal and rapid electrical activation sequence of the left ventricle is essential for synchronous and coordinated myocardial contraction for optimal LV performance.

1.2.2 Pathophysiology of abnormal ventricular activation

1.2.2.1 Adverse haemodynamic effects of left bundle branch block

The normal physiologic electrical activation of the left ventricle can be disrupted in patients with structural heart diseases, such as dilated cardiomyopathy, as manifested by the occurrence of intraventricular conduction defect with left bundle branch block (LBBB) and/or widening of QRS duration. During LBBB, the ventricular activation starts in the right ventricle, and the left ventricle is activated by a slow right-to-left transseptal conduction, which then propagates into the LV cavity at the middle third and/or the apical third of the LV septum before spreading through the whole LV cavity (Vassallo et al. 1984). Because this propagation of electrical impulses in LBBB is primarily through the slowly conducting myocardium (0.3-1 m/s) instead of the His-Purkinje system, the total LV activation time is prolonged. This abnormal electrical activation sequence leads to LV mechanical dyssynchrony with inefficient cardiac performance due to internal transfer of work between the early and late activated region of the chamber (Prinzen et al. 1999). In fact, cardiac functional abnormality, including prolonged LV isovolumetric contraction and relaxation times, abbreviation of LV filling, and RV-LV asynchrony in systole and diastole have been demonstrated in patients with LBBB (Grines et al. 1989). More importantly, the presence of LBBB has been shown to be an independent predictor of cardiac mortality and morbidity in patients with systolic heart failure (Baldasseroni et al. 2002).

1.2.2.2 Adverse haemodynamic effects of right ventricular apical pacing

During RV apical pacing, the surface electrocardiogram pattern simulates that of spontaneous LBBB. Similar to LBBB, the LV activation during RV apical

pacing initiates with slow transseptal activation through the myocardium and then exits to the LV endocardial cavity at the interventricular septum. However, it has been postulated that after exiting into the left ventricle, the paced wavefronts may reengage the intact distal Purkinje system with a more rapid LV depolarisation to activate the rest of the left ventricle (Wyndham et al. 1980). Nonetheless, the latest activated region has consistently been the inferolateral base during RV apical pacing. Adverse haemodynamic effects of RV apical pacing have been long recognised in the mammalian heart and the animal model (Prinzen & Peschar 2002). The authors demonstrated that in canine hearts with experimental LBBB, LV pacing significantly improves left ventricular pump function. Similarly, Burkhoff et al demonstrated that the LV contractile strength changes with the sites of ventricular pacing and shows a linear inverse relationship between the changes in QRS duration (Burkhoff, Oikawa, & Sagawa 1986). In experimental and clinical studies, there is a rightward shift of the pressure-volume relationship during the LV end-systolic phase, and the left ventricle operates at a larger volume during RV apical pacing (Prinzen & Peschar 2002). These acute haemodynamic changes are associated with a decrease in both LV stroke volume and the maximal rate of rise in LV pressure (+dP/dt). Furthermore, both short-term and long-term clinical studies have demonstrated a reduction of LV ejection fraction (LVEF) by 5% to 10% with RV apical pacing (Tse et al. 2002). In addition, RV apical pacing may also lead to impairment of diastolic function with a reduction of diastolic filling time and maximal rate of fall of LV pressure (−dP/dt). Several mechanisms (Fig 1.1) have been proposed for the mechanical inefficiency during abnormal LV electrical activation and contraction during RV pacing (Sweeney & Prinzen 2006). First, the early

activated portion of LV close to the pacing site contracts at low chamber pressure and stretches the opposing non-contracting wall. This stretching causes an increased force of contraction because of the local Frank-Starling mechanism and further delays the shortening of the late activated portion of the LV. As a result, the late activated portion elicits contraction at higher wall stress because the early activated region is in a period of systolic stiffening and imposes loading on the early activated portion. This reciprocated stretching and contraction of opposing LV walls leads to wasting of energy because of internal transfer of mechanical work and inefficient contraction. Indeed, recent advances in echocardiographic technique with tissue Doppler imaging have provided further insight to the occurrence of LV dyssynchrony after RV pacing. In patients with congenital AV block or iatrogenic AV block after AV nodal ablation for atrial fibrillation (Tops et al. 2006), a substantial proportion of patients developed new onset echocardiographic evidence of intra- and/or interventricular dyssynchrony, which was associated with deterioration of LV function. Second, the changes in LV contraction pattern during RV apical pacing result in redistribution of regional myocardial mechanical work and perfusion. In experimental study (Lee et al. 1994), regional myocardial oxygen consumption and perfusion at the early activated region near the pacing site are decreased because of a reduction in mechanical loading. Similarly, clinical studies have demonstrated a reduction in regional LVEF at the site of stimulation and the presence of perfusion defects in up to two thirds of RV apically paced patients without any significant coronary artery disease (Tse et al. 2002). Interestingly, the change in coronary perfusion at the pacing site is reversible upon cessation of pacing.

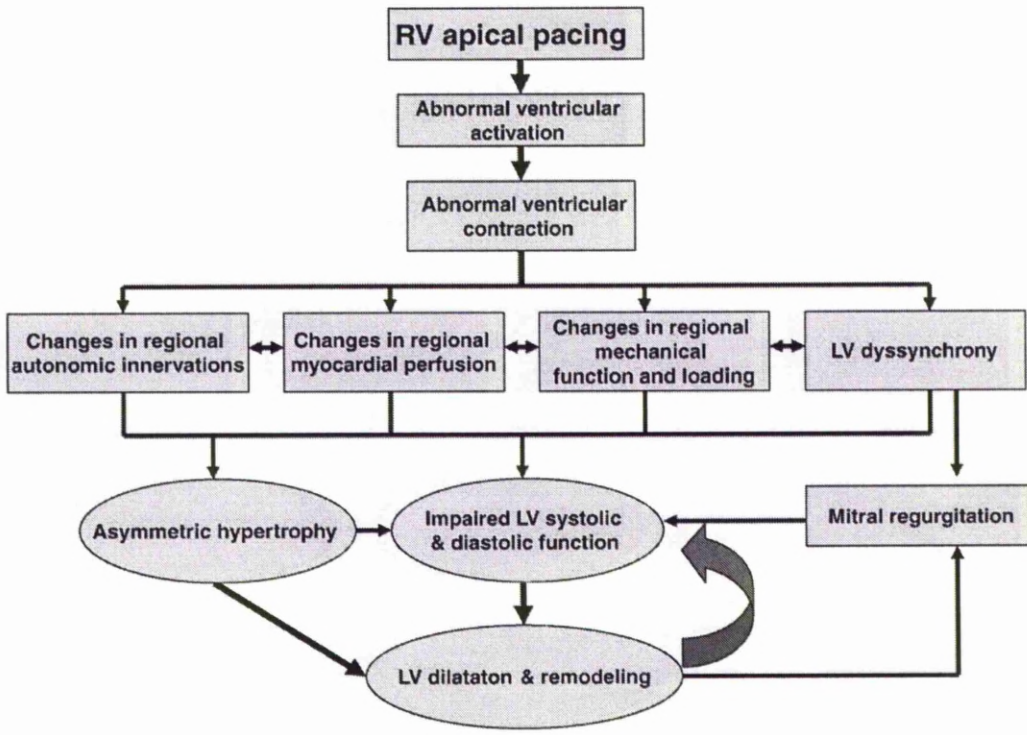


Figure 1.1: Proposed mechanisms for the adverse effects on ventricular function and remodelling with RV apical pacing (Sweeney & Prinzen 2006).

Third, experimental studies have shown that prolonged RV apical pacing leads to asymmetric LV hypertrophy and ventricular remodelling with LV dilatation (Prinzen et al. 1995; van Oosterhout et al. 2001). Asynchronous LV activation causes hypertrophy over the late activated portion of the left ventricle because of an increase in local mechanical loading due to prestretching by the early activated portion. In addition, redistribution of sympathetic innervations after RV pacing also contributes to asymmetrical LV hypertrophy due to a local increase in catecholamine release (Lee et al. 1994). Furthermore, pronounced histologic changes with myofibrillar disarray, dystrophic calcification, and disorganised mitochondria have been observed after RV apical pacing (Karpawich et al. 1990). Finally, mitral regurgitation has been observed after chronic RV apical pacing, in rare occasions, necessitating mitral valvular replacement (Le, Klug, &

Lacroix 1996). Indeed, Chen et al have recently reported that new onset or worsening of mitral regurgitation can be observed in a significant proportion of patients after chronic RV apical pacing. Maurer et al have demonstrated that RV apical pacing can induce mitral regurgitation in a canine model of RV pacing (Maurer et al. 1984). Although the mechanisms remain unclear, it has been postulated that a reduction of the trans-mitral pressure gradient and increased papillary muscle tethering forces due to LV remodelling and desynchronised papillary muscle contraction may contribute to the development of mitral regurgitation after RV apical pacing. In patients with HF and LBBB, the reduction in mitral regurgitation after cardiac resynchronisation therapy is associated with an increased transmitral pressure gradient (the closing force) due to more coordinated LV contraction (Breithardt et al. 2003). Furthermore, Kanzaki et al have demonstrated in a similar cohort of patients with HF that the reduction in the fraction of mitral regurgitation is significantly correlated with shortening of interpapillary muscle time delay, suggesting that papillary muscle dyssynchrony may contribute to the development of mitral regurgitation (Kanzaki et al. 2004).

1.2.2.3 Optimal choice of pacing site to preserve left ventricular function

In patients with low-degree or intermittent AV conduction abnormalities, the use of minimal pacing modes can significantly reduce the percentage of ventricular pacing. However, in those patients who have high-degree AV block, reducing the percentage of ventricular pacing is not feasible, and alternative ventricular pacing sites other than RV apical may result in a better cardiac performance. The ideal alternative ventricular pacing site should be a single site located in the right

ventricle that can be easily and safely achieved, should have similar long-term lead stability, sensing, and pacing threshold as RV apical pacing, and is without additional risk and cost.

RV outflow tract/RV septal pacing sites are the most studied alternative RV sites for permanent pacing. Interestingly, RV outflow tract was the first reported site of pacing used in the human implant of the endocardial pacing lead. RV pacing sites other than RV apex were not commonly used until the recent advances in the use of active fixation endocardial lead systems. For practical consideration, RV outflow tract/septal pacing is not inferior to RV apical pacing, in terms of long-term stability, feasibility, and efficacy, and appears to be associated with a low risk of RV perforation and diaphragmatic stimulation, and easy to extract. Furthermore, it is may be that pacing at the septal aspect of the RV outflow tract results in a shorter LV activation time and possibly less ventricular dyssynchrony. However, there are significant discrepancies in the published data concerning the potential benefits of RV outflow tract/septal pacing over RV apical pacing (Tse et al. 2002). Two potential reasons for the differing results may be related to imprecise definitions of RV outflow tract/septal pacing sites and the duration of follow-up in those studies. Laske et al studied pacing performance in swine hearts and suggested that pacing at the RV mid-septum region is required to stimulate the interventricular conduction system to cause a more synchronous ventricular activation pattern (Laske et al. 2006). Furthermore, the adverse LV remodelling effect of RV apical pacing may take a longer period to manifest, especially in patients with normal LVEF. As a result, only clinical studies with more precise definition of the RV outflow tract pacing site and a long duration of follow-up (>6 months) showed that RV septal pacing preserved

LV function (Victor et al. 2006). One of the major issues related to RV septal pacing is to define the optimal site for lead placement in the septum. Most published studies defined the RV septal region by fluoroscopy. On the other hand, a more synchronous ventricular activation pattern during RV septal pacing can be reflected by a narrow QRS duration. Indeed, a shorter paced QRS duration has been shown to correlate with better LVEF during the acute pacing phase (Schwaab et al 1999). Therefore, it is likely that, other than the use of fluoroscopic landmarks, the use of additional parameters, such as paced QRS width or morphology or echocardiographic indexes, is needed to define optimal RV septal pacing sites.

1.3 History of cardiac pacing

In 1899, J A McWilliam reported in the British Medical Journal his experiments in which application of an electrical impulse to the human heart in asystole caused a ventricular contraction and that a heart rhythm of 60-70 beats per minute could be evoked by impulses applied at intervals equal to 60-70/minute. In 1932, the American physiologist Albert Hyman, working independently, described an electro-mechanical instrument of his own, powered by a spring-wound hand-cranked motor. Hyman himself referred to his invention as an "artificial pacemaker", the term continuing in use to this day. An external pacemaker was designed and built by the Canadian electrical engineer John Hopps in 1950. This was a substantial external device using vacuum tube technology to provide transcutaneous pacing. It was somewhat crude and painful to the patient in use and, being powered from an AC wall socket, carried a

potential hazard of electrocution of the patient by inducing ventricular fibrillation. A number of innovators, including Paul Zoll, made smaller but still bulky transcutaneous pacing devices in the following years using a large rechargeable battery as the power supply. In 1957, engineer Earl Bakken of Minneapolis, Minnesota, produced the first wearable external pacemaker. This pacemaker, housed in a small plastic box, had controls to permit adjustment of pacing heart rate and output voltage and was connected to electrode leads which passed through the skin of the patient to terminate in electrodes attached to the surface of the myocardium of the heart. The first clinical implantation into a human of a fully implantable pacemaker was in 1958 at the Karolinska Institute in Solna, Sweden, using a pacemaker designed by Rune Elmqvist. Surgeon Åke Senning connected electrodes attached to the myocardium of the heart by thoracotomy. The device failed after three hours. A second device was then implanted which lasted for two days. The world's first implantable pacemaker patient, Arne Larsson, went on to receive 26 different pacemakers during his lifetime. He died in 2001, at the age of 86. In 1959, temporary transvenous pacing was first demonstrated by Furman et al. in which the catheter electrode was inserted via the patient's basilic vein (Furman et al. 1959). The first use of transvenous pacing in conjunction with an implanted pacemaker was by Parsonnet in the USA, Lagergren in Sweden and Jean-Jaques Welti in France in 1962-63. The transvenous, or per-venous, procedure involved incision of a vein into which was inserted the catheter electrode lead under fluoroscopic guidance, until it was lodged within the trabeculae of the right ventricle. This method was to become the method of choice by the mid-1960s. In the late 1960s, several companies, including ARCO in the USA, developed isotope powered

pacemakers, but this development was overtaken by the development in 1971 of the lithium-iodide cell by Wilson Greatbatch. Lithium-iodide or lithium anode cells became the standard for future pacemaker designs.

At present, pacemakers are implanted in a variety of patients. The primary purpose of a pacemaker is to maintain an adequate heart rate, either because the heart's native pacemaker is not fast enough, or there is a block in the heart's electrical conduction system. Modern pacemakers are externally programmable and allow the cardiologist to select the optimum pacing modes for individual patients. Some combine a pacemaker and defibrillator in a single implantable device. Others have multiple electrodes stimulating differing positions within the heart to improve synchronisation of the lower chambers of the heart.

1.4 Indications for permanent cardiac pacing

In the early days of pacing, atrioventricular (AV) block was the most common conduction disorder for which a pacemaker was prescribed. While indications have expanded considerably, AV block remains one of the main indications for permanent pacing. There are different types of AV block which must be considered as a progressive disorder that delays and ultimately blocks conduction of the electrical impulse through the AV node into the ventricle. First degree AV block occurs when the electrical signal gets delayed at the AV node before it can pass to the ventricles. This manifests on the surface ECG as an abnormally long PR interval. First degree AV block is most probably benign and patients are usually asymptomatic. There are two types of second degree AV block. Type I

second degree AV block (also called Mobitz I or Wenckebach) is characterised by a progressive prolongation of PR interval before a blocked beat. It is usually benign but pacing can be considered if accompanied by documented symptoms. Type II second degree AV block (also called Mobitz II) is characterised by a stable PR interval and a periodic missing of QRS complex. Pacing should be considered if documented symptoms are present. In third degree AV block (also called complete heart block), impulses do not travel through the AV node. Therefore, the ventricles beat independently from atrial activity (atrioventricular dissociation). Pacing is indicated for these patients, even in the absence of symptoms as it provides prognostic as well as symptomatic benefits. Nowadays, sinus node dysfunction (also called sick sinus syndrome or SSS) is the most common arrhythmic constellation that indicates pacing. It describes sinus bradycardia, sinus arrest, sinoatrial block, and tachy-brady syndrome. Sinus node dysfunction is a clear indication for pacing only when associated with documented symptoms. Pacing in this category of patients provides symptomatic but not prognostic benefits. There are other less common indications for pacing such as carotid sinus syndrome or pacing to prevent certain arrhythmias. The decision to implant a permanent pacemaker is an important one and should be based on solid clinical evidence. The joint committee of the American College of Cardiology and the American Heart Association was formed in the 1980s to provide uniform criteria for pacemaker implantation. These guidelines were first published in 1984 and most recently revised in 2008 in conjunction with the Heart Rhythm Society (Epstein et al. 2008).

1.5 Quality of life and functional status following pacemaker implantation

Despite the fact that the number of indications for implantation of cardiac pacemakers is still increasing, most of these devices are implanted to prevent bradyarrhythmias due to disorders of the sinus node or of the specific cardiac conduction system. In the 1950s, pacemaker therapy was introduced with a main objective to improve survival. The subsequent introduction of atrioventricular synchronous pacemakers (DDD, AAI) and ventricular rate adaptive pacemakers (VVIR) showed improved haemodynamics and maximal exercise capacity compared to the former introduced fixed rate ventricular pacemakers (VVI). Efficiency of these more sophisticated pacemaker therapies can be defined as the relationship between the benefits of these pacemaker therapies, as represented by survival and quality-of-life (QOL), and the costs associated with them (Gribbin et al. 2004). Few pacemaker recipients perform vigorous exercise in daily life, comparable to maximal exercise capacity, one of the parameters used to evaluate these benefits in previous studies. Therefore, this clinical outcome parameter may be of little value as an indicator of a patients' QOL and efficiency of pacemaker therapy. Subjective cardiovascular symptoms and patients' perceived health might provide a better measure of the value of a certain kind of stimulation method ("pacing mode"). Hence, assessment of QOL is of increasing importance in the evaluation of pacing modes, especially in this era of sophisticated pacing devices and the associated escalating costs. Implantation of a more expensive device should be objectively and subjectively justified and beneficial. The expanding interest in QOL has led to a wide range of questionnaires.

The decision of which instrument to use may be based on several criteria (Stofmeel et al. 2000). First, it is important that a questionnaire measures what it is supposed to. This is defined as its validity. The key question is if the scale is valid for a particular application in a specific population. The assessment of validity commonly begins with content validity; do the selected items reflect the study object? A first approach to establish content validity is to ask patients and experts in the field to critically review the content of the scale. Next, more formal statistical procedures are used to test criterion and construct validity. Criterion validity indicates the effectiveness of a test in predicting an individual's standing on some outcome or criterion. Scores on a health related QOL questionnaire might be compared to objective measures of cardiac functioning (e.g., New York Heart Association [NYHA] classification, 6-minute walking distance). Construct validity is the extent to which a theoretical construct or trait is measured by a test. In multidimensional questionnaires, it is important to examine if each scale of the questionnaires reliably measures a distinct aspect of health. In addition, inspection of correlations with similar (convergent) and dissimilar (discriminate) measures constitute evidence that the test measures this theoretical construct. Second, it is important to evaluate if a questionnaire can reproduce similar scores within one subject under the same circumstances. This is called reliability of a questionnaire. More formal, reliability is defined as the proportion of observed variation in scores that reflects actual variation in health levels. Two types of reliability are distinguished: inter-rater agreement or observer variation (do different raters obtain the same result in the same individual) and test-retest reliability (is the equal result obtained on a second assessment of the same

patient). Finally, it is useful to check if a selected questionnaire was previously used in a study with a similar population to judge the feasibility and to allow comparisons to other research.

Quality of life measures of pacemaker patients were appraised by Stofmeel et al (Stofmeel et al. 2000). They searched MEDLINE (1985-1998) for studies assessing quality-of-life in general and in pacemaker patients. This search resulted in 65 studies. From these 65 studies, 14 studies using multi-item questionnaires for evaluating QOL in DDD pacing compared to VVIR pacing were selected for review. In this paper, they found that the SF-36 appears to be the best among generic questionnaires because of its psychometric characteristics and experience of use. Concerning disease specific instruments, many quality of life questionnaires lack rigorous psychometric validation, which constitutes a serious limitation. Previous studies suggested that implantation of atrioventricular pacemakers improves quality-of-life compared to ventricular pacemakers, but since no well-designed and validated questionnaire exists, these results should be interpreted with caution. The best outcome measure to evaluate quality-of-life in pacemaker patients would be a combination of a generic health profile with established reliability and validity supplemented with a cardiovascular assessment adjusted to suit pacemaker patients. By doing so, individual scores can be compared within a disease cohort and to same-aged, non diseased persons, as well as other diseased populations. They recommended that the development and validation of such an instrument is needed.

Both dual chamber and rate adaptive single chamber pacing have been shown to offer benefits compared with fixed rate ventricular pacing in terms of improved haemodynamics, increased treadmill exercise tolerance, and reduced symptoms; however, it is not clear to what extent these changes translate in to clinical benefit for the typical patient (Toff et al. 1997). Quality of life studies have shown conflicting results although there is considerable evidence of patient preference for physiological pacing modes. Much of the clinical data supporting the use of physiological pacing is derived from short term studies of relatively small numbers of patients, often younger than the average. In many instances, crossover study designs have been used in patients who have already been fitted with physiological pacing systems and who were, presumably, pre-selected as being more likely to benefit from them (Toff et al. 1997). The United Kingdom Pacing and Cardiovascular Events (UKPACE) trial (Toff et al. 2005). was a multicenter, randomised, parallel-group trial, 2021 patients 70 years of age or older who were undergoing their first pacemaker implant for high-grade atrioventricular block were randomly assigned to receive a single-chamber ventricular pacemaker (1009 patients) or a dual-chamber pacemaker (1012 patients). In the single-chamber group, patients were randomly assigned to receive either fixed-rate pacing (504 patients) or rate-adaptive pacing (505 patients). The primary outcome was death from all causes. Secondary outcomes included atrial fibrillation, heart failure, and a composite of stroke, transient ischemic attack, or other thromboembolism. The quality of life was assessed using a composite questionnaire comprising two widely used generic instruments, the SF-36 and the EuroQoL EQ-5D. These were selected as they were considered reliable and well validated, with ample normative data, and they

can both be administered within a few minutes by personnel with minimal training. The median follow-up period was 4.6 years for mortality and 3 years for other cardiovascular events. The mean annual mortality rate was 7.2 % in the single-chamber group and 7.4 % in the dual-chamber group (hazard ratio, 0.96; 95 % confidence interval, 0.83 to 1.11). They found no significant differences between the group with single-chamber pacing and that with dual-chamber pacing in the rates of atrial fibrillation, heart failure, or a composite of stroke, transient ischemic attack, or other thromboembolism. They concluded that in elderly patients with high-grade atrioventricular block, the pacing mode does not influence the rate of death from all causes during the first five years or the incidence of cardiovascular events during the first three years after implantation.

One of the most commonly used QOL measures is the Minnesota living with heart failure (MLWHF) questionnaire (Bennett et al. 2002 & Rector et al. 1987). It is used in a completely different cohort to patients requiring pacing as a treatment for bradyarrhythmias. As indicated by its name, MLWHF is mainly used in patients with heart failure to measure their response to either medical or device intervention. It was used in the majority of trials on biventricular pacing such as the MIRACLE study (Abraham et al. 2002) and the CARE-HF study (Cleland et al. 2005). Despite its wide use, the validity of the MLWHF as a measure of therapeutic response was questioned in some studies (Rector et al. 1987).

1.6 Peak oxygen consumption as a measure of exercise capacity and cardiac function

Physical disability has the potential to reduce an individual's quality of life. Objective evaluation of functional capacity can thus be used to categorise the relative severity of any pathological condition. It can also be used to provide prognostic information and quantitative assessment of therapeutic interventions. In cardiac dysfunction secondary to any cause and in the absence of other organ or system dysfunction, it may provide indirect information about the extent of cardiac function. In practical terms, any test of function should be available, cost effective and acceptable to the subject under evaluation. In scientific terms it must be representative, validated and reproducible. At present no index of functional capacity completely fulfils all the above criteria. Due to the high incidence of heart disease and the level of functional disability exhibited by cardiac patients, much of the research into functional capacity has concentrated on this subgroup of the patient population. Despite complex central and peripheral compensatory mechanisms, it is important to recognise that the initial insult is to the heart itself. It is therefore logical to evaluate the heart directly, but to consider it in the broader context of circulatory homeostasis.

In healthy subjects, cardiac output (l/min), and heart rate (beats/min), increase linearly with increasing work rate (Donald et al. 1955). Work rate, is measured in "METS" (metabolic equivalents) and is derived from the average resting oxygen consumption for a 70 kg, 40-year-old man. It is equal to 3.5 ml/min per kilogram. Systolic blood pressure (mmHg) also increases during incremental exertion, as does diastolic pressure, though to a lesser extent (Donald et al. 1955). Oxygen

consumption (VO_2 in ml/min) depends on the combined processes of pulmonary ventilation and respiratory gas diffusion, cardiac output, and skeletal muscle oxygen utilisation. When describing VO_2, normalisation is usually made using body mass (ml/kg/min). The relationship between VO_2 and work rate is initially linear until a point is reached where further increments in work are accompanied by a constant rate of oxygen consumption (Albouaini et al. 2007). This is known as the maximal oxygen consumption and care should be taken to distinguish this from peak oxygen consumption, which represents the highest achievable value during a test. A plateau response is rarely seen except in very determined subjects such as trained athletes. Carbon dioxide production (VCO_2 in ml/min) initially increases slowly relative to VO_2 due to metabolism of available substrates and the greater solubility of carbon dioxide in tissue. It subsequently increases as dictated by the ratio of the time constants of VCO_2 and VO_2, known as the respiratory exchange ratio (RER). If lactic acidosis occurs during exercise due to the onset or progression of anaerobic metabolism, VCO_2 increases faster than VO_2 because of the additional carbon dioxide produced during the buffering of bicarbonate. At this point the subject exceeds their anaerobic threshold. As exercise continues the respiratory exchange ratio exceeds the value of 1.0. Minute ventilation (VE in l/min) depicts the volume of air inspired in one minute and mirrors the response of VCO_2 (Ross 2003). Ventilatory equivalents for oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2) represent the ratios of minute ventilation to each gas respectively, and are regarded as markers of respiratory effort for given levels of gas exchange. Metabolic activity in skeletal muscle increases during exertion, necessitating an improvement in limb blood flow, which is achieved by an increase in cardiac output, perfusion pressures and local

vasodilatation. Exercise testing is employed extensively in modern medical practise. The standardisation of procedures and advanced technology used, require integrated supervision from medical and technical staff. The use of International guidelines ensures patient safety (Ross 2003). An exercise electrocardiogram is one of the first investigations carried out when screening for ischaemic heart disease.

Cardiopulmonary exercise tests are used in the assessment of a range of subjects from athletes to cardiac patients (the method is explained in chapter 2.18). Programmes can be designed to enhance a specific function, for example the ability to perform at exercise levels exceeding the individual's anaerobic threshold. Thus, an improved tolerance to severe exertion can be developed. Similarly the quantitative nature of results from exercise tests can be used to classify the severity of disability occurring due to a pathological condition such as chronic heart failure. Data from exercise tests can also be used to provide prognostic information and serial testing can objectively evaluate the success of therapeutic interventions (Bocchi et al. 1995). In the case of patients with cardiac failure, cardiopulmonary exercise testing forms part of the selection process for cardiac transplantation referral (Ross 2003).

1.7 Detrimental clinical effects of right ventricular apical pacing

As early as 1925, Wiggers et al demonstrated that epicardial RVA pacing in open-chested dogs was associated with a diminished rate of change in left ventricular pressure (dP/dt) and dyssynchronous left ventricular contraction

pattern. It was postulated that this resulted from slower transmyocardial conduction compared to the normal rapid conduction mediated by the His-Purkinjie system. Another study confirmed that pacing induced cardiac dyssynchrony as assessed by radionuclide angiography resulting in deterioration in cardiac performance (Boucher et al. 1983). Further support for the detrimental effects of artificial pacing was seen in 1986 (Adomian & Beazell 1986) , when investigators produced complete heart block in 12 dogs and paced them electrically at the RVA for 3 months. Myofibrillar disarray was observed in 9 (75%) of these dogs.

In the 1980s, the detrimental haemodynamic consequences of RVA pacing led to the introduction of dual chamber sequential pacing to maintain atrioventricular synchrony (Boucher et al. 1983). However, despite this, subsequent studies provided further evidence that RVA pacing continued to result in dyssynchronous left ventricular activation, and therefore impaired haemodynamic function (Little et al. 1982; Park, Little, & O'Rourke 1985).

In 1997, a key paper was published by Anderson et al (Andersen et al. 1997) in which they randomised 225 patients with sick-sinus syndrome to either single-chamber atrial pacing (n=110) or single-chamber ventricular pacing (n=115). They found that after a mean follow-up of 3.3 years, atrial pacing was associated with significantly less atrial fibrillation and thromboembolism whereas there was no significant difference in mortality and heart failure between the two groups. The detrimental effects induced by ventricular pacing were maintained when the patients were examined 8 years later. They recommended that patients with sick-

sinus syndrome should be treated with an atrial rather than ventricular pacing system for the above mentioned benefits and to avoid the unfavourable symptoms of atrioventricular desynchronisation in the form of pacemaker syndrome. In 2001, Tantengco et al (Tantengco, Thomas, & Karpawich 2001) assessed the long-term global LV function in 24 patients who were paced from the RVA at a young age. The mean follow-up was 9.5 years. They demonstrated impaired systolic and diastolic LV function in the paced group when compared to the control group. They recommended exploring alternative pacing sites that aimed to provide normal biventricular activation, especially in paediatric patients requiring long-term pacing.

In 2002, the Dual-Chamber and VVI Implantable Defibrillator (DAVID) trial (Wilkoff et al. 2002) was conducted on 506 patients with an indication for an implantable cardioverter defibrillator (ICD) without any indication for ventricular pacing. Patients were randomised to either ventricular backup pacing at 40/min (VVI-40; n=256) or dual-chamber pacing with a relatively short atrioventricular (AV) interval (DDDR-70; n=250). The combined end point was death or hospitalisation for heart failure. The DAVID investigators demonstrated that in patients with LVEF $\leq$ 40%, the dual-chamber pacing offered no clinical advantage over ventricular backup pacing. Sharma et al revisited the DAVID trial in 2005 to determine whether right ventricular pacing is an independent predictor of the composite outcome (Sharma et al. 2005). They found that the best separation for predicting endpoints occurred with DDDR RV pacing > 40% vs DDDR RV pacing $\leq$ 40% (P = .025). Patients with DDDR RV pacing $\leq$ 40% had similar or better outcomes to the VVI backup group (P = .07). Correction for baseline variables predictive of the composite outcome in the (nonpaced) VVI

group (use of nitrates, increased heart rate, and increased age) did not change the findings for RV pacing (P = .008). In contrast, atrial pacing was not predictive of worse outcomes. They concluded that these results suggest, but do not prove, a causal relationship between frequent RV pacing and adverse outcomes in patients with left ventricular ejection fraction ≤40%.

Sweeney et al, in 2003, published the Mode Selection Trial (MOST) (Sweeney et al. 2003). This is a 6-year, randomised trial of DDDR versus VVIR pacing in SND. Cumulative percent ventricular paced (Cum%VP) was determined from stored pacemaker data. Baseline QRSd < 120 ms was observed in 1339 patients (707 DDDR, 632 VVIR). Cum%VP was greater in DDDR versus VVIR (90% versus 58%, P < 0.001). Cox models demonstrated that the time-dependent covariate Cum%VP was a strong predictor of HF hospitalisation in DDDR (hazard ratio [HR], 2.99 [95% CI, 1.15 to 7.75] for Cum%VP > 40%) and VVIR (HR 2.56 [95% CI, 1.48 to 4.43] for Cum%VP > 80%). The risk of AF increased linearly with Cum%VP from 0% to 85% in both groups (DDDR, HR 1.36 [95% CI, 1.09, 1.69]; VVIR, HR 1.21 [95% CI 1.02, 1.43], for each 25% increase in Cum%VP). Model results were unaffected by adjustment for known baseline predictors of HF hospitalisation and AF. They, therefore, concluded that ventricular desynchronisation imposed by ventricular pacing even when AV synchrony is preserved increases the risk of HF hospitalisation and AF in SND with normal baseline QRSd. Nielsen et al. (Nielsen et al. 2003), in the same year, published a randomised study of patients with SSS and normal AV conduction to AAIR, DDDR with a short AV delay, or DDDR with a long AV delay. The mean follow-up was 2.9 years. DDDR pacing with a short AV delay resulted in a reduced LV fractional shortening (LVFS). Interestingly, in 2003, Simantirakis et

al studied 16 patients with a chronic RVA pacing to assess the effects of restoration of normal ventricular activation (Simantirakis et al. 2003). They concluded that the restoration of normal conduction acutely enhanced the contractile function without affecting myocardial oxygen consumption.

In 2004, Thambo et al (Thambo et al. 2004) performed echocardiography and exercise tests in 23 patients with congenital complete heart block before DDD pacemaker implantation and after at least 5 years of RVA pacing. They demonstrated that RVA pacing induced LV dyssynchrony with deleterious remodelling, dilatation, and asymmetrical hypertrophy. There was also a reduction in the overall exercise capacity. In the same year, Puggioni et al (Puggioni et al. 2004) published the OPSITE study-Acute, in which they compared LV pacing with RVA pacing in 44 patients undergoing AV junction ablation for permanent atrial fibrillation (AF). This study was a randomised single blind crossover trial in which all patients had two leads. The authors performed intrapatient comparison of the QRS width and echocardiographic parameters of the two groups. They demonstrated that ejection fraction (EF) following rhythm regulation increased by 17.6% in the LV pacing group and by 11.2% in the RV pacing group. The mitral regurgitation score decreased by 16.7% and 0%; and the diastolic filling time increased by 15.6% and 12.7% respectively. When compared to RV pacing, LV pacing resulted in a 5.7% increase in EF and 16.7% decrease in the mitral regurgitation (MR) score, with 4.8 % shorter QRS. They concluded that rhythm regulation achieved by AV junction ablation improved EF in both groups. However, LV pacing provided an additional modest but favourable haemodynamic effect. This effect seemed to be

equal in patients with both depressed and preserved systolic functions and in those with or without native left bundle branch block (LBBB).

In 2005 Steinberg et al (Steinberg et al. 2005), assessed whether RVA pacing in the ICD arm of the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) was associated with an unfavourable outcome. During a 20-month follow-up, patients (n = 369) having high cumulative right ventricular pacing (>50%), had a higher incidence of new or worsened heart failure (30% vs 17%, P = 0.002; hazard ratio 1.9) and heart failure or death (50% vs 20%, P = 0.004; hazard ratio 1.8) compared to patients (n = 198) with infrequent right ventricular pacing. In addition, patients in the high-frequency pacing group had significantly more episodes of ventricular tachycardia events requiring shock or antitachycardia pacing by the defibrillator than did patients in the low-frequency pacing group (hazard ratio 1.5, P=0.025).

A year later, Kindermann et al randomised 30 patients with an EF $\leq$ 40% and a standard indication for permanent ventricular pacing to either RVA pacing or biventricular pacing (Kindermann et al. 2006). This was a crossover study and patients had 3 months in each pacing mode. They demonstrated significant superiority of biventricular pacing to conventional RVA pacing with regard to LV function, quality of life, and maximal as well as submaximal exercise capacity. In the same year Lieberman et al. assessed haemodynamic data on 33 patients (17 patients with EF > 40% and 14 patients with EF < 40%) during atrial and dual chamber pacing from the RVA, RV free wall, RV septum, LV free wall,

and biventricular (Lieberman et al. 2006). They concluded that RV pacing at one or more sites worsens LV function in patients with or without LV dysfunction.

The SAVE PACe trial was published in 2007 by Sweeney et al (Sweeney et al. 2007). They randomly assigned 1056 patients with sick sinus syndrome and intact AV conduction to receive conventional dual chamber pacing or dual chamber minimal RV pacing. The mean follow-up was 1.7 years. They demonstrated that dual chamber minimal RV pacing prevented ventricular desynchronisation and moderately reduced the risk of AF in patients with SSS. As a result of the detrimental effects RVA pacing, the authors recommended that pacing at this site should be either minimised or an alternative RV pacing site considered. In patients with sinus node dysfunction, minimising RVA pacing may be attempted by programming an extended atrioventricular delay, atrioventricular search hysteresis, or minimum ventricular pacing algorithms that search for and promote intrinsic atrioventricular conduction. Programming strategies, however, are not relevant for patients with atrioventricular conduction disturbance or patients who have undergone atrioventricular node ablation and require permanent ventricular pacing. Therefore, other RV sites must be evaluated in an attempt to avoid the potential detrimental effects of RVA pacing.

1.8 Selective site right ventricular pacing

The term selective site pacing (SSP) refers to pacing at targeted RV sites while alternate site pacing refers to pacing at sites other than RVA (Lieberman et al. 2004). It reflects the fact that the site is selected by the implanter in expectation of a more physiological depolarisation pattern and better haemodynamic

response (de Cock, Giudici, & Twisk 2003), with less detrimental remodelling (Harris & Gammage 2000), and reduced long term complications such as perfusion defects and heart failure (Karpawich et al. 1991). Right ventricular outflow tract (RVOT) is the most targeted non-RVA site. In order to clarify the RVOT, this site will be defined anatomically, fluoroscopically and electrocardiographically. This is essential in order to standardise procedures and permit the comparison of the different sites.

1.8.1 Anatomical definition

There was no agreed consensus on the anatomical definition of selective pacing sites until 1999 when Giudici and Karpawich (Giudici & Karpawich 1999) proposed the following:

- *RV inlet septal pacing*: above, on, or beneath the annulus of the septal/anterior tricuspid valve (TV) leaflets resulting in a relatively normal QRS morphology and axis.
- *RV infundibular septal pacing*: proximal to pulmonic valve distal to, or near the crista supraventricularis resulting in LBBB with a vertical axis.
- *RV outflow septal pacing* (was most commonly referred to as RVOT): near the septal/moderator band insertion at a mid-position on the RV septum resulting in LBBB with a vertical axis.
- *RV apical septal pacing*: proximal to septal moderator band continuity; this does not typically produce a vertical QRS axis.

Later, in 2004, Lieberman et al formally defined the RVOT borders. They stated that in the anteroposterior (AP) projection, the lower RVOT border is a line

extending from the tricuspid valve (TV) apex to the border of the RV (Lieberman et al. 2004). The pulmonary valve is the upper RVOT border. They also, for simplicity, divided the RVOT into 4 quadrants, horizontally by a line midway between the pulmonary valve and the RVOT lower border, and vertically by a line that connects the pulmonary valve to the RVOT lower border (dividing the RVOT into four quadrants: high septal, low septal, high free wall, and low free wall).

Mond et al, in 2007, published a review in which RVOT anatomy, radiographic views, 12-lead ECG appearances, and a novel stylet shape for positioning the RV lead were discussed (Mond et al. 2007). They explained that the septal RVOT (figures 1.2 & 1.3) is a misnomer, as much of it abuts the proximal ascending aorta and thus the superior and maybe part of the inferior RVOT "septum" lies above the aortic valve. Therefore, using the strict anatomical definition of a septum as a structure that can be removed without exiting the heart, only part of the inferior portion of the RVOT septum can be considered as truly septal. They also explained that from an electrophysiologist's perspective, the walls of the RVOT can be divided into four segments; septal, anterior, posterior, and free.

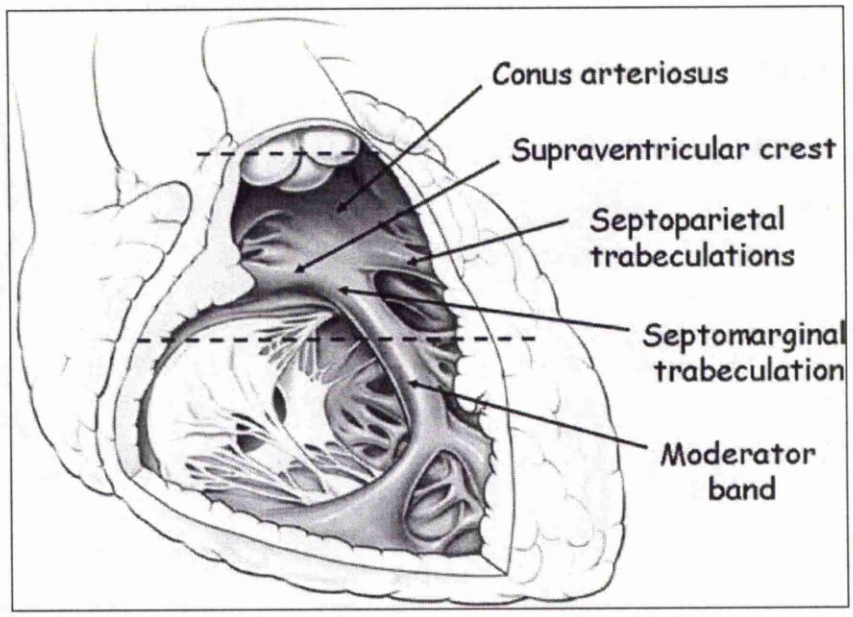


Figure 1.2: Illustration of the RVOT highlighting the RV septal anatomy. The RVOT is bordered by the pulmonary valve above and the superior aspect of the tricuspid apparatus below (Mond et al. 2007)

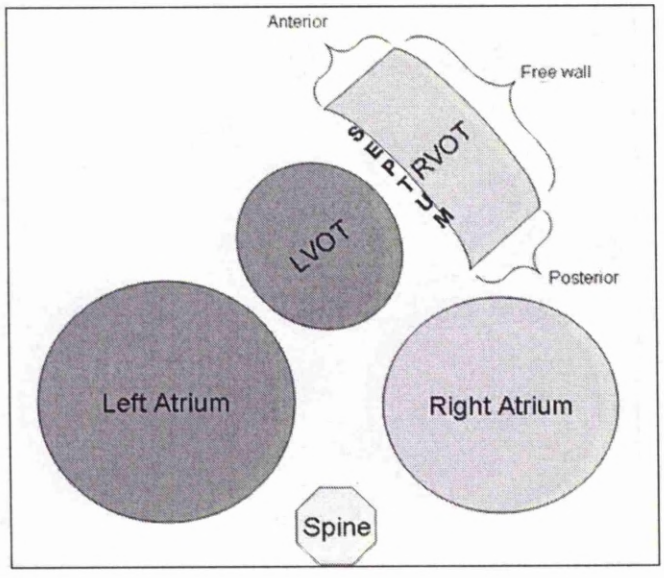


Figure 1.3: Schematic of a cross-section of the chest to demonstrate the relationship of the four areas of the RVOT to surrounding structures. Depending on the level of the RVOT, behind the septum lies either the left ventricle (LV) or ascending aorta (Ao). Adapted from (Mond et al. 2007).

1.8.2 Fluoroscopic definition

Lieberman et al defined the RVOT lower border by extending a pacing catheter parallel to the RV inferior border from the TV apex to the lateral RV border in the AP or the right anterior oblique (RAO) views (figure1.4) (Lieberman et al. 2004) . The upper RVOT border is determined by positioning a pacing catheter through the pulmonary valve (PV) (noted by the loss of R wave on the intracardiac electrogram). The actual RVOT-PV junction is then identified by the appearance of dominant R waves as the catheter is withdrawn into the RV. The RAO view helps in determining the upper and lower halves of the RVOT. However, to differentiate RVOT septum from free wall, the LAO (left anterior oblique) view is used.

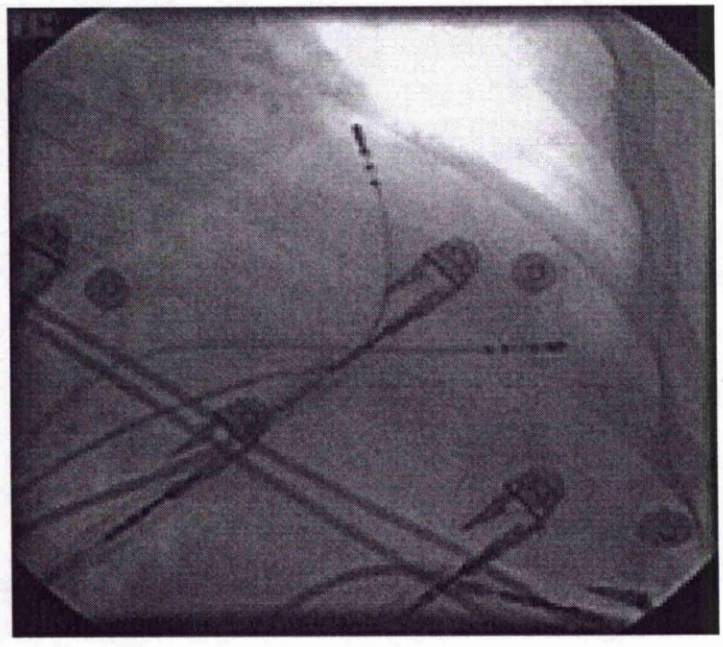


Figure 1.4: RVOT upper and lower fluoroscopic borders as shown in the right anterior oblique view (RAO) during an electrophysiology study with two catheters defining these borders (Lieberman et al. 2004)

Later in 2007, Mond et al described that for RVOT lead placement, four views can potentially be helpful:

1- The postero-anterior (PA) view is helpful for determining if the lead lies within the RVOT upper and lower borders (Figures 1.5 & 1.6). This view, however, gives little help as to which RVOT segment the lead is actually attached to. RVOT free wall leads often point in an upward or superior direction, although this finding is not universal.

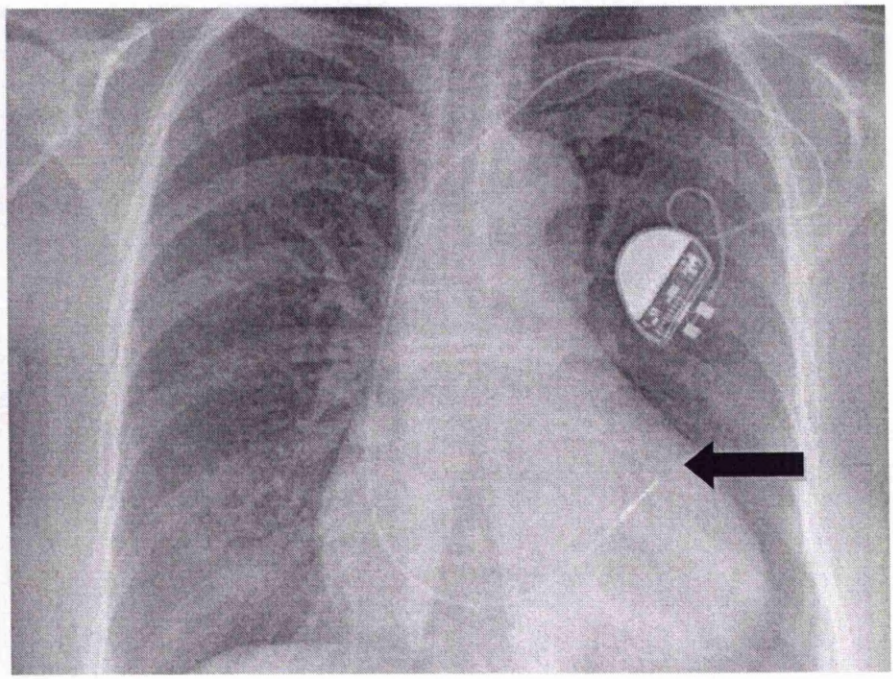


Figure 1.5: CXR in the PA position showing RV lead that appears to be fixed within the RVOT borders (black arrow points the lead tip)

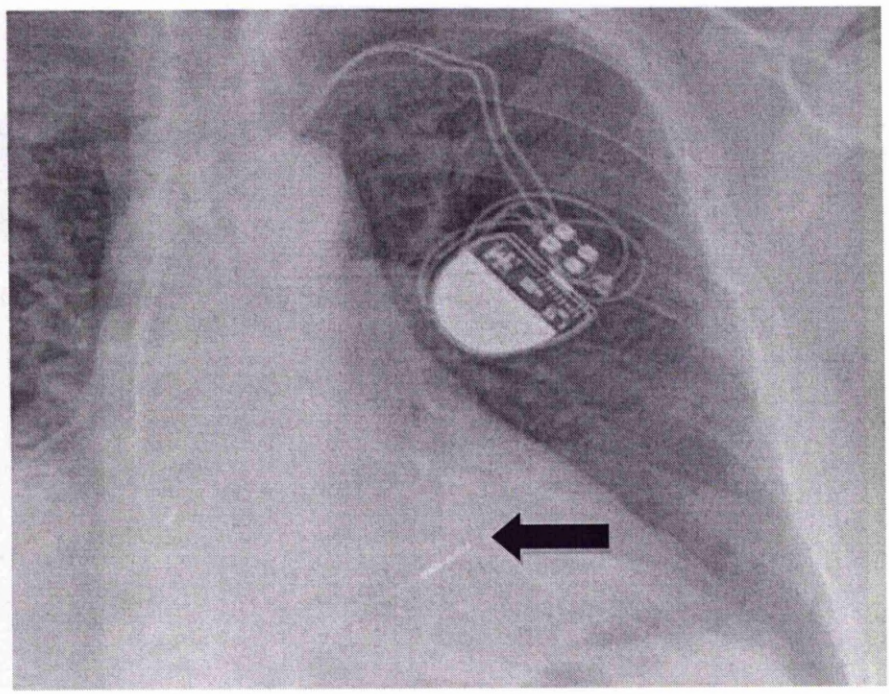


Figure 1.6: CXR in the PA position showing RV lead fixed to the septum below the RVOT borders (black arrow points the lead tip)

2- The 40◦ right anterior oblique (RAO) view helps confirm RVOT positioning (Figure 1.7). It is not unusual for a lead to enter the coronary sinus and lie within the great cardiac vein. The RAO confirms the posterior aspect of the lead in the cardiac venous system. The same principle can be applied to RV apical pacing and inadvertent positioning of the lead in the middle or lateral cardiac vein. This view does not tell us to which part of the RVOT the lead is attached.

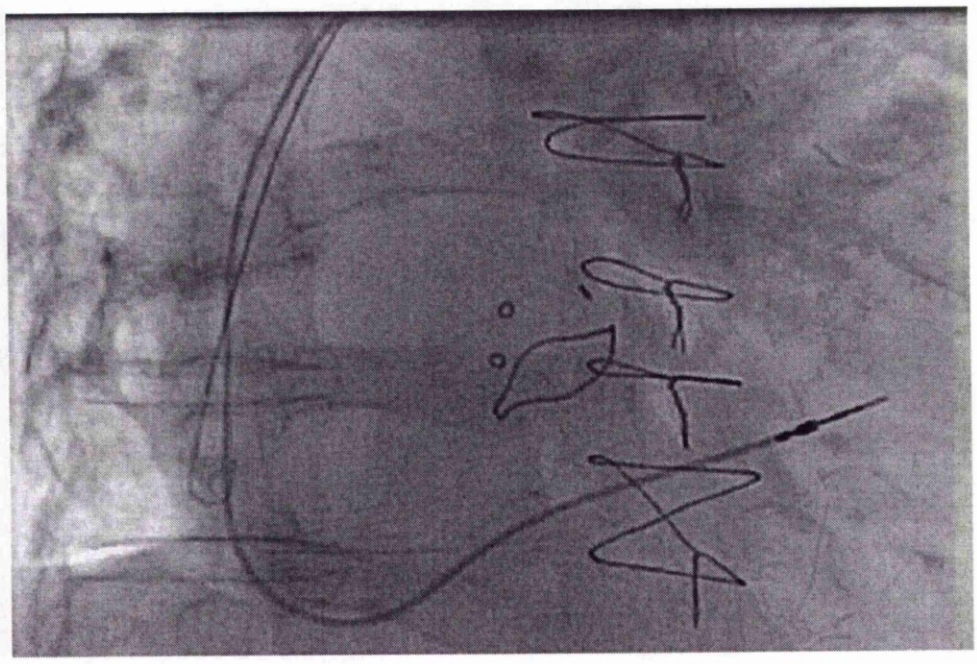


Figure 1.7: Right Anterior Oblique (RAO) view showing RV lead fixed within the RVOT borders in a patient who had a previous coronary bypass operation with aortic valve replacement

3- The 40◦ left anterior oblique (LAO) view is best view to define the septal and free wall aspects of the RVOT. The septal position is characterised by a posterior orientation of the lead tip, which faces toward the right (Figure 1.8) and the free wall site by a leftward anterior orientation.

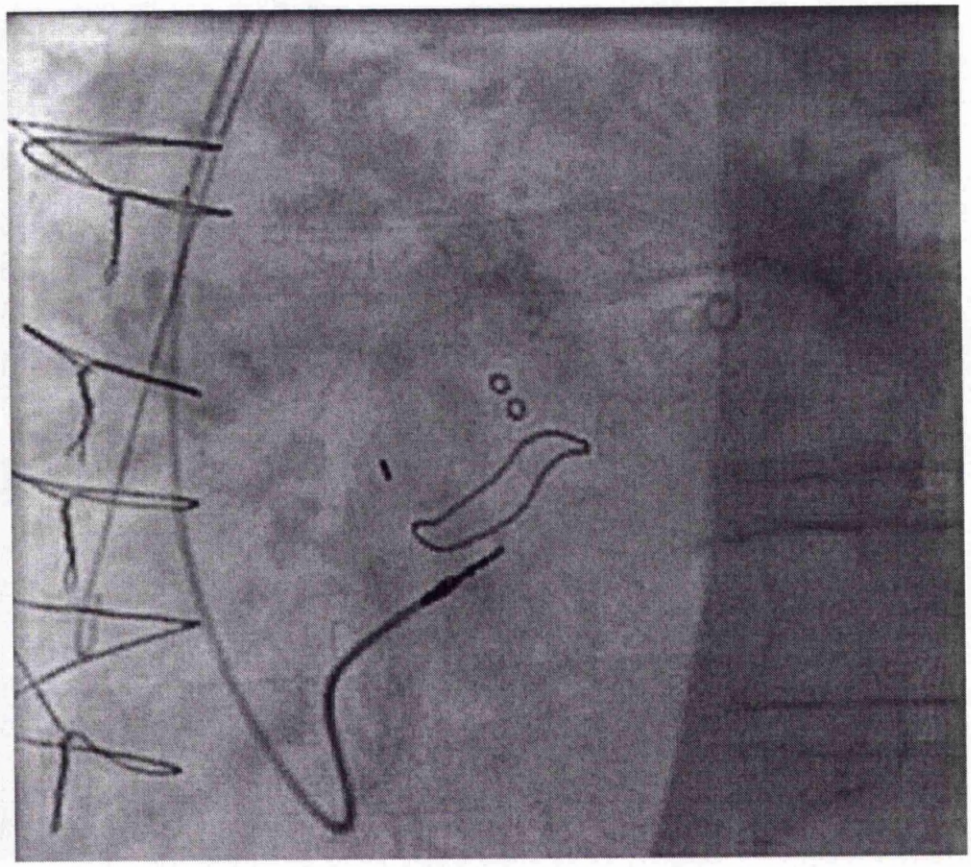


Figure 1.8: Left Anterior Oblique (LAO) view for the same patient in figure 1.9 confirming lead attachment to the RVOT septum.

4- The 90◦ left lateral (LL) view is also very helpful, but difficult to achieve during an implant using single plane fluoroscopy, because of sterile drapes, lead shields, arm boards, and monitoring equipment. A posterior projection of the lead tip indicates septal placement and is 100% specific (McGavigan et al. 2006). In comparison, a lead on the free wall passes anteriorly toward the sternum (Figures 1.9, 1.10, and 1.11).

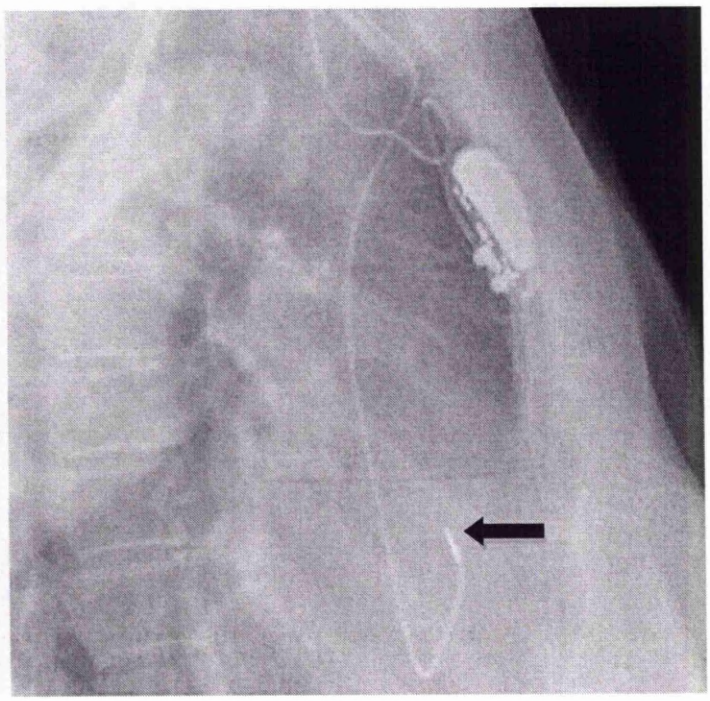


Figure 1.9: Lateral CXR confirming RV lead attachment to the RVOT septum (black arrow points the lead tip)

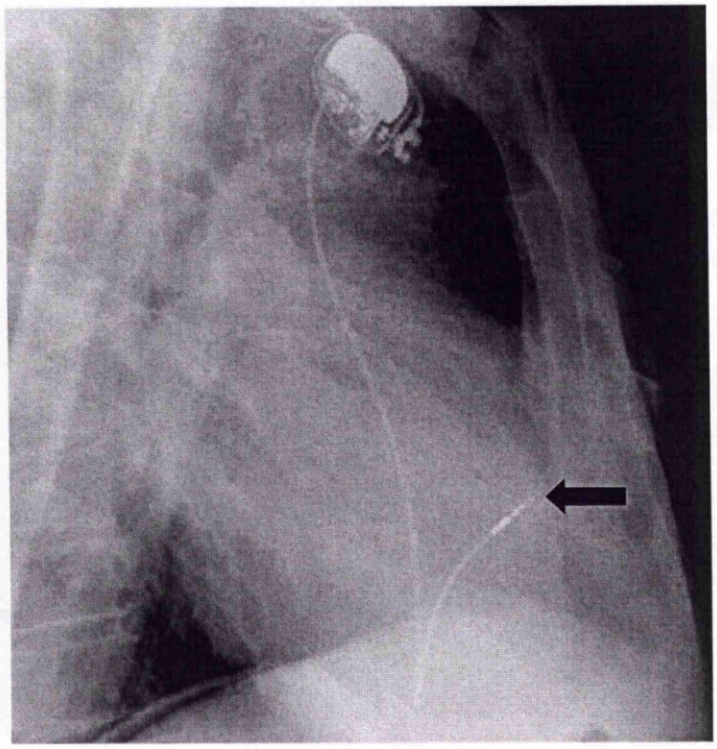


Figure 1.10: Lateral CXR with RV lead attached to the RVOT free wall (black arrow points the lead tip)

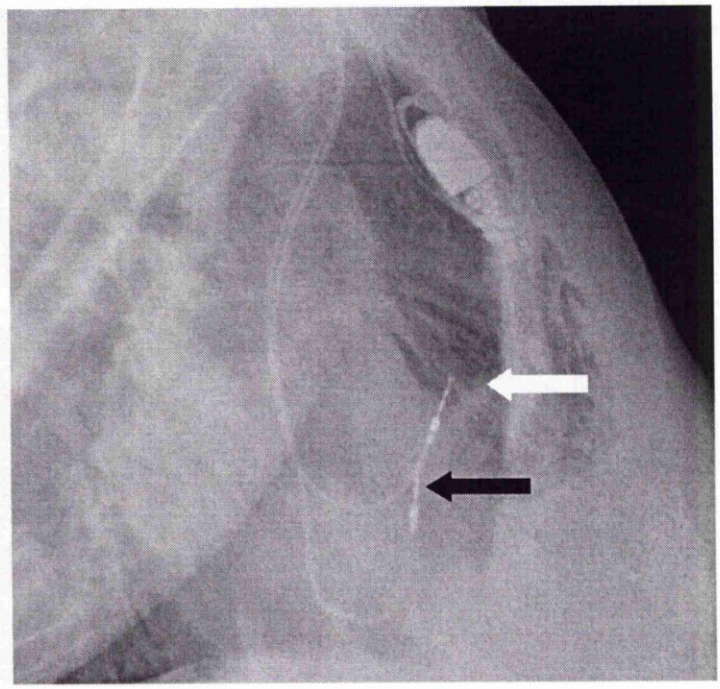


Figure 1.11: Lateral CXR with RV lead attached to the RVOT anterior wall (black arrow points the ventricular lead tip while the white arrow points to the atrial lead tip)

1.8.3 Electrocardiographical definition

Lieberman et al described the electrocardiographic findings in lead I and AVF in relation to where the RVOT quadrant was paced (Table 1.1) (Lieberman et al. 2004).

Table 1.1

	Lead I	**Lead AVF**
High septal (infundibular)	-	+
Low septal (outflow)	-	-/+
High free wall (infundibular)	+	+
Low free wall (outflow)	+	-/+

Mond et al also demonstrated correlation between the 12-lead ECG and lead position (Mond et al. 2007). The septal RVOT is a more posterior and leftward structure than the free wall and this is reflected in the typical ECG patterns of pacing at these sites. Septal pacing produces a shorter QRS duration (McGavigan et al. 2006; Mera et al. 1999; Stambler et al. 2003; Tse et al. 2002) and typically a negative or isoelectric vector in lead I (Figure 1.12). This feature has a 90% positive predictive value for septal placement. Conversely, free wall sites are associated with prolonged QRS duration, notching of the inferior leads (particularly lead III), and a positive vector in lead I (McGavigan et al. 2006). Pacing at the anterior wall provides variation between these two appearances and frequently has an almost isoelectric vector in lead I.

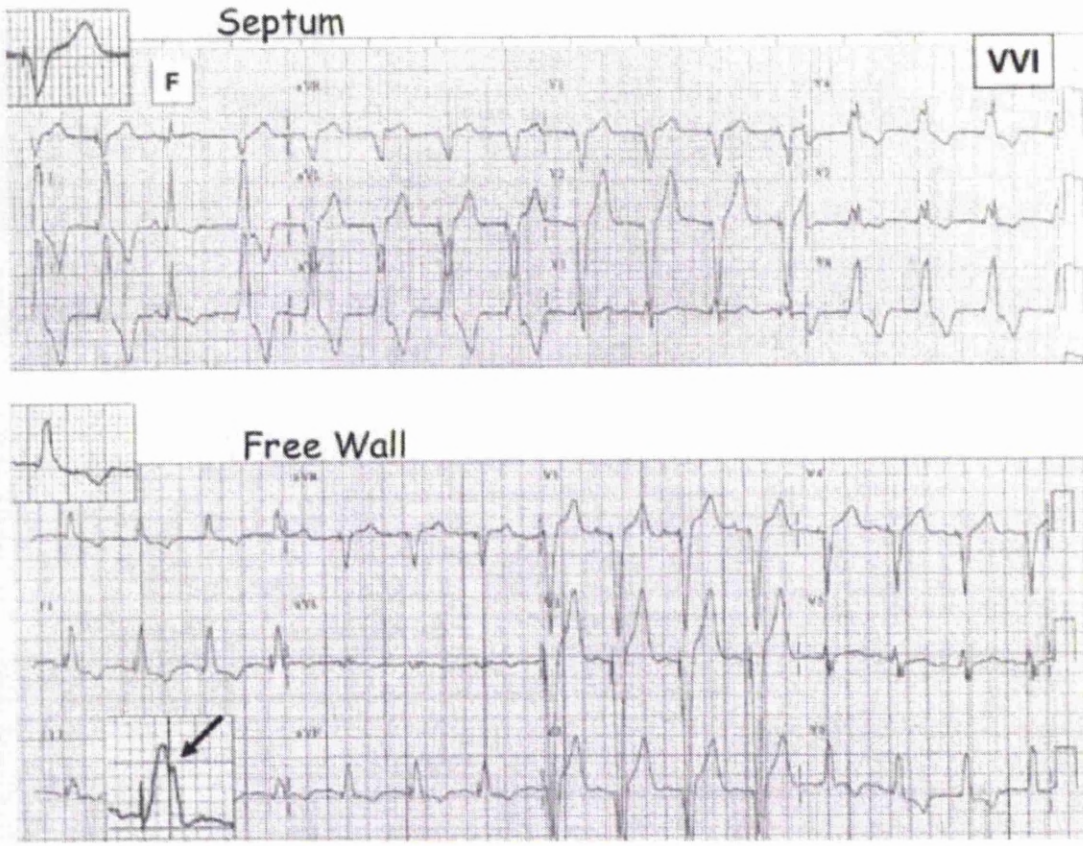


Figure 1.12: Typical ECG appearances of pacing from the RVOT free wall and septum. Lead 1 has been enlarged to show the differences between these sites with a QS wave for septal pacing and an R wave for the free wall. Notching of the QRS in lead III (enlarged) is often seen with free wall pacing. A fusion beat (F) is noted on the first tracing (Mond et al. 2007).

Hillock et al (Hillock, Stevenson, & Mond 2007), illustrated a helpful method to shape the stylet by which the ventricular lead can be reproducibly positioned to the RVOT septum. This can be achieved by initially creating a generous primary curve with the terminal 2 cm of the wire bent to form a secondary curve creating a swan neck deformity. Finally, and to be able to reliably point the lead tip towards the septum, the secondary curve is modified to make the last 2 cm point

posteriorly (Figures 1.13 & 1.14). They demonstrated that septal RVOT pacing results in a narrower QRS duration, compared to anterior or free wall pacing (136 vs 155 ms, $P < 0.001$). Alternatively, leads can be delivered to the RVOT using steerable or shaped catheters.

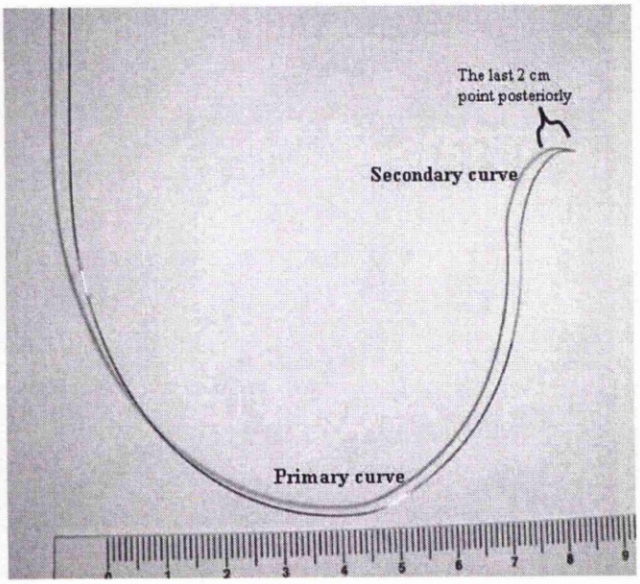


Figure 1.13: The prepared stylet with a generous primary curve and a terminal 2 cm bend to form a secondary curve creating a swan neck deformity. The secondary curve is then modified to make the last 2 cm point posteriorly.

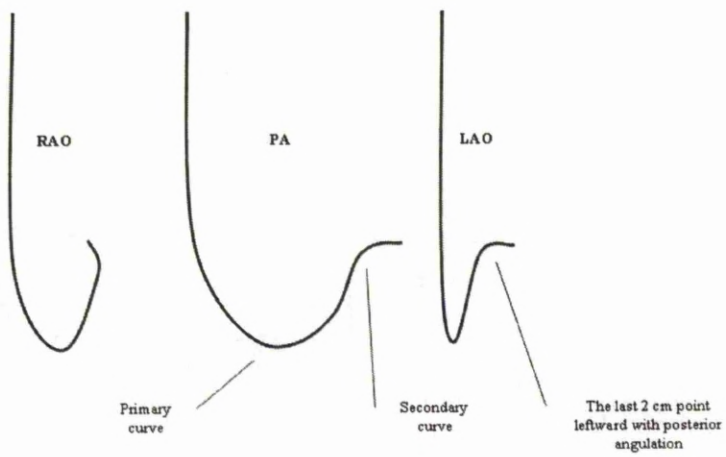


Figure 1.14: Schematic illustration of the stylet appearance in different fluoroscopic projections.

1.9 Trials on selective site pacing

Due to the potential detrimental effects of RVA pacing, SSP has been evaluated. Selective site pacing trials in humans were discussed in the 1980s, but the technical application only occurred in the early 1990s. This delay was due to the fact that long-term studies of SSP on humans have been hindered by many factors (Gammage & Marsh 2004). Firstly, there was a lack of uniform definitions for selective pacing sites; this may also have contributed to the conflicting results of published data. Secondly and until relatively recent times, there was an inability to place leads at specific sites with adequate stability and reproducibility (passive fixation leads were designed to be placed in the RVA). Thirdly, the mechanical and electrical performance of most pacing leads remains uncertain if placed in non-traditional sites. Thus, valid randomised controlled trials (RCT) have been difficult to design and conduct. In addition, the introduction of cardiac resynchronisation therapy (CRT) led to some confusion with regard to the role of, and patient selection for, SSP. Unlike CRT, SSP is largely designed to optimise LV function by minimising or abolishing RVA pacing induced detrimental effects. Selective site pacing is not an alternative or competitor for CRT; this confusion has lead to misleading conclusions from a number of studies with the result that consideration of SSP has been hindered (Brady & Hammill 2003; Stambler et al. 2003). There is a growing consensus of agreement that patients with a pacemaker indication with a prospectively high-degree of ventricular stimulation, reduced LV-function, with or without signs of heart failure, should receive a biventricular pacing device (Doshi et al. 2005). However, this is not evidence based and several large multicentre studies are currently underway to explore the best pacing option in patients with standard

pacing indications and variable left ventricular function who do not meet the current criteria for CRT (e.g. BLOCK-HF study, PREVENT-HF study, BIOPACE study). Table 1.2 shows most previous trials conducted on SSP, presented in a chronological order (Table 1.2.A shows the observational trials while Table 1.2.B shows the prospective randomised trials).

Table 1.2.A: Observational Trials on Selective Site Pacing

Study	Objectives	N&Design	F U	Findings
Benchimol et al, 1966	Compare haemodynamics with RV outflow, RV midportion, and RV inflow tract pacing	6 observational	acute	No difference in the cardiac output, stroke volume, and mean BP between sites.
Barold et al, 1969	Compare haemodynamics with RV inflow and outflow tract pacing	52 observational	acute	Haemodynamic sequelae of pacing the RV outflow and inflow are similar.
Cowell et al, 1994	Compare septal and apical RV pacing in patients with heart failure	15 observational	acute	Apical VDD pacing did not increase the CO significantly, whereas septal VDD pacing did.
Alboni et al, 1998	Compare acute haemodynamics during DDD pacing with different RV lead position (RVA, RVS, and RVOT)	21 observational	acute	No difference in cardiac function when pacing from RVA, RVS, or RVOT
Deshmunkh et al, 2004	Compare Direct His Bundle Pacing (DHBP) with RVA pacing in patients with cardiomyopathy (EF 23%±11%), persistent AF, & normal QRS	39 non-randomised	mean FU 42 months	DHBP is safe, effective and increases EF, cardiopulmonary reserve and improves NYHA class when compared to RVA pacing.
Stephen Vlay, 2006	Examine technical, procedural, and stability of RVOT-P	460 retrospective	9 yrs experience	84% implantation success over the 9-yrs period. No significant difference in pacing threshold, sensing, or impedance between RVA pacing and RVOT-P.
Vanerio et al, 2008	Compare all-cause mortality in RVA pacing (95 pts)and RVOT-P (55pts) in pts > 70% paced	150 retrospective	5 yrs	32% died in the RVOT group with 51% in the RVA group (P=0.02). RVOT-P appears to improve medium and long-term survival

Medi & Mond 2009	To assess long-term RVOT lead performance	100 retrospective	1 year	long-term RVOT lead performance is satisfactory and comparable to traditional pacing sites.

Table 1.2. B: Prospective Randomised Trials on Selective Site Pacing

Study	Objectives	N&Design	F U	Findings
Brian et al, 1991	Compare RVA pacing with RVOT pacing	33 randomised	73 months	long-term electrical performance and complications were comparable the in both groups.
Giudici et al, 1997	Compare RVA with RVOT pacing	89 randomised	acute	18.8% improvement in CO by velocity time integral in RVOT-P compared with RVA pacing
Buckingham et al, 1997	Compare pacing either RVA, or RVOT or both	11 randomised	acute	Trend for better CO in the RVOT or both sites pacing. QRS was significantly narrower in the dual site pacing.
Karpawick and Mital, 1997	Evaluated LV function after pacing RA, RVA, and RV septum in young patients with normal cardiac anatomy	22 randomised	acute	LV function is maintained by septal and deteriorates with RVA pacing.
Buckingham et al, 1998	Examine the acute effects of RVOT, RVA, and dual site pacing in patients with low EF (mean EF 32%)	14 randomised	acute	No statistically significant differences between pacing sites. Trend towards better parameters in RVOT and dual site pacing.
de Cock et al, 1998	Compared cardiac index in RVA and RVOT pacing	17 randomised	acute	Mean cardiac index was greater with RVOT pacing at all heart rates (85, 100 and 120).
Mera et al, 1999	Compare ventricular function during high RV septal and apical pacing after His-bundle ablation for refractory atrial fibrillation	12 randomised cross-over	2 months	Septal pacing resulted in a narrower QRS, greater fractional shortening, and a greater resting (but not exercise related) EF.
Victor et al, 1999	Compare RVOT with RVA pacing in patients with chronic atrial tachyarrhythmia and complete AV block	16 prospective randomised crossover	4 months then 3 months	No significant differences were found in NYHA class, EF, exercise time, and PVO_2. The results were identical whether EF < 40% or > 40%
Schwaab et al, 1999	Investigate the correlation between LV function and QRS duration obtained by alternate RV pacing sites	14 randomised	acute	Shorter QRS with alternate site. This correlated with homogenisation of LV contraction and improvement in systolic function but the differences in EF were minor (mostly a change of < 10%).

Kolettis et al, 2000	Compare LV haemodynamics during short-term AV sequential pacing from RVA and RVOT in normal hearts.	20 randomised	acute (5 min)	Pacing of both sites dropped BP with no significant difference between sites. CO was also unchanged between sites, but maximum negative dP/dt decreased significantly with RVA only.
Tse et al, 2002	Compare RVOT with RVA pacing in Pts with CHB	24 randomised	18 months	No difference at 6 months, but at 18 months: RVOT patients had better EF, less perfusion defects and less RWMAs
Stambler et al,(the ROVA study) 2003	Compare RVOT & RVA pacing in patients with NYHA class II-III HF (EF<40%) & chronic AF & bradycardic indication (VVIR)	103 randomised, crossover	9 months	QoL→ no difference between RVA, RVOT, or dual site pacing. LVEF was higher at 9 months in RVA pacing
Occhetta et al, 2006	Compare RVA pacing with para-Hisian pacing in patients with chronic AF and narrow QRS who underwent AVN ablation	16 randomised crossover	2 six-month periods	No significant improvement in NYHA class, QOL, 6 MWT, MR, TR& interventricular electromechanical delay during the para-Hisian pacing.
Res et al, (the BRIGHT study) 2007	Evaluate bifocal pacing (RVA & RVOT) in patients with indication for CRT (EF < 35%)	42 randomised crossover	6 months	Bifocal pacing improved EF, NYHA, 6MWT, and MLWHF score when compared to VVI back up pacing (40bpm).
Cate et al, 2008	To assess whether echocardiography can aid in selecting the optimum pacing site	14 randomised	acute 5-min	RVOT and apical pacing comparably worsen the echocardiographic normal LV

For better understanding and classification of these trials, the main findings will be presented in an attempt to answer the following 3 questions:

1- Is SSP feasible and safe?

2- Does SSP provide better acute LV haemodynamics compared to RVA pacing?

3- Does SSP provide better intermediate and long-term LV haemodynamics compared to RVA pacing?

1- Is selective site pacing feasible and safe?

The first randomised trial on SSP was conducted in 1991 by Barin et al. They randomised 33 consecutive patients requiring ventricular pacing to either RVA pacing or RVOT pacing. The mean follow up was 73 months. This study showed that long-term electrical performance and complications were comparable in both groups; this paved the way for future clinical studies using non-apical RV sites (Barin et al. 1991).

A larger study evaluating 460 consecutive RVOT implants was published in 2006 by Stephen Vlay who reported an overall 84% implantation success over a 9-year period (Vlay 2006). The success rate was higher at 92% in the second half of the study period. In a subgroup comparison, at 20 months, of RVA and RVOT pacing, there were no significant differences in pacing threshold, R-wave sensing, or pacing lead impedance. Lead dislodgment occurred in only 1 of 460 patients. Reasons for failure to implant in the RVOT included: inability to find a stable position with adequate pacing and sensing thresholds (related to anatomy, scarred myocardium, pulmonary hypertension, and tricuspid regurgitation), haemodynamic instability limiting time for implant, and a learning curve. Long-term stability and lead performance were excellent. Medi and Mond (Medi & Mond 2009) retrospectively studied a total of 100 patients with ventricular lead placement on the RVOT septum undergoing pacemaker implantation for bradycardia indications. They confirmed lead positioning with the use of fluoroscopy. Long-term (1 year) follow-up was obtained in 92 patients. This study confirmed satisfactory long-term performance with leads placed on the RVOT septum, comparable to traditional pacing sites. In summary, RVOT

placed leads perform as well as RVA placed leads in the short, intermediate, and long-term.

2- Does selective site pacing provide better acute left ventricular haemodynamics compared to right ventricular apical pacing?

Trials assessing acute haemodynamics with SSP have provided conflicting results. Several trials showed no difference (or statistically insignificant difference) in acute cardiac haemodynamic variables (CO, EF) between RVA pacing and RVOT pacing (Barold et al. 1969; Benchimol & Liggett 1966; Buckingham et al. 1998; Lieberman et al. 2006; Padeletti et al. 2007; ten Cate et al. 2008) Meanwhile a few randomised trials suggested better acute LV haemodynamics with RVOT pacing (Buckingham et al. 1997; de Cock et al. 1998; Giudici et al. 1997; Karpawich & Mital 1997). However, it should be stressed that the results of these trials have been obtained in different clinical settings, using variable endpoints obtained with different techniques. It should also be emphasised that LV haemodynamics are affected differently when biventricular pacing is used for a heart failure indication compared to pacing to prevent the consequences of bradyarrhythmias. Due to this inconsistency of the clinical studies and the non-standardised definition of the SSP site, it is still unclear whether SSP provides better acute LV haemodynamics when compared to RVA pacing. It is possible that positive or negative remodelling in LV function can be a prolonged process and thus cannot be detected in the acute phase.

3- Does selective site pacing provide better intermediate and long-term functional status and left ventricular haemodynamics compared to right ventricular apical pacing?

The assessment of intermediate and long-term LV haemodynamics in SSP has faced many challenges. Firstly, long-term follow up has proved difficult due to the fact that the majority of these patients are elderly with different indications for pacing and multiple comorbidities. Secondly, there is the inherent anatomic heterogeneity in the SSP site. Additionally, studies on intermediate and long-term LV haemodynamics have utilised differing methodologies (prospective/ retrospective; crossover or parallel groups). The outcome measures have also differed with some "soft endpoints" utilised and possible investigator influence due to lack of blinding procedures. Consequently, these studies have produced conflicting results once more and have been subject to much criticism. The methodology and outcomes of the more robust trials will be reviewed in detail.

In the study by Victor et al, investigators compared the haemodynamic effects of RVOT pacing with RVA pacing in 16 patients with chronic atrial tachyarrhythmia and complete AV block over a 7 month period in a randomised crossover fashion. LVEF was $\geq$ 40% in 10 patients and $\leq$ 40% in 6 patients (Victor et al. 1999). A DDDR pacemaker was connected to 2 ventricular leads. The RVA lead was connected to the ventricular port whist the RVOT lead was connected to the atrial port. The pulse generator was programmed to either AAIR (hence RVOT pacing) or VVIR (hence RVA pacing) for 4 months before crossing over to the other pacing site for a further 3 months. No significant differences were found in New York Heart Association (NYHA) class, EF,

exercise time, and maximal oxygen uptake. The results were identical in those patients with an EF < 40% and in those with an EF > 40%. The lack of positive results may reflect the small sample size, the relatively short period of follow-up or the inequity in the two periods of evaluation. It is also possible in this study that the presence of two ventricular leads has affected the right ventricular haemodynamics by inducing tricuspid regurgitation especially in those with a LVEF < 40%.

In 2003, the ROVA study (Stambler et al. 2003) investigators evaluated RVA, RVOT, and dual site pacing in 103 patients with NYHA class II-III heart failure (EF < 40%) and chronic AF with a conventional bradycardic pacing indication (VVIR pacemaker). This was a randomised crossover trial. The authors showed no difference in QOL or LVEF between RVA, RVOT, or dual site pacing at 3 months. However, after 9 months, LVEF was higher (P=0.04) in those assigned to RVA rather than RVOT pacing. It would be interesting to conduct such a study for a longer duration to ascertain whether pacing-induced LV remodelling, and possibly QOL scores, take longer to be significantly detected. As this study included only patients with LVEF < 40%, it is quite possible that pacing will result in more deleterious haemodynamic effects in comparison to patients with normal or near normal systolic LV function.

The first positive study was published in 1999 by Mera et al. They studied 12 patients undergoing His-bundle ablation for control of ventricular rate in chronic atrial fibrillation (Mera et al. 1999). A DDDR generator was implanted with the RVA lead connected to the ventricular port and the RV septum lead to the atrial

port. This enabled a randomised crossover design, with pacing for 2 months at each site commencing immediately after successful ablation and implantation of the device. Septal leads were positioned using electrocardiographic (ECG) criteria and patients were paced with a lower rate of 80 beats per min. Septal pacing resulted in a significantly narrower QRS, greater fractional shortening, (0.31 ± 0.05 vs. 0.26 ± 0.07, $P < 0.05$) and a greater resting (but not exercise related) EF (0.51 ± 0.14 vs. 0.43 ± 0.10, $P < 0.05$). Chronic pacing parameters were similar at both sites.

The second positive study was published in 2002 (Tse et al. 2002). Investigators studied the effect of pacing site on myocardial perfusion and LV function by randomising 24 patients with complete AV block to receive RVA or RVOT leads. There was no difference between the two groups at 6 months, but at 18 months, RVOT patients had a higher EF, less perfusion defects and regional wall motion abnormalities (RWMA). They concluded that RVOT pacing prevented the long-term deleterious effects of RVA pacing.

A further important study was published in 2007 by Res eta al [The BRIGHT study, (Res et al. 2007)]. Bifocal pacing (combined RVA and RVOT pacing) was evaluated in 42 patients with NYHA III-IV, EF < 35%, QRS ≥ 120msec, and LBBB. This was a crossover study in which patients were randomised to receive either bifocal pacing or the control mode (VVI back-up pacing at 40 bpm), each for a period of 3 months. Patients with bifocal RV pacing showed significant improvement in EF, NYHA, 6MWT and MLWHF score.

All-cause mortality was only studied retrospectively by Vanerio et al in 2008 (Vanerio et al. 2008). They studied 150 consecutive patients who underwent pacemaker implantation for complete AV block (spontaneous or after AV node ablation), symptomatic second-degree AV block, and symptomatic atrial fibrillation with slow ventricular response. During follow-up, 18 patients (32%) died in the RVOT group and 49 (51%) in the RVA group (log-rank p=0.02). Cox regression multivariate analysis showed that only 2 variables correlated with survival; outflow tract pacing had a negative correlation with P = 0.006 and LVEF < 40% showed a positive correlation with P = 0.003. They concluded that RVOT-P appears to improve medium/ long-term survival and recommended conducting prospective randomised trials with a greater number of patients to confirm these findings.

All these studies were conducted on a small number of patients with relatively short follow up periods. LV remodelling is a prolonged process and further work is clearly indicated with longer follow-up and prospective evaluation of mortality.

1.9.1 Ongoing trials on selective site pacing

Ongoing trials were recently reviewed by Kaye et al (Kaye, Stambler, & Yee 2009). They assessed 3 randomised prospective multicenter clinical trials that are still in progress. These studies compare the long-term effects of RV apical versus septal pacing on left ventricular (LV) function. The three trials are the Optimize RV Selective Site Pacing Clinical Trial (Optimize RV), the Right Ventricular Apical and High Septal Pacing to Preserve Left Ventricular Function (Protect

Pace), and the Right Ventricular Apical versus Septal Pacing (RASP). Whist each study differed slightly in design and study population, combined, they would follow approximately 800 patients requiring frequent or continuous ventricular pacing for up to 3 years using the single primary end point of LVEF. Unfortunately, the Optimize RV trial was terminated early due to limited resources. The Protect Pace trial has finished recruiting and is yet unpublished. Finally, the RASP trial is struggling to recruit the required number of patients.

1.9.2 His and para-Hisian pacing

In theory, and in patients without bundle branch block, ventricular lead implantation at the His bundle would be ideal. By using the His-Purkinje conduction system, biventricular depolarisation would be physiologic and result in simultaneous contraction of both ventricles. Therefore this potential pacing site warrants specific separate discussion.

Deshmukh et al reported the first results of chronic direct His bundle pacing (DHBP) in 18 patients (Deshmukh et al. 2000). Although they were able to pace the heart with a paced QRS almost identical to the intrinsic activation, the study demonstrated clear challenges to His-bundle pacing. Lead implantation required electrophysiological mapping and was successful in 12 out of 18 patients only with a mean procedure time of almost 4 hours. The mean pacing threshold was as high as 2.4 V at 0.5 msec. Exit block or lead dislodgment occurred in 2 of the 12 patients. Finally, sensed R waves were below 1.5 mV in 8 of these 12 patients. In another study, by the same group, direct His bundle pacing was compared with RVA pacing in 54 patients with cardiomyopathy (EF 23% ± 11%), persistent AF,

and normal QRS (Deshmukh & Romanyshyn 2004). Direct His bundle pacing was successful in 39 patients (72%). Twelve patients who received an RVA lead also underwent cardiopulmonary testing. After a mean follow-up of 42 months, 29 patients were alive with a mean EF improving from 23% to 33% and NYHA functional class improving from 3.5 to 2.2. Cardiopulmonary exercise testing revealed longer exercise time in direct His bundle pacing compared to RVA pacing (280 ± 104s vs. 255 ± 110s), higher O_2 uptake (16 ± 4 ml/kg/min vs. 15 ± 4 ml/kg/min), and later anaerobic threshold (145 ± 74s vs. 126 ± 71s). They concluded that direct His bundle pacing was safe, effective and increased cardiopulmonary reserve when compared to RVA pacing.

In 2006, Zanon et al reported a higher success rate of 92% (24 out of 26 patients) when a steerable catheter was used with a mean procedure time of 75 min (Zanon et al. 2006). More recently, the same group studied myocardial perfusion using Tc99m-SestaMIBI in 12 patients with one lead positioned in the RVA and another in the His bundle (Zanon et al. 2008). Direct His bundle pacing was superior to RVA pacing in preserving the physiologic distribution of myocardial blood flow and reducing mitral regurgitation and LV dyssynchrony (as assessed on echocardiography and tissue Doppler imaging).

Another area of potential interest is the concept of Para-Hisian pacing which is defined as pacing with an intrinsic QRS different from the paced one in either morphology or duration, and widening of the QRS with voltage reduction due to loss of His bundle capture. Para-Hisian pacing was compared with RVA pacing in 16 patients with chronic AF and narrow QRS who had undergone AVN

ablation (Occhetta et al. 2006). Occhetta et al implanted a dual-chamber pacemaker connected to a screw-in lead positioned in close proximity to the His bundle and another lead in the RVA. After two randomised six-month periods (with para-Hisian and RVA pacing), there was a significant improvement in NYHA functional class, QOL, 6 minute walk test, mitral regurgitation, tricuspid regurgitation and interventricular electromechanical delay during para-Hisian pacing.

In conclusion, recent improvements in lead technology and delivery systems make direct His bundle pacing and para-Hisian pacing feasible. However, this requires EP mapping, takes longer, carries a higher risk of sensing or pacing failure, and a higher lead dislodgment rate. Hence, all studies to date used a second "back up" RVA lead.

1.10 Study rationale and objectives

The long-term harmful effects of RVA pacing have been well described and accepted. It is clear that selective site ventricular pacing is rapidly evolving. However, most studies on SSP have been relatively small, with variable design and different end points. They have therefore provided conflicting results. There is a paucity of long-term data from carefully designed studies. Of particular concern is the fact that patients with impaired LVEF are at even greater risk from RVA pacing. The large landmark trials, such as the DAVID study, recommend minimisation of RVA pacing by using atrial based pacing modes to maintain AVN conduction. However, in patients who require ventricular pacing, the results of SSP trials have been disappointing. The optimal RV pacing site which

provides the best haemodynamic and clinical benefit is yet to be confirmed. This "optimal" pacing site could actually vary between patients and therefore may need to be individualised based on the pacing indication, LVEF, or other unknown factors.

Assuming that RVOT pacing can preserve the LV haemodynamics and therefore produce better cardiac output, this should be reflected in a better functional performance in patients receiving RVOT rather than RVA leads. The overall functional performance can be objectively assessed by measuring the peak oxygen consumption on CPET. None of the previous studies comparing RVOT with RVA pacing, but one (Victor et al. 1999), included PVO_2 as a study outcome. In this study by Victor et al only 16 patients with chronic atrial tachyarrhythmia and complete AV block were included.

Our study is a single-centre, single blinded, randomised prospective trial. We evaluated the effects of RVOT pacing on the haemodynamic and functional recovery of patients requiring permanent right ventricular pacing. The primary outcome was cardiopulmonary functional capacity as measured by peak oxygen consumption (PVO_2). Secondary endpoints included: exercise time, NYHA heart failure functional class, MLWHF score, SF-36 score, QRS duration, left ventricular ejection fraction, left ventricular end-diastolic diameter, mitral regurgitation grade, and CARE-HF dyssynchrony criteria.

CHAPTER TWO

Methods

2.1 Summary of the protocol

Title of Study	A Study Evaluating the Effects of Selective Site Pacing on the Haemodynamic and Functional Recovery in Patients Requiring Permanent Right Ventricular Pacing
Planned Study Period	March 2006 to January 2009
Study Design	Single-centre (Liverpool Heart and Chest Hospital), randomised, prospective
Number of Subjects	50
Eligibility	Patients requiring permanent right ventricular pacing: 1- Patients with atrial fibrillation or flutter requiring AV nodal ablation on symptomatic grounds. 2- Patients with chronic AVN disease requiring permanent pacing.
Objectives	To investigate: • Whether patients who require permanent right ventricular pacing derive haemodynamic and functional benefit from RVOT pacing compared to RVA pacing. • The effect of RVOT and RVA pacing on quality of life, resting Echocardiographic parameters and sub maximal exercise.
Endpoints	**Primary endpoints** • Cardiopulmonary functional capacity as measured by peak VO_2 (ml/kg/min) **Secondary endpoints** • Exercise time • New York Heart Association Classification • Systolic cardiac function determined by measuring ejection fraction (%) • Left ventricular size as assessed by measurement of the left ventricular end diastolic diameter (mm) • Quantitative assessment of mitral valve regurgitation • Evidence of left ventricular dyssynchrony Measurement of pulmonary and aortic ejection systolic delays, as well as inter and intra-ventricular mechanical delays • QRS width (ms) • Minnesota Living With Heart Failure scale (MLWHF) • Short-form 36 quality of life index

2.2 Hypothesis

We hypothesised that pacing at the right ventricular outflow tract compared with right ventricular apex achieves better cardiopulmonary exercise capacity and dynamic cardiac function in patients requiring constant right ventricular pacing.

2.3 Inclusion criteria

Patients were included in the study if they had the ability to provide informed consent and had either atrial fibrillation or flutter requiring AV nodal ablation, or chronic high-grade AVN block (Mobitz II or grade III AVN block).

2.4 Exclusion criteria

Patients were excluded from the study if they had one or more of the following:

i- Indication for implantable cardioverter defibrillator or biventricular pacemaker.

ii- Exercise limitation due to other pathological process e.g. angina, respiratory, neurological or rheumatological disease

iii- Significant valvular heart disease

iv- Current or recent participation in any other clinical investigation

v- Life expectancy less than 2 years

vi- Percutaneous or surgical revascularisation within 3 months

vii- Patient inability to independently comprehend the patient information sheet or inability or unwillingness to provide informed consent

2.5 Definition of study outcomes

2.5.1 Primary endpoint

Cardiopulmonary functional capacity was assessed using a cycle ergometer and a standard ramp protocol with one minute increments in 10 watt work load. The maximal value of oxygen utilisation per minute corrected for body mass, peak VO_2 (ml/kg/min), was taken as the peak exercise value, provided the anaerobic threshold has been exceeded.

2.5.2 Secondary endpoints

i- Exercise time was measured in seconds from the onset of exercise to the point of termination.

ii- New York Heart Association Functional Capacity Class as revised by the Criteria Committee of the American Heart Association in 1994 was applied.

Class I: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or angina.

Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or angina.

Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea, or angina.

Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

iii- Ventilatory equivalent for O2 at 1L/ VO2 as defined: the minute ventilation at an oxygen consumption of 1 litre per minute.

iv- Left ventricular systolic function as determined by:

1- The ejection fraction (EF) measured by Simpson's rule of discs

2- Left ventricular outflow tract velocity time index (VTI)

3- Left ventricular size as determined by the measurement of left ventricular end -diastolic diameter (LVEDD) in the parasternal long axis view using M-mode Echocardiography (after making sure it is perpendicular to the short axis parasternal view)

v- Left ventricular dyssynchrony as defined by 2 of the following 3 criteria:

1- Aortic pre-ejection delay > 140 ms (atrioventricular)

2- Aortic pre-ejection delay minus pulmonary pre-ejection delay > 40ms (inter-ventricular)

3- Posterolateral latency (D1 > D2) (intra-ventricular)

vi- QRS width determined by a standard 12-lead ECG (150 Hz, 25 mm/s, and 10 mm/mV) measurement from the onset of the Q wave to the end of the S wave (Nishiyama et al. 1993) .

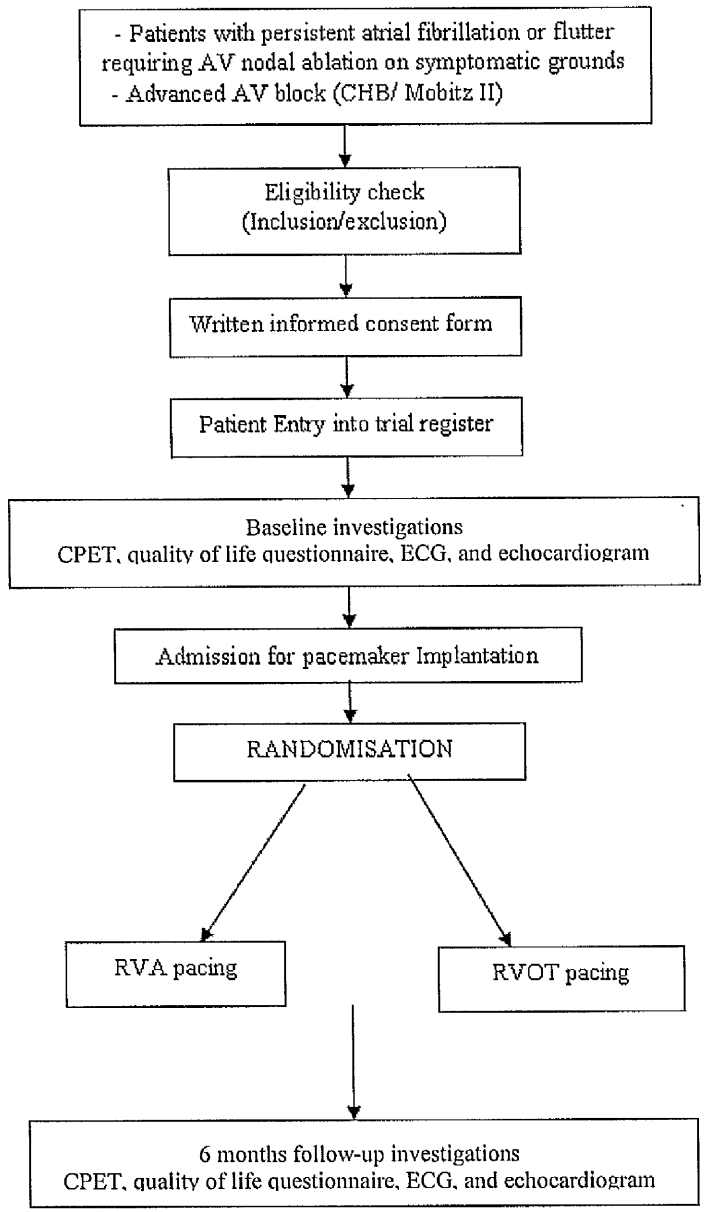
vii- Health-related quality of life indices using the Minnesota Living with Heart Failure scale and the Short-form-36. The Minnesota Living with Heart failure is a 21-item self-administered questionnaire quantifying different clinically-relevant aspects of the heart failure status including: physical limitation, treatment satisfaction and disease perception/quality of life. The short-form SF-36 is a general survey of health status and an outcome measure in clinical practice, and can be used together with disease-specific instruments for patient evaluation. The survey was either self-administered or completed by an interviewer when the patient was incapable of filling the questionnaire due to visual impairment. This was performed by reading the form and recording patient's answers.

2.6 Major adverse cardiac events

- Death
- Ventricular Fibrillation, requiring cardioversion
- Cardiac Arrest, requiring CPR
- Lead displacement
- Pneumothorax
- Haematoma, requiring evacuation
- Failure to capture of pacing lead
- Pericardial effusion
- Cardiac tamponade
- Hospitalisation for heart failure

2.7 Recruitment

Study patients were recruited into the trial from the routine clinical waiting list, and from the hospital wards (Liverpool Heart and Chest Hospital) .Those consented for the trial were included in the trial register.



2.8 Consent procedure

Patients from the routine waiting list for AV node ablation were pre-screened for inclusion/exclusion criteria and were informed about the trial by the investigators. Suitable in-patients with chronic high grade AVN block were also approached, providing they met the inclusion criteria and they were not requiring temporary pacing. Eligible patients were then approached for consent and given the patient information leaflet (see appendix 1). Consent included an explicit initial acceptance of the trial-related requirement for follow-up echocardiography, cardiopulmonary exercise tests and quality of life questionnaires. Patients had access to the information sheet approved by the local ethics committee (see appendix 2). Patients were free to ask questions to the investigators and were offered the opportunity to reflect on the issue or to seek advice from other sources such as family members or other health professionals involved in their care. Patients only entered the active phase having provided informed written consent. Patients who dropped out prior to randomisation and after registration, were logged onto the CONSORT diagram but were not included in the intention to treat analysis.

2.9 Pre-pacemaker implantation assessments

At baseline, prior to randomisation, all patients underwent standard routine clinical assessment. The collected data consisted of demographics, previous history, previous cardiac investigations, and current medication. Patients were required to complete the Minnesota Living with Heart Failure, SF36 quality of life questionnaires and assessment of heart failure status (see CRF in appendix 3). An electrocardiogram, an echocardiogram and a cardiopulmonary exercise

test were performed (methods of performing this will be detailed later in this chapter).

2.10 Randomisation

Patients were randomised in equal proportion into the two experimental groups (RVA versus RVOT pacing groups) using a local proprietary database. Block randomisation with random block sizes of 2, 4 and 6 was used to ensure numerical balance between the groups throughout the randomisation period. Key data were entered prior to randomisation, and then random allocations were generated. Once randomised, the patient was enrolled and data contributed to the primary outcomes.

2.11 Details of pacemaker implantation

All 50 patients had pacemaker implantation according to standard clinical practice. The pacemaker right ventricular lead was implanted at the RVA or RVOT positions according to the randomisation code as detailed below. A post-implantation chest radiograph (CXR) was taken routinely in the postero-anterior and lateral positions. A pacemaker interrogation was also performed to make sure that the sensing and pacing threshold were satisfactory. The lower rate limit was programmed to 60 in all cases with the rate response on. Patients in need of AVN ablation had this performed at a subsequent hospital admission.

Method 1 (right ventricular apical selective site pacing)

The RVA site was defined as the most inferior and lateral position providing acceptable pacing parameters (R wave of $\geq$ 6 mV and a pacing threshold of $\leq$ 1.0 V) in the right anterior oblique view.

Method 2 (right ventricular outflow tract selective site pacing)

The RVOT site was defined as a position below the pulmonary valve and above a line drawn parallel to the RV inferior border, extending from the apex of the tricuspid valve (His) to the border of the RV in an antero-posterior view, with acceptable pacing parameters (as above). In cases of inability to achieve satisfactory pacing parameters, a different RVOT pacing site was chosen.

2.12 Baseline and follow-up investigations

All patients had an echocardiogram, cardiopulmonary exercise test and completed quality of life questionnaires at baseline (before randomisation and pacemaker implantation) and at 6 months post-pacemaker implantation. The investigators were not aware of the lead position at follow-up. The investigators accept that longer term follow up may yield further results but collection of such data was beyond the remit and resources of this thesis.

Table 2.1: Investigations at baseline and follow-up		
Measurement	**Baseline**	**6 months**
QOL Questionnaires	SF-36 and MLWHF	SF-36 and MLWHF
ECG and Echocardiography	QRS width, LVEF, LV size, LVEDD, LV dyssynchrony, mitral valve regurgitation	QRS width, LVEF, LV size, LVEDD, LV dyssynchrony, mitral valve regurgitation
Cardiopulmonary Exercise test	Peak VO_2, ET, end-tidal PC O_2, VE for O_2 at 1L/ V O_2	Peak VO_2, ET, end-tidal PC O_2, VE for O_2 at 1L/ VO_2
Adverse events monitoring	Death, VT, VF, lead displacement, pneumothorax, haemothorax	Death, VT, VF, lead displacement, pneumothorax, haemothorax

2.13 Time and event schedule

Table 2.1: Time and event schedule				
Event	**Screening**	**Pre-Procedure**	**Post-Procedure**	**6 months follow-up**
Screen log	x			
Informed consent signed	x			
Entry into trial register	x			
Inclusion/exclusion criteria met	x			
Physical Examination	x			
Medical History	x			
Randomisation		x		
Quality of life Questionnaire	x			x
Echocardiography	x			x
Cardiopulmonary Exercise test	x			x

2.14 Trial coordination

The Clinical Trials Unit (CTU) at Liverpool Heart and Chest Hospital provided a central randomisation service, production of the final protocol, case record forms (CRFs), and a trial specific database (see appendix 3).

2.15 Ventricular lead positioning

2.15.1 Right ventricular apex

Entrance into the pulmonary artery on X-ray screening confirms that the lead has traversed the right ventricle and is neither in the atrium nor in the coronary sinus. The lead was then pulled back as the stylet is advanced. Once the lead tip falls toward the apex, the patient was asked to inspire deeply and the lead was advanced into place. This procedure is often accompanied by ventricular ectopy, the absence of which suggests that the lead is not in the ventricle. An alternative method used to gain entry to the ventricle was to form the stylet into a dogleg or a J shape and use it to direct the lead across the tricuspid valve. Once in the right ventricle, the shaped stylet was replaced with a straight one to facilitate positioning at the apex. The ideal fluoroscopic appearance of the right ventricular apical lead is one in which the lead's tip is well to the left of the spine and is pointing anteriorly and slightly caudal (in the anteroposterior projection it may not be possible to distinguish whether a lead is in a posterior coronary vein, the left ventricle, or the right ventricular apex).

2.15.2 Right ventricular outflow tract

As the RVOT is less trabeculated than the RVA, the use of an active-fixation lead is required. To place a lead in the outflow tract or septum, the lead was prolapsed into the pulmonary artery as described above. The lead is then withdrawn after inserting a curved stylet as described in Figure 1.15 and applying torque to drive the tip into the septum, so the lead tip can be fixed. If the pacing and sensing parameters were not satisfactory an alternative position were tried. All lead positions were confirmed by both left anterior oblique and right anterior oblique views in the laboratory.

2.16 Health related quality of life measures

Standardised health-related quality of life (HRQOL) measures are critical for a number of purposes. These include evaluating the progress in achieving health goals, assessing health disparities across different segments of the population, and measuring the effectiveness of health care interventions for age-related diseases. Below are brief descriptions of the two tools used in our study to assess the quality of life.

2.16.1 Minnesota Living with Heart Failure questionnaire

The Minnesota Living with Heart Failure questionnaire was designed in 1984 to measure the effects of heart failure and treatments for heart failure on an individual's quality of life. The content of the questionnaire was selected to be representative of the ways heart failure can affect the key physical, emotional,

social and mental dimensions of quality of life without being too long to administer during clinical trials or practice. To measure the effects of heart failure symptoms, functional limitations and psychological distress on an individual's quality of life, the MLHFQ asks each person to indicate using a 6-point (zero to five) Likert scale how much each of 21 facets prevents them from living as they desire.

The questionnaire assesses the impact of common physical symptoms - shortness of breath, fatigue, peripheral oedema, and difficulty sleeping - and psychological symptoms of anxiety and depression. In addition, the effects of heart failure on physical and social functioning are incorporated into the measure. Since treatments might have side effects in addition to ameliorating symptoms and functional limitations produced by heart failure, questions about side effects of medications, hospital stays and costs of care are also included to help measure the overall impact of a treatment on quality of life. Although the MLHFQ incorporates relevant aspects of the key dimensions of quality of life, the questionnaire was not designed to measure any particular dimension separately

2.16.2 The short form-36 health survey

The SF-36 was developed from work done by the RAND Corporation and the Medical Outcomes Study (MOS), based on the measurement strategy of the RAND Health Insurance Study in the 1980s. SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health

utility index. The SF-36 covers the following quality of life aspects: Physical Function (PF), Role Limitation (RL), Bodily pain (BP), Social Function (SF), General Mental Health (GMH), Role Limitation due to Emotional Problem (RLEP), Vitality, Energy, or Fatigue (VEF), General Health Perception (GMH), and Health Compared to Last Year (HCLY). The SF-36 can be either self-administered or administered by a trained interviewer, either in person or by telephone. Over the years, the SF-36 has been used in surveys of general and specific populations, for comparing the relative burden of diseases across different sub-groups and in differentiating the health benefits produced by health care treatments.

2.17 Echocardiogram

All echocardiogram studies were performed by one operator who is accredited by the British Society of Echocardiography (BSE) to minimise the inter-observer variability. If in doubt, it was discussed with a second accredited operator until agreement reached.

2.17.1 Left ventricular size measurement

This was measured using M-mode at mid ventricular level. This was achieved by optimising the parasternal long axis view with the septum and the posterior wall lying parallel. The M-mode cursor was then placed through opposing walls so that it intersects both at right angles. The left ventricular end diastolic diameter (LVEDD) was then measured from endocardium to endocardium edge at the end of diastole (Figure 2.1).

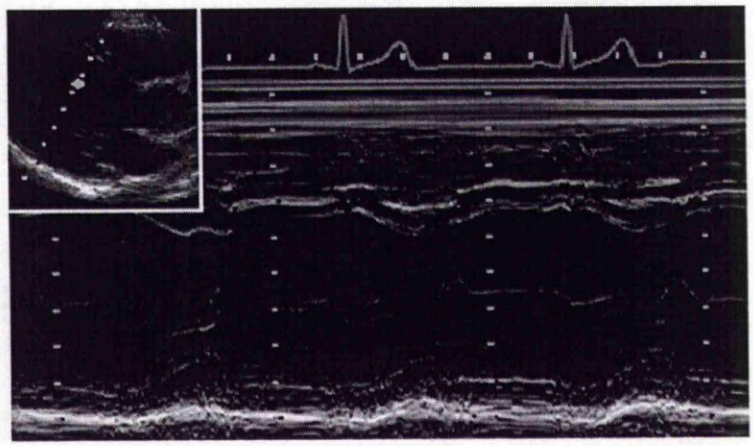


Figure 2.1: Parasternal long axis view showing the septum and the posterior wall.

2.17.2 Assessment of left ventricular global systolic function

This was assessed using Simpson's method. This method is based on the principle of slicing the left ventricular cavity from apex down to the mitral valve annulus into a series of discs. The volume of each disc is then calculated automatically and disc volumes are added together to provide the total left ventricular volume. This was performed in two perpendicular planes (2-chamber and 4-chamber views) in both systole and end-diastole. This method was only used when a clear visualisation of the endocardium was possible in both 2-chamber and 4-chamber views.

2.17.3 Velocity time integral

This was calculated by obtaining a 5-chamber view and positioning the pulsed wave Doppler sample in the left ventricular outflow tract (LVOT). The LVOT spectrum is then traced and the area automatically calculated.

2.17.4 Dyssynchrony Assessment

Echocardiography has been extensively used to assess mechanical LV dyssynchrony. Many simple and complex methods were utilised in the field of cardiac resynchronisation therapy in an attempt to improve patient selection. In a prospective, multicenter setting, the Predictors of Response to CRT (PROSPECT) study tested the performance of these parameters to predict CRT response. It was concluded that there is no single echocardiographic measure of dyssynchrony that may be recommended to improve patient selection for CRT beyond current guidelines (Chung et al. 2008). In our study, we adopted simple reproducible criteria to assess LV dyssynchrony (Cleland et al. 2006) accepting that the pacing indication in our patients is different compared to patients undergoing CRT and that these LV dyssynchrony criteria were in fact validated and tested only in CRT candidates.

i- Aortic Pre-Ejection delay (APE)

This was measured in milliseconds (msec) and represents the distance between the start of the electrical depolarisation (beginning of QRS complex on the surface electrogram) and the start of the mechanical ejection at the level of the aortic valve (beginning of the VTI waveform on continuous wave Doppler, Figure 2.2). Three measurements were made and the mean was taken. In the CARE-HF trial (Cleland et al. 2006), this was considered abnormal if measured > 140 msec.

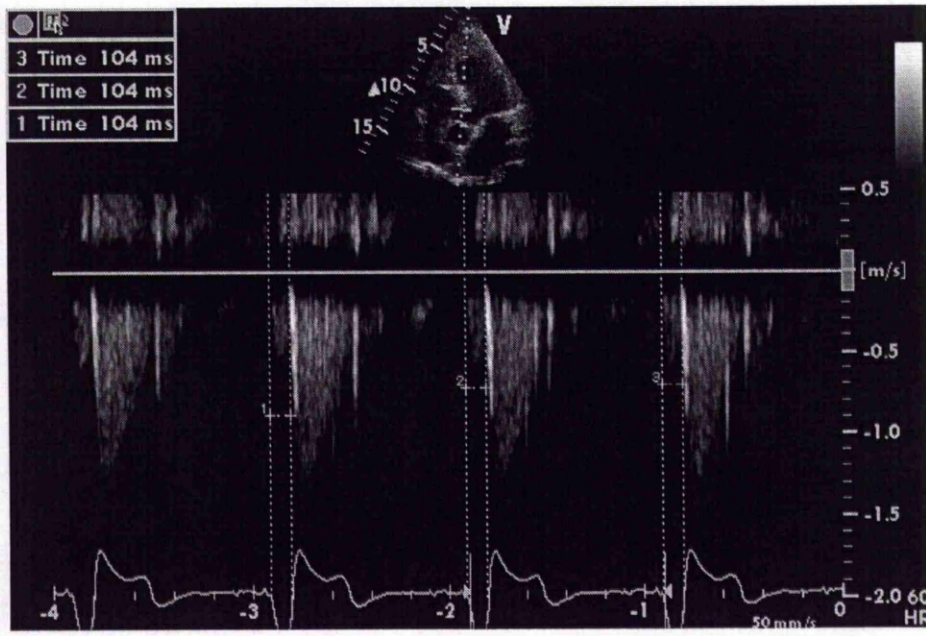


Figure 2.2: APE measurement. It is the time between the start of the electrical depolarisation (beginning of QRS) to the start of the mechanical ejection as depicted by the dotted lines. In this case 3 measurements were made (104 msec)

ii- Pulmonary pre-ejection delay

This was measured in milliseconds (msec) and represents the distance between the start of the electrical depolarisation (beginning of QRS on the surface electrogram) and the start of the mechanical ejection at the level of pulmonary valve (beginning of the VTI waveform on continuous wave Doppler, Figure 2.3). Three measurements were made and the mean was taken. The interventricular delay was then calculated by deducting the PPE from the APE. In the CARE-HF trial, this was considered abnormal if measured > 40 msec.

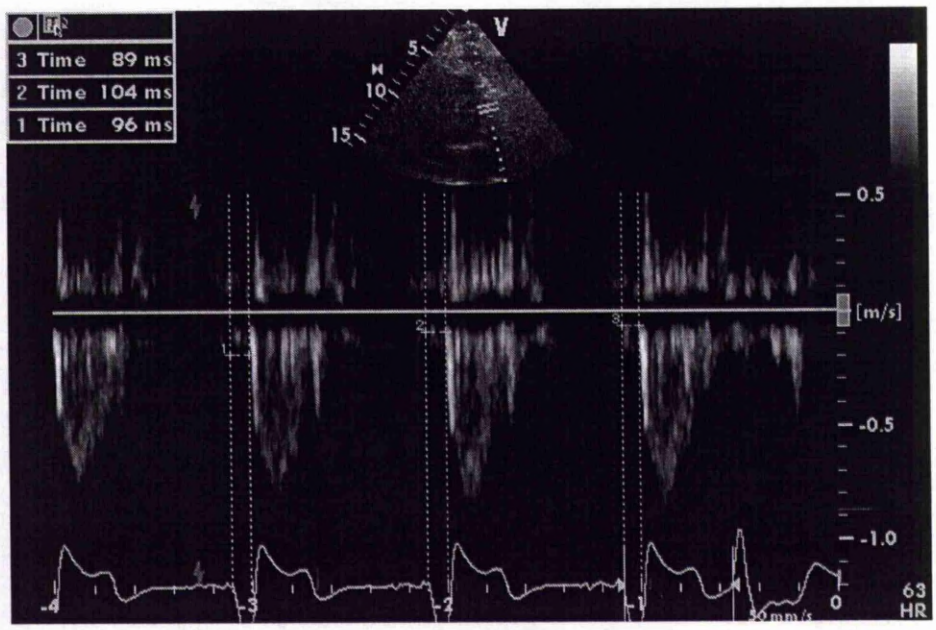


Figure 2.3: PPE measurement. It is the time between the start of the electrical depolarisation (beginning of QRS) to the start of the mechanical ejection at the level of the pulmonary valve. In this case 3 measurements were made (the mean is 96 msec).

iii- Postero-lateral latency (intra-ventricular dyssynchrony, D1>D2)

D1 is measured in milliseconds (msec) and represents the distance between the start of the electrical contraction (beginning of QRS on the surface electrogram) to the peak excursion of the LV posterior wall (Figure 2.4). Three measurements were made and the mean was taken. D2 is measured from the beginning of the QRS to the start of mitral valve opening in diastole (beginning of E wave on pulse wave Doppler, Figure 2.5). The LV is considered dyssynchronous if D1 > D2 (CARE-HF study).

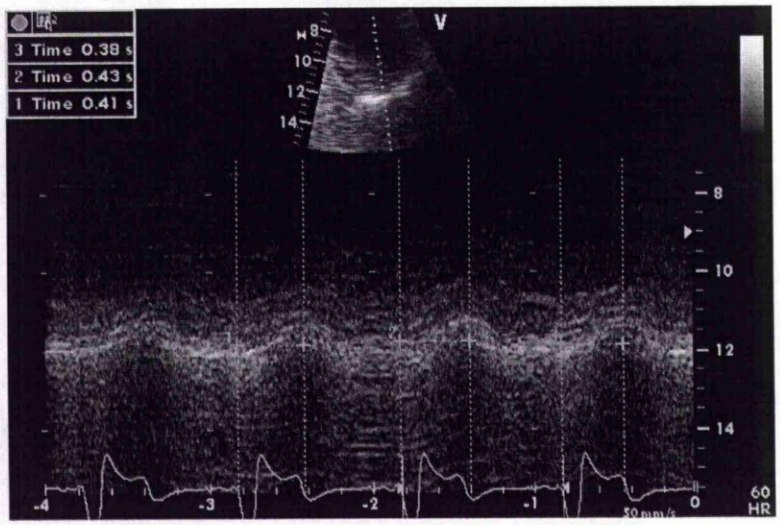


Figure 2.4: D1 measurement. The distance between the start of the electrical contraction (beginning of QRS) to the peak excursion of the LV posterior wall (mean value 410 msec).

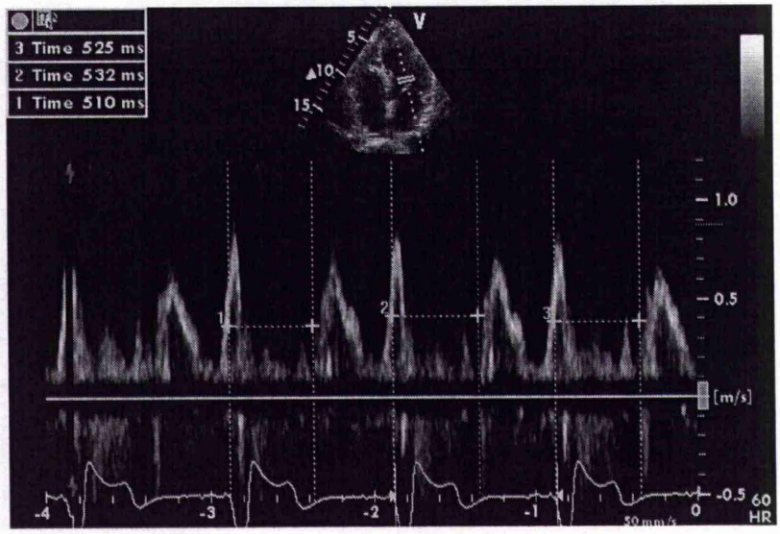


Figure 2.5: D2 measurement. It is the distance between the start of the QRS to the beginning of E wave on pulse wave Doppler (mean value 523 msec).

2.18 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) provides assessment of the integrative exercise responses involving the pulmonary, cardiovascular, haematopoietic, neuropsychological, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function. This non-invasive, dynamic physiologic overview permits the evaluation of both submaximal and peak exercise responses, providing the physician with relevant information for clinical decision making. The use of CPET in patient management is increasing with the understanding that resting pulmonary and cardiac function testing cannot reliably predict exercise performance and functional capacity and that the overall health status correlates better with exercise tolerance rather than with resting measurements (Ross 2003).

CPET involves measurements of respiratory oxygen uptake (VO_2), carbon dioxide production (VCO_2), and ventilatory parameters during a symptom-limited exercise test. Peak exercise capacity is defined as the maximum ability of the cardiovascular system to deliver oxygen to exercising skeletal muscle and of the exercising muscle to extract oxygen from the blood. Consequently, exercise tolerance is determined by three factors: pulmonary gas exchange; cardiovascular performance, including the peripheral vascular tree; and skeletal muscle metabolism.

Several different methods exist for measuring ventilation and respiratory gas parameters during exercise. Most clinical systems rely on breath-by-breath analysis techniques because they provide the best measures of the metabolic

response to exercise. A non-rebreathing valve is connected to a mouthpiece to prevent mixing of inspired and expired air (Figure 2.6 (Albouaini et al. 2007)). Oxygen and carbon dioxide gas analysers are usually incorporated in a "metabolic cart" designed specifically for functional testing. Respiratory volumes are computed by integrating the air flow signals over the time of inspiration and expiration. Average minute volumes are derived from the breath-by-breath data multiplied by the respiratory rate.

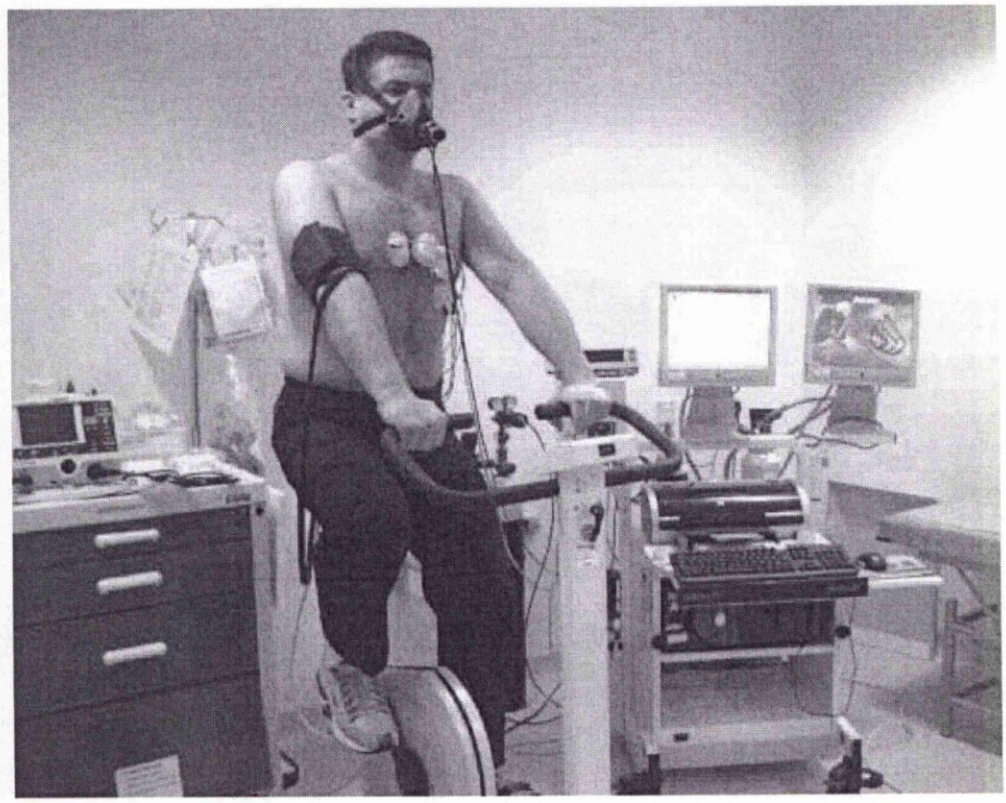


Figure 2.6: CPET machine using the Cycle ergometry. A non-rebreathing valve is connected to a mouthpiece with continuous ECG and blood pressure monitoring. Resuscitation equipments should be on hand (Albouaini et al. 2007).

Many different protocols are used for functional testing (Table 2.3). The purpose of the test and the functional capabilities of the patient determine the choice of protocol. In evaluating patients with CHF, both bicycle and treadmill protocols have been used. We used the bicycle protocol in this study. The rate of workload progression is somewhat arbitrary, although it has been suggested that optimal exercise duration for functional assessment on the bicycle is between 8 and 17 minutes (Buchfuhrer et al. 1983). Bicycle work is quantified in watts. The initial workload for patients with CHF patients is usually 20 to 25 watts and increased by 15 to 25 watts every two minutes until maximal exertion is reached. Alternatively, the workload can be computer controlled for electronically-braked bicycle ergometers, and a ramp protocol (e.g., 10 watts/min) is often used. The modified Naughton protocol is recommended for treadmill exercise testing in patients with heart failure (Naughton et al. 1963). This protocol is designed to increase the workload by approximately 1 MET (3.5 mL O_2/kg/min) for each two minute stage. In our study, the cycle ergometry was used as it requires less muscle training, is safer in elderly patients and easier to conduct in patients with other comorbidities. Although it would have been ideal for the subjects to undergo a familiarisation session this was not feasible due to the time scale from patient presentation to pacing procedure.

Table 2.3: Exercise Equipment: Cycle Ergometry Vs Treadmill

	Cycle	Treadmill
Peak Oxygen content (PVO_2)	lower	higher
Work rate measurement	yes	no
Blood gas collection	easier	more difficult
Noise and artefacts	less	more
Safety	safer	less safe?
Weight bearing in obese	less	more

Degree of leg muscle training	less	more
More appropriate for	patients	active normal subjects

2.18.1 Oxygen uptake and peak Oxygen uptake

Oxygen uptake (VO_2) is determined by cellular O_2 demand up to some level that equates to maximal rate of O_2 transport, which then is determined by that maximal rate of transport. As VO_2 increases with increasing external work, one or more of the determinants of VO_2 approach limitations (e.g., SV, HR, or tissue extraction) and VO_2 versus work rate may begin to plateau. This plateau in VO_2 has traditionally been used as the best evidence of VO_2 max.

The main determinants of a normal PVO_2 are genetic factors, quantity of exercising muscle, age, sex, and body size. It can also be affected by training and patient motivation. PVO_2 should be expressed in absolute values (litres per min) and as a percentage of the predicted value. VO_2 can increase from a resting value of about 3.5 ml/kg/min (about 250 ml/min in an average individual) to PVO_2 values about 15 times the resting value (30–50 ml/kg/min). Athletes may attain values over 20 times their resting values (up to 80 ml/kg/min).

Figure 2.7 is an example of a normal CPET using Bruce protocol on a cycle ergometer. Table 2.2 shows the normal values of parameters derived from CPET. A typical example of CPET in HF patient is shown in Figure 2.8.

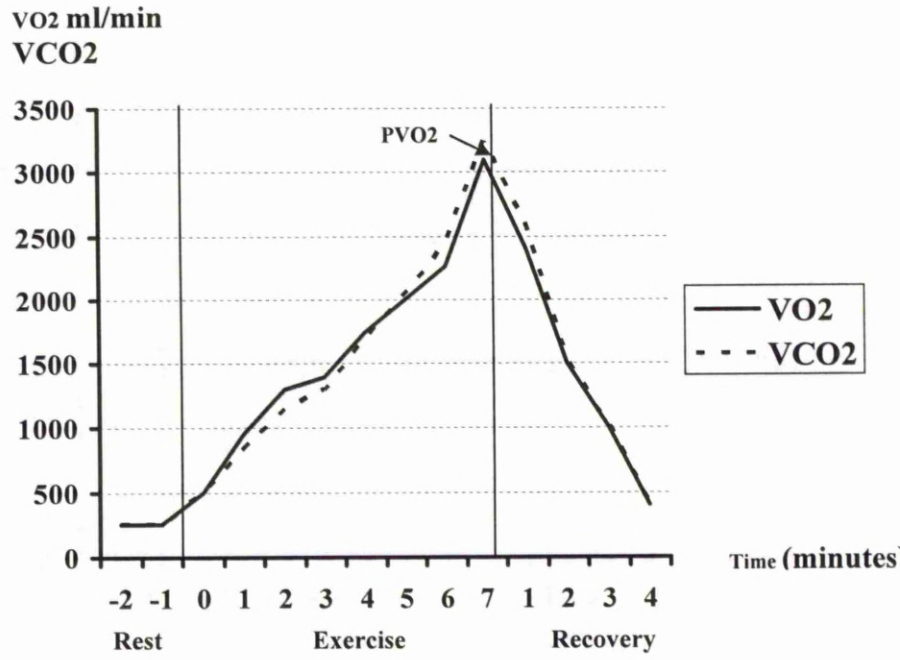


Figure 2.7: CPET in a healthy man using Bruce protocol. The progressive linear increase in VO2 is noted, reaching a steady state after 2 min in each of the first two stages. PVO2 was 3.09 litres /min.

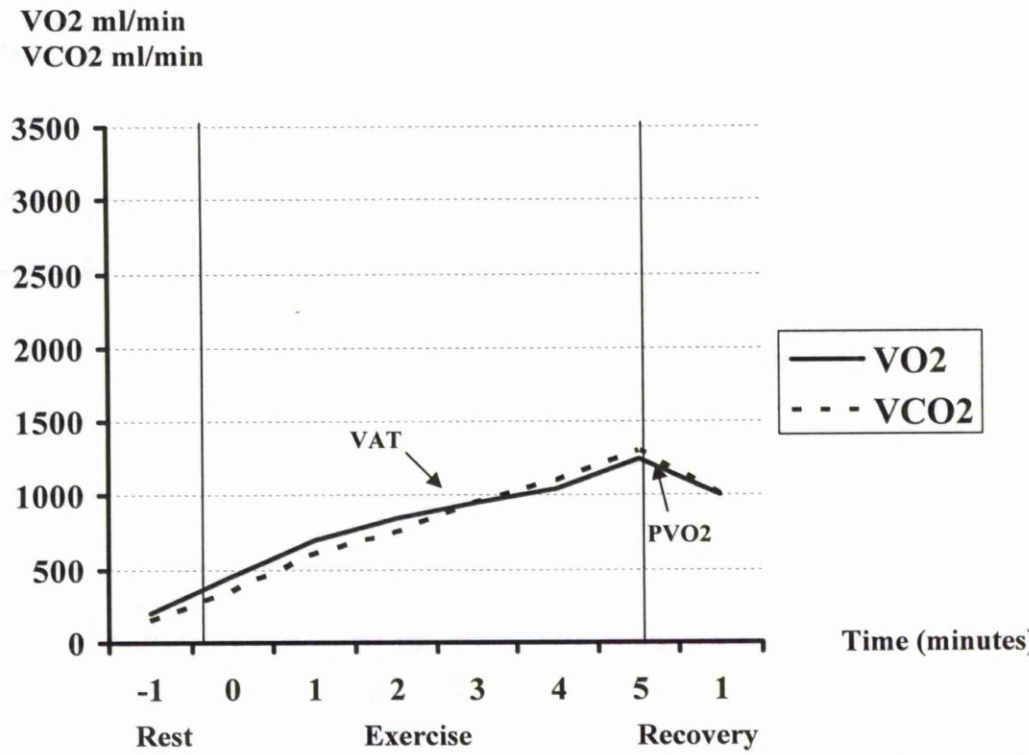


Figure 2.8: CPET in a 46 year old man with cardiomyopathy in NYHA class III. A modified Bruce protocol was used. The patient reached a PVO_2 of 14 ml/kg/min (4 METs), 42% of predicted for age, gender, and weight. VAT occurred at VO_2 of 955 ml/min (slopes intersection point). This blunted cardiopulmonary response is typical in severe cardiomyopathy.

Table 2.2 Normal CPET parameters	
Variables	**Normal Value**
Peak oxygen content (PVO_2)	> 84% predicted
Ventilatory anaerobic threshold (VAT)	> 40% PVO_2 (40-80%)
Maximum heart rate (HRmax)	> 90% age predicted
Heart rate reserve (HRR)	<15 Beats/min
Blood pressure (BP)	< 220/90
O_2 Pulse (VO_2/HR)	>80%
Ventilatory Reserve (VR)	MVV-VEmax >11L or VEmax /MVV x 100 <85%
Respiratory rate (RR)	< 60 breaths/min
Minute ventilation/ carbon dioxide output ratio (VE/VCO_2) at VAT	< 34

2.19 Power calculation and statistical analysis

Sample size calculations were focused on the primary end point assuming an absolute increment of 1.5ml/kg/min in peak VO2 in the RVOT group compared to the RVA group. This was based on the studies by Victor et al and Kinderman et al (HOBIPACE) which demonstrated a mean peak VO2 of 16.2 ml/kg/min in patients after RVA pacing. Allowing for a 5% non compliance or drop out rate the minimum number of patients required to detect a significant ($p<0.05$) difference between RVA and RVOT pacing with a power of 90% was 50.

The primary statistical analyses were as per intention to treat. Secondary analyses were as per protocol basis (per treatment received). Data were expressed as percentages, mean value ± standard deviation (confidence interval), or as median (minimum, maximum). Continuous variables were compared using Student's t-test assuming normal distributions or Wilcoxon rank sum test for variables with non-normal distributions. Dichotomous variables were compared via the χ^2 test and Fisher's exact test. In all tests, P-values of 0.05 or less were considered significant.

Descriptive Statistics methodology was used on SPSS for Windows Version 11.0.0 (Sep. 2001) and StatsDirect Version 2.7.2 (Sep. 2008). Initially, Baseline characteristics were explored to exclude significant differences between the RVA and RVOT arms. After FU, the following tests were performed for further analyses:

I- Wilcoxon Signed Ranks Test to compare baseline and FU variables in the whole study population (e.g. comparing baseline EF in the whole study population with the FU EF) and in each study arm.

II- Mann-Whitney Test to compare variables differences between RVA and RVOT groups (intention to treat analysis), e.g. compare the change (difference between baseline and FU) in EF in the RVA group with the change in the RVOT group. As per protocol analysis was also performed.

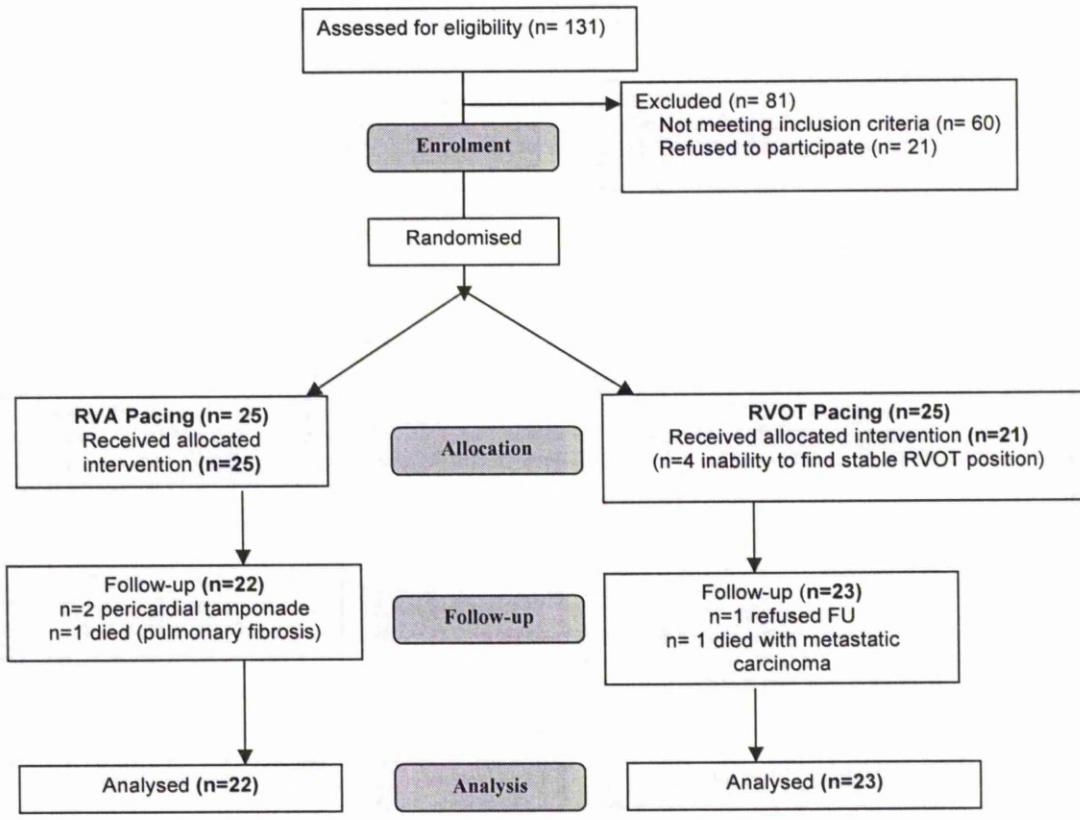
CHAPTER THREE

Results

3.1 Overview

We screened 131 patients. A total of 60 failed to meet study criteria. A further 21 declined participation (CONSORT Flow Diagram, Figure 3.1). The study population therefore consisted of 50 patients with a mean age of 73 ± 8 years. Demographic and medical characteristics were similar in the RVA and RVOT groups (Table 3.1). There were no significant differences between the groups in terms of sex distribution, comorbidities, pacing indications, medical treatment and heart failure classification. Patients were randomised to either RVA (n=25) or RVOT (n=25) pacing. Follow up was performed on 22 patients (88%) in the RVA group (CONSORT Flow Diagram). One patient died due to an unrelated cause and the other two had serious adverse events (pericardial effusion on implantation). In the RVOT group, 23 patients (92%) completed the study follow-up. One patient died with an unrelated cause and one refused follow-up. Four patients (16%) allocated to have RVOT had RVA lead due to an inability to find a stable RVOT lead position with satisfactory parameters. These patients remained in the RVOT group for intention to treat analysis. However, if included in the RVA group, analysis was conducted on per protocol basis. On reviewing the chest X-ray (both postero-anterior and lateral) in the RVOT group, the right ventricular lead was positioned in the free RVOT wall in 10 cases, in the anterior RVOT in 9 cases, and in the RVOT septum in 2 cases.

Figure 3.1: CONSORT flow diagram



3.2 Baseline characteristics of the whole study population

The study population consisted of 50 patients with a mean age of 73 ± 8. Thirty two patients were males (64%) and 18 females (36%). The mean BMI was 27.6 ± 6. Table 3.1 shows the demographic and medical characteristics of the whole study population and that of each study group. This table demonstrates the distribution of patients between both study groups with regard to background medical history as well as medical treatment.

The mean NYHA class was 2.2 ± 0.6 in the whole study population with a mean Minnesota score of 48 ± 19. The mean QRS duration was 110 ± 22 msec. Baseline left ventricular ejection fraction (EF) varied between 40% and 77% (mean of 59 ± 7.8). All subjects had a left ventricular end-diastolic diameter (LVEDD) of < 60 mm (mean of 48 ± 6). The mean Ex Time and peak oxygen consumption (PVO_2) were 371 ± 157 sec and 16.5 ± ml/kg/min consecutively.

Table 3.1: Baseline characteristics of the study population

	Whole Study Mean ± SD	**RVA Group** Mean ± SD	**RVOT Group** Mean ± SD
Age	73 ± 8.5	74 ± 8	72 ± 8
Males	32 (64%)	17 (68%)	15 (60%)
Females	18 (36%)	8 (32%)	10 (40%)
Height	170 ± 8.2	171 ± 7.8	170 ± 8.7
Weight	80 ± 21	79 ± 23	82 ± 19

BMI	27.6 ± 6.3	26.8 ± 7.3	28.4 ± 5.1
Hypertension	28%	30%	26%
Hyperlipidaemia	18%	20%	16%
Diabetes	12%	12%	12%
Smoker/ ex-smoker	19%	20%	18%
Previous MI	6%	10%	2%
Previous HF	4%	6%	2%
PVD	2%	2%	2%
Beta blocker	10%	10%	10%
Calcium antagonist	20%	22%	18%
ACE-I	17%	20%	14%
ARB	8%	10%	6%
Aspirin	20%	20%	20%
Clopidogrel	6%	10%	2%
Statin therapy	21%	24%	18%
Digoxin	7%	6%	8%
NYHA	2.2 ± 0.6	2.2 ± 0.6	2.2 ± 0.6
Minnesota score	48 ± 19	47 ± 21	50 ± 17
QRSd (msec)	111 ± 23	106 ± 20	114 ± 24
LVEDD (mm)	48 ± 5.9	47 ± 5.8	49 ± 6
EF (%)	59 ± 7.8	57 ± 7.4	60 ± 8
Ex Time	371 ± 157	366 ± 180	378 ± 131
PVO_2 (ml/kg/min)	16.5 ± 4.3	16.8 ± 5	16.0 ± 3
Variables are presented as mean ± SD when appropriate			

3.3 Baseline characteristics of each study group

Baseline demographic and medical characteristics were similar in both RVA and RVOT arms (Table 3.1). Patients Sex distribution was well matched between the RVA and RVOT groups (2-sided P value = 0.55 on Pearson Chi-Square analysis). With regard to the previous medical background, history of hypertension, hyperlipidaemia, diabetes, and smoking were similarly distributed between both study groups. Five patients in the RVA group had a previous myocardial infarction with one patient in the RVOT group (2-sided P value = 0.082 on Pearson Chi-Square analysis). Three patients in the RVA group had previous episode of heart failure with one patient in the RVOT group (2-sided P value = 0.30 on Pearson Chi-Square analysis).

Each arm had 14 patients with chronic high grade AV block and 11 patients listed to have ablation of the AV node as part of ablate and pace strategy, as seen in Table 3.2 (2-sided P value = 0.41 on Pearson Chi-Square analysis).

Table 3.2: Indication for pacing in each study group

Indication	RVA group (n=)	RVOT group (n=)
Persistent atrial fibrillation	4	7
Paroxysmal atrial fibrillation	6	3
Atrial flutter	1	0
Atrial tachycardia	0	1
AV block	14	14
Total	25	25

The majority of patients in both arms were patients in NYHA heart failure class II with no significant inter-group differences in NYHA baseline class (2-sided P

value = 0.82 on Pearson Chi-Square analysis). All patients but one had either no mitral regurgitation (MR) or grade-I MR with no significant inter-group variation, as seen in Table 3.3 (2-sided P value = 0.89 on Pearson Chi-Square analysis).

Table 3.3: NYHA functional class at baseline in each study group

NYHA Class	RVA group (n=)	RVOT Group (n=)
I	2	3
II	16	14
III	7	8
Total	25	25

3.4 Analysis of the cardiopulmonary exercise test data

The Cardiopulmonary Pulmonary Exercise Test was performed on 21 patients at the baseline (12 RVA and 9 RVOT) and on 34 patients at the follow up (17 in each study group). This was due to the fact that high grade AV block is a relative contraindication for CPET and that a significant proportion of the study population was elderly with functional limitation due to a non cardiac cause limiting their ability to ride on the cycle ergometer.

This study was not able to detect any significant improvement in exercise time or PVO_2 (primary endpoint) in either arm or any inter-arm differences (Table 3.4 and 3.5).

Table 3.4: Mean PVO_2 at baseline and at follow up

	Baseline	6 month FU	P value
RVA	18.6 ± 5.2	17 ± 5.1	NS
RVOT	15.8 ± 3.6	14.9 ± 4.1	NS

Table 3.5: Mean exercise time at baseline and at follow up

	Baseline	6 month FU	P value
RVA	382 ± 184	333 ± 207	NS
RVOT	369 ± 137	340 ± 161	NS

On comparing the changes (between baseline and FU) in PVO_2 between arms, the average change was -1.6 ± 3.9 in the RVA arm and -0.9 ± 2.7 in the RVOT arm, P = 0.95. As per protocol analysis revealed similar findings; the average

change was -1.2 ± 3.8 in the RVA arm and – 1.3 ± 2.7 in the RVOT arm, P = 0.76.

3.5 Analysis of NYHA class data

NYHA heart failure class analysis of the whole study population showed significant improvement; NYHA class dropped from 2.22 ± 0.6 at baseline to 1.6 ± 0.7 at the 6 month follow-up, P value < 0.0001 on Wilcoxon Signed Ranks Test. Table 3.6 shows the change in NYHA class in each study group. Figure 3.1 is the Box and Whisker diagram representing the values of NYHA class in each study group.

Table 3.6: Mean NYHA functional class at baseline and at follow up

	Baseline	6 month FU	P value
RVA	2.23 ± 0.61	1.86 ± 0.83	< 0.001
RVOT	2.22 ± 0.67	1.43 ± 0.66	< 0.001

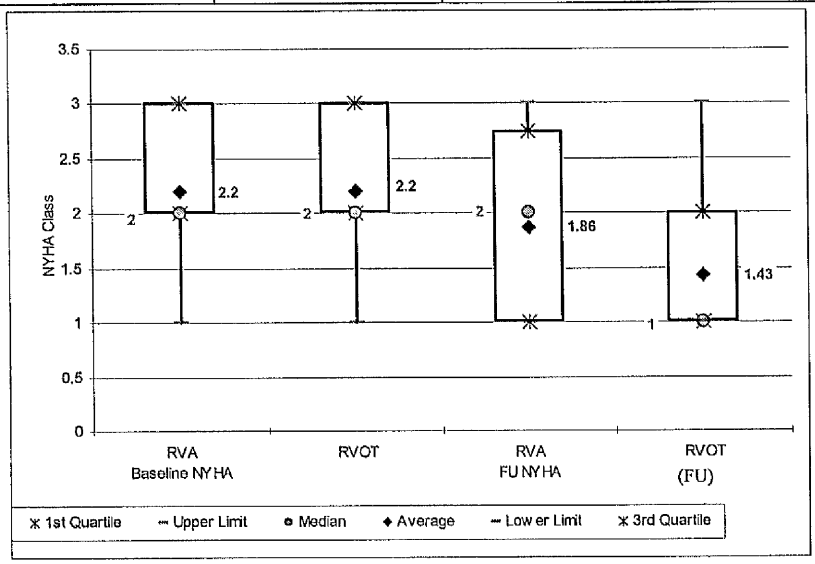


Figure 3.1: Box and Whisker diagram showing baseline and FU values of NYHA class in both study groups.

On comparing the degree of improvement between the study groups (the degree of NYHA class drop in each arm), the intention to treat analysis showed no superiority in the RVOT arm. NYHA class dropped by a mean of 0.36 ± 0.78 in the RVA group and by 0.78 ± 0.67 in the RVOT group, P=0.08. When as per protocol analysis was performed, RVOT patients had significantly greater improvement; NYHA class dropped by a mean of 0.38 ± 0.80 in the RVA group and by 0.84 ± 0.60 in the RVOT group, P=0.04.

3.6 Analysis of Minnesota questionnaire score

MLWHF scores improved dramatically on FU in the whole study population. The mean score decreased from 48 ±19 to 22 ± 24, P < 0.0001 on Wilcoxon Signed Ranks Test. Table 3.7 shows the change in MLWHF scores in each study group.

We compared the degree of MLWHF score improvement between the study groups (the drop in the MLWHF score in each study arm). Table 3.7 shows the individual MLWHF scores for each individual study patient, while Figure 3.2 represents the Box and Whisker diagram of the MLWHF scores in both study groups. The intention to treat analysis showed greater improvement in the RVOT arm; MLWHF score dropped by 21 ± 22 in the RVA group and by 32 ± 19 in the RVOT group, P = 0.041 (Mann-Witney test). When as per protocol analysis was performed, RVOT patients had also significantly greater improvement; MLWHF score dropped by 22 ± 21 in the RVA arm and by 32 ± 20 in the RVOT arm, P=0.45 on Mann-Witney Test.

Table 3.7: MLWHF score in both study groups					
	RVA Group			RVOT Group	
	Baseline	FU		Baseline	FU
	14	3		3	0
	17	3		13	NA
	22	0		16	0
	28	9		27	3
	28	14		35	3
	28	57		41	6
	28	NA		43	34
	30	30		45	2
	31	4		47	9
	34	NA		51	7
	37	11		51	10
	43	0		52	3
	44	17		52	2
	45	37		55	8
	46	NA		57	4
	50	7		59	16
	52	21		59	0
	52	56		60	68
	60	3		61	22
	65	62		61	27
	68	31		62	55
	78	70		63	26
	79	5		70	NA
	82	76		71	74
	84	61		83	33
Mean	45.80	26.23		49.48	17.91
SD/ CI	20.85/ 8.17	25.79/10.10		18.79/7.36	21.86/8.57

Table 3.8: Mean MLWHF scores at baseline and at follow up			
	Baseline	**6 month FU**	**P value**
RVA (n=22)	47.1 ± 21.7	26.2 ± 25.7	< 0.001
RVOT (n=23)	50.1 ± 17.4	17.9 ± 21.8	< 0.001

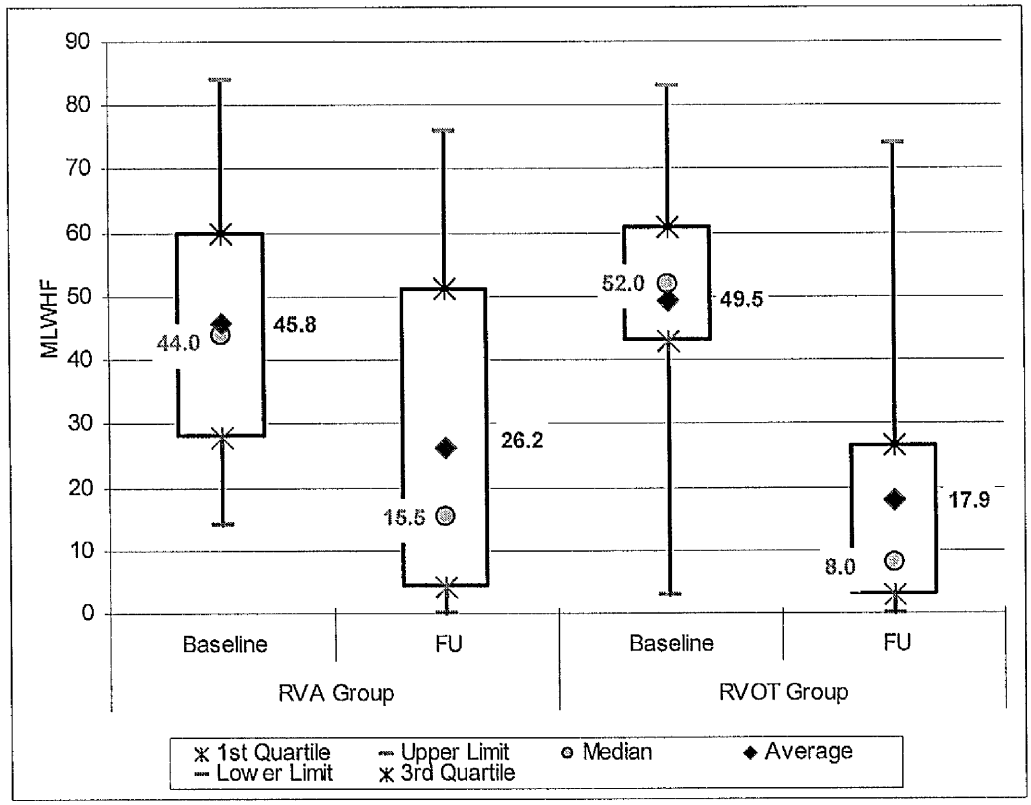


Figure 3.2: Box and Whisker diagram showing baseline and FU MLWHF scores in both study groups.

3.7 Analysis of short form--36 health survey

This health survey covers the following quality of life aspects:

PF, Physical Function

RL, Role Limitation

BP, Bodily Pain

SF, Social Function

GMH, General Mental Health

RLEP, Role Limitation due to Emotional Problem

VEF, Vitality, Energy, or Fatigue

GHP, General Health Perception

HCLY, Health Compared To Last Year

SF-36 scores have improved dramatically on FU in the whole study population (Wilcoxon Signed Ranks Test). The only exception was in 2 areas: the Bodily Pain and the General Mental Health. Table 3.9 shows the change in SF-36 scores in each study group.

Table 3.9: Short form-36 Health Survey mean scores on baseline and FU

	Baseline score (M ± SD)	FU score (M ± SD)	2-sided P Value Wilcoxon Test
Physical Function (PF)	36 ± 23	60 ± 30	**
RVA	42 ± 26	53 ± 27	*
RVOT	31 ± 21	68 ± 32	**
Role limitation (RL)	19 ± 34	60 ± 42	**
RVA	23 ± 38	53 ± 44	**
RVOT	14 ± 31	66 ± 40	**
Bodily Pain (BP)	68 ± 28	69 ± 27	0.9
RVA	69 ± 27	68 ± 25	0.9
RVOT	67 ± 30	69 ± 30	0.9
Social function (SF)	50 ± 29	69 ± 29	**
RVA	46 ± 31	64 ± 32	**
RVOT	51 ± 25	73 ± 25	**
General Mental Health (GMH)	59 ± 21	66 ± 21	0.06
RVA	60 ± 21	60 ± 23	1
RVOT	57 ± 21	72 ± 18	*
Role Limitation due to Emotional Problem (RLEP)	31 ± 44	56 ± 43	*
RVA	48 ± 49	53 ± 43	0.06
RVOT	17 ± 36	60 ± 43	**
Vitality Energy Fatigue (VEF)	36 ± 20	54 ± 22	**
RVA	40 ± 21	47 ± 21	*
RVOT	34 ± 19	60 ± 21	**
General Health Perception (GHP)	48 ± 20	56 ± 24	0.045
RVA	50 ± 23	54 ± 23	0.06
RVOT	44 ± 18	57 ± 24	*
Health Compared to Last Year (HCTLY)	25 ± 20	78 ± 29	**
RVA	25 ± 20	70 ± 32	**
RVOT	24 ± 22	85 ± 25	**

(**) = P < 0.005

(*) = P < 0.05

On comparing the degree of improvement between the study groups (the increases in the SF-36 scores), the intention to treat analysis using Mann-Whitney Test revealed a significant improvement in favour of RVOT pacing in the following areas: (1)-Physical Function where the average increase in PF score was 11.2 ± 26 in the RVA arm and 36.6 ± 28 in the RVOT arm, P = 0.005. (2)- Role Limitation due to Emotional Problem where the average increase in RLEP score was 4.5 ± 54 in the RVA arm and 43.3 ± 46 in the RVOT arm, P = 0.016. (3)- Vitality Energy fatigue where the average increase in VEF score was 7.2 ± 24 in the RVA arm and 26.3 ± 27 in the RVOT arm, P = 0.024.

The same findings were shown when as per protocol analysis was performed. The P values of the differences in the following areas PF, RLEP, and VEF were 0.001, 0.031, and 0.045 consecutively.

Tables 3.10, 3.11 & 3.12 show the PF, RLEP, and VEF scores for each individual study patient, while Figures 3.3, 3.4, and 3.5 represent the Box and Whisker diagram of these scores in both study groups.

Table 3.10: Physical Function scores (SF-36)					
	RVA Group			RVOT Group	
	Baseline	FU		Baseline	FU
	0	17		0	33
	6	56		0	6
	11	83		6	6
	11	NA		6	11
	17	33		6	89
	17	28		11	100
	22	22		11	61
	22	NA		17	100
	22	78		22	33
	28	39		27	72
	33	33		33	72
	39	56		33	94
	39	28		33	44
	39	78		39	83
	44	17		39	100
	44	33		39	NA
	44	NA		44	100
	50	33		44	94
	55	39		50	100
	61	94		50	NA
	66	72		50	33
	72	67		56	72
	72	100		61	89
	94	94		67	83
	94	72		72	94
Mean	40.08	53.27		32.64	68.22
SD/CI	25.84/10.13	27.12/10.63		21.35/8.37	32.86/12.88

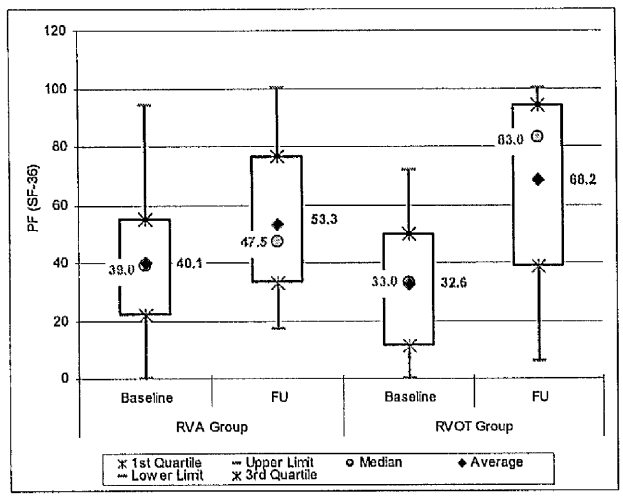


Figure 3.3: Box and Whisker diagram showing baseline and PF scores in both study groups.

Table 3.11: Role Limitation due to Emotional Problem Scores (SF-36)					
	RVA Group			RVOT Group	
	Baseline	FU		Baseline	FU
	0	67		0	0
	0	100		0	30
	0	NA		0	100
	0	0		0	0
	0	0		0	100
	0	NA		0	100
	0	100		0	100
	0	0		0	33
	0	NA		0	100
	0	33		0	0
	0	0		0	NA
	0	67		0	33
	0	33		0	0
	33	100		0	0
	33	0		0	100
	100	33		0	0
	100	0		0	100
	100	100		0	100
	100	100		0	67
	100	0		33	67
	100	67		67	100
	100	100		100	NA
	100	100		100	67
	100	67		100	100
	100	100		100	100
Mean	42.64	53.05		20.00	60.74
SD/CI	48.61/19.05	43.2716.96		38.50/15.09	43.53/17.06

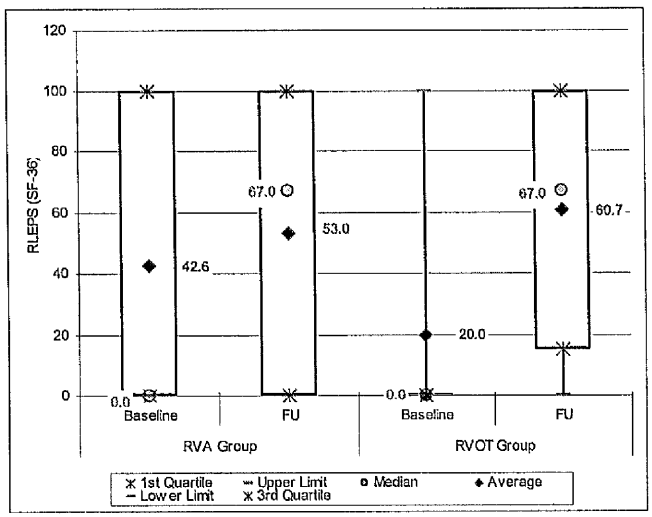


Figure 3.4: Box and Whisker diagram showing baseline and FU RLEPS scores in both study groups.

Table 3.12: Vitality Energy Fatigue Scores (SF-36)					
	RVA Group			RVOT Group	
	Baseline	FU		Baseline	FU
	0	15		0	25
	5	65		5	60
	10	45		5	65
	15	NA		10	75
	25	50		15	70
	25	20		15	NA
	25	15		20	45
	25	60		20	100
	30	NA		25	65
	30	65		30	30
	30	NA		30	15
	30	50		30	65
	35	40		30	75
	35	35		30	70
	40	30		40	70
	45	75		50	50
	55	10		50	40
	55	35		50	90
	60	80		55	40
	60	40		55	65
	60	55		55	80
	60	50		60	85
	65	50		60	NA
	65	70		60	40
	75	90		65	75
Mean	38.40	47.50		34.60	60.65
SD/CI	20.60/8.07	21.80/8.54		20.20/7.91	21.60/8.46

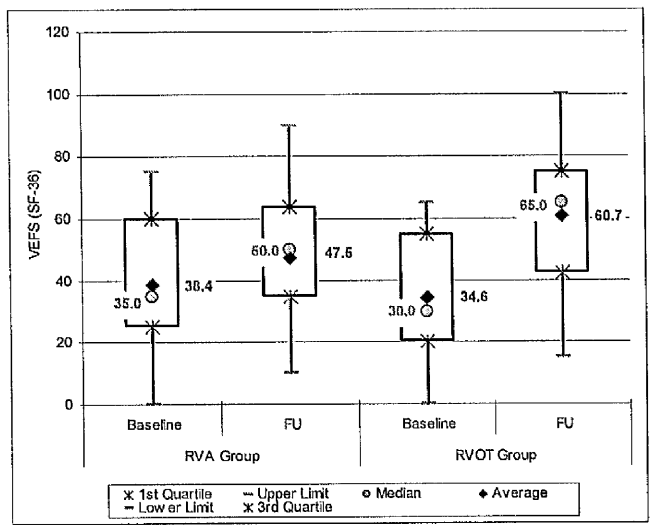


Figure 3.5: Box and Whisker diagram showing baseline and FU VEF scores in both study groups.

3.8 Analysis of electrocardiogram findings

On analysing the whole study population, QRS duration, as expected, has dramatically increased from a mean of 110 ± 22 msec on baseline to a mean of 170 ± 20 msec on follow-up (P value < 0.0001 on Wilcoxon Signed Ranks Test).

We compared the QRSd prolongation between both arms (i.e. whether patients randomised to RVA pacing tend to have more QRSd prolongation). QRSd prolongation was not significantly more pronounced in the RVA group (P=0.91 on intention to treat analysis and P = 0.25 on as per protocol analysis, Mann-Whitney Test).

When the post-implant ECGs in the RVOT group were analysed, negative or isoelectric QRS vector in lead I was seen in 43% of the RVOT implants.
We also reviewed the CXR in the RVOT group (both PA and lateral), acquired post pacemaker implantation. The right ventricular lead was positioned in the free RVOT wall in 10 cases, in the anterior RVOT in 9 cases, and in the RVOT septum only in 2 cases. The QRSd in the 2 septal RVOT positions were 179msec and 188mec.

3.9 Analysis of echocardiography findings

Echocardiogram data analysis revealed that the CARE-HF (Cardiac Resynchronisation in Heart Failure trial) echo dyssynchrony criteria were met in 4 patients (2 in each arm) at the baseline assessment and in 11 patients at the FU

(6 RVA and 5 RVOT). Two out of four patients with dyssynchrony on baseline (one in each arm), were found to have dyssynchrony on FU as well.

On analysing the whole study population (Wilcoxon Signed Ranks Test), EF dropped by 6.1%, from 59.1±7.8 to 53±8.8, P<0.0001, mitral regurgitation (MR) grade dropped by 0.27 (P=0.007), APE was longer by 41 msec (P<0.0001). The drop in LVOT-VTI was insignificant at 1.5 cm (from 21 ± 4 to 20 ± 6, P=0.058). We were unable to detect any significant change in LVEDD.

We analysed whether the changes (differences between the baseline and the follow up values) in the echocardiography parameters, were more pronounced in one arm more than the other. Both intention to treat and as per protocol analyses showed no difference between both arms (e.g. EF dropped by 7.2 ±6.2 in the RVA arm and by 5.17 ± 4.5 in the RVOT arm, P = 0.58)

Tables 3.13, 3.14 show the APED and IVD for each individual study patient, while Figures 3.6 and 3.7represent the Box and Whisker diagram of these values in both study groups.

Table 3.13: Aortic Pre-Ejection Delay in both study groups					
	RVA Group			RVOT Group	
	Baseline	FU		Baseline	FU
	36	83		20	120
	40	100		53	160
	53	104		55	148
	55	155		55	55
	55	120		59	105
	55	205		60	141
	61	78		60	60
	62	144		61	110
	67	NA		63	135
	71	130		63	131
	75	114		64	122
	80	163		65	65
	80	126		74	122
	83	185		83	104
	90	140		85	85
	95	115		87	144
	100	168		90	130
	100	122		98	NA
	106	125		111	155
	118	NA		115	150
	125	144		127	126
	130	NA		130	NA
	147	104		143	136
	147	147		155	104
	NA	139		173	173
Mean	84.63	132.32		85.96	120.91
SD	31.85	31.16		37.09	31.60

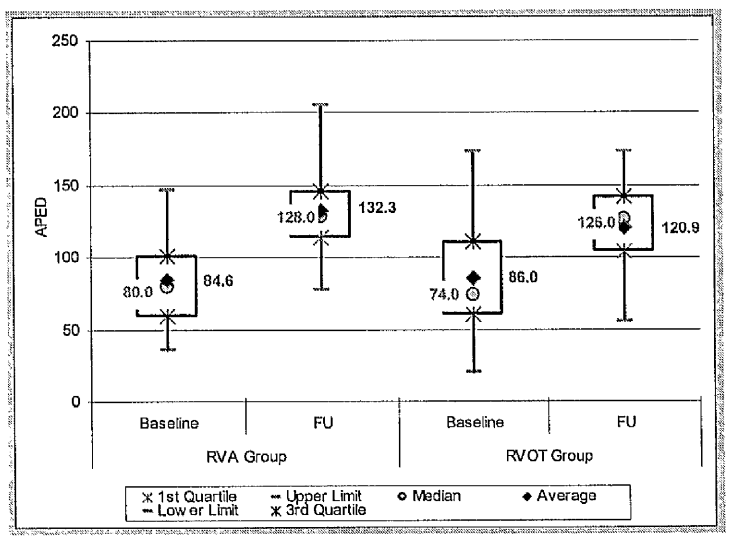


Figure 3.6: Box and Whisker diagram showing baseline and FU values of APED in both study groups.

Table 3.14: Interventricular Delay in both study groups					
	RVA Group			RVOT Group	
	Baseline	FU		Baseline	FU
	-22	8		-45	30
	-10	37		-39	41
	-8	-5		-17	NA
	-4	40		-14	-14
	-3	39		-8	-8
	0	80		-7	-7
	4	65		3	-4
	8	44		7	20
	10	65		7	5
	13	60		10	11
	20	63		12	50
	20	45		14	100
	23	15		20	20
	25	32		21	14
	27	NA		25	55
	29	NA		29	NA
	33	80		30	81
	35	38		40	48
	40	NA		47	-14
	44	44		50	15
	50	50		53	50
	50	22		54	48
	51	-11		59	79
	62	8		60	46
	NA	35		67	20
Mean	20.71	38.82		19.12	29.83
SD	22.40	25.10		30.52	31.59

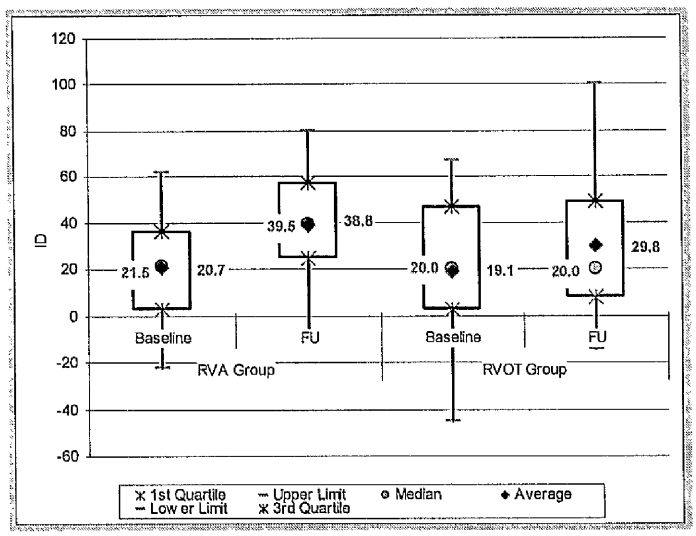


Figure 3.7: Box and Whisker diagram showing baseline and FU values of IVD in both study groups.

3.10 Analysis of other variables

Three patients had hospital admissions with symptoms of heart failure; all were in the RVA arm (this was not statistically significant, P=0.13)

In summary, at 6 months, RVOT pacing was not superior to RVA in terms of PVO_2. In contrast, RVOT pacing offered a more significant improvement in health-related quality of life scores, a feature that was strongly related to the superiority in NYHA class scores. Both RVA and RVOT pacing comparably worsened the echocardiogram parameters.

CHAPTER FOUR

Discussion

The potential detrimental effects of RVA pacing have been well described. As a result, several large trials such as DAVID study have recommended minimisation of RVA pacing by using atrial based preferential pacing modes to maintain AVN conduction. However, in patients who require ventricular pacing, alternative sites have been postulated to be superior. The results of SSP trials have generally been disappointing with no consistent significant benefit being demonstrated at any one site. The results of our study do however add to an emerging evidence base supporting the utilisation of RVOT compared to RVA pacing.

In our study, the majority of those screened were excluded as they were elderly and frail with non-cardiac exercise limitation. This made recruitment difficult. Previous studies on SSP were conducted on small number of patients. In the study by Victor et al, investigators compared the haemodynamic effects of RVOT and RVA pacing in 16 patients with chronic atrial tachyarrhythmia and complete AV block over a 7 month period in a randomised crossover fashion (Victor et al. 1999). No significant differences were found in NYHA class, EF, exercise time, and PVO_2. The small number of patients studied might explain the negative results. A larger randomised crossover study, (the ROVA study) was published in 2003 (Stambler et al. 2003) in which investigators compared RVA, RVOT, and dual site pacing in 103 patients with NYHA class II-III heart failure (EF < 40%) and chronic AF with a conventional bradycardic indication. The authors showed no difference in QOL between RVA, RVOT, or dual site pacing at 3 months. However, after 9 months, LVEF was higher (P=0.04) in those assigned to RVA rather than RVOT pacing. This significant difference noted at

the 9 month follow up may be explained by the fact that LV remodelling may be a long process. As this study included only patients with LVEF < 40%, it is quite possible that pacing will result in more deleterious haemodynamic effects in comparison to patients with normal or near normal systolic LV function.

Other small studies have however, provided positive results such as the study by Mera et al. They studied 12 patients undergoing His-bundle ablation for uncontrolled chronic AF and showed that septal pacing resulted in a narrower QRS, greater fractional shortening, and a greater resting LVEF than RVA (Mera et al. 1999). Another positive study was by Tse et al (Tse et al. 2002) where the investigators studied the effect of pacing site on myocardial perfusion and LV function by randomising 24 patients with complete AV block to receive RVA or RVOT leads. There was no difference between the two groups at 6 months, but at 18 months, RVOT patients had a better EF, less perfusion defects and regional wall motion abnormalities. Unfortunately, both studies were conducted on relatively small numbers and did not assess patients QOL or functional capacity.

In our study, we were not able to detect any significant changes in PVO_2 in either group or any inter-group differences. This may be attributed to the fact that CPET was performed on only 21 patients at baseline (12 RVA and 9 RVOT) and 34 at the follow-up. Another compounding factor was the heterogeneity of the RVOT lead position; the right ventricular lead was positioned in the free RVOT wall in 10 cases, in the anterior RVOT in 9 cases, and in the RVOT septum in 2 cases. This may reflect the large number of implanting physicians within our centre and the variation in practice and technique.

Four patients randomised to RVOT actually received a RVA lead due to problems with stability and pacing parameters. Therefore, per protocol analysis was also performed as well as intention to treat. The results from per protocol analysis were only different in terms of NYHA classification which demonstrated a significant difference in favour of RVOT pacing. No statistical difference in the primary end point could be established using either form of analysis. Quality of life indices analyses revealed significant superiority of RVOT lead position on both intention to treat and per protocol analyses. Electrocardiogram analysis did not show any significant differences between the groups. This could be attributed to the fact that the RVOT lead was only fluoroscopically positioned. Finally, on echocardiography, there were no differences between the groups; again this may be explained by the relatively short follow-up and the fact that LV remodelling is a prolonged process.

All-cause mortality has only been evaluated retrospectively in one study by Vanerio et al in 2008 (Vanerio et al. 2008). They studied 150 consecutive patients who underwent pacemaker implantation for advanced AV block and symptomatic atrial fibrillation with slow ventricular response. During the mean follow-up of 3.4 years, 32% died in the RVOT group compared to 51% in the RVA group, $p = 0.02$. They concluded that RVOT pacing appears to improve medium-long term survival and recommended conducting prospective randomised trials to confirm these findings. This is clearly an observational study that was retrospectively conducted with all of the inherited potential confounders in such studies. The main confounder, in my opinion, is that the implanting physician is probably biased towards implanting RVOT leads in healthier and

younger subjects. Although our study is a prospective one but it was not powered or designed to study a mortality difference especially with the relatively short follow-up of 6 months.

4.1 Statistical analysis

4.1.1 Statistical tests

In our study, nonparametric tests were used primarily to analyse the data as most variables were not normally distributed. Nonparametric tests are sometimes called distribution free statistics because they do not require that the data to fit a normal distribution. More generally, nonparametric tests require less restrictive assumptions about the data. Another important reason for using these tests is that they allow for the analysis of categorical as well as rank data (such as the NYHA functional class). However, parametric tests are often preferred because they are more robust and they have greater power efficiency, in other words, they have greater power relative to the sample size. Parametric statistical procedures assume that the variables are normally distributed. A significant violation of the assumption of normality can seriously increase the chances of committing either a Type I or II error (depending on the nature of the analysis and the non-normality). Data transformation is utilised for improving normality. One way of data transformation is the logarithmic method. We applied this method to our non-normally data variables using SPSS and reanalysed the data using a parametric test. Both parametric and nonparametric tests, in our study, showed similar results. Independent samples T-test showed no difference between RVA and RVOT groups with regard to PVO2, LVEDD, LVEF, and QRS duration (P =

0.70, 0.81, 0.21, and 0.93 consecutively). On the other hand, RVOT was superior to RVA pacing in term of MLWHF scores. The drop in the score was more in RVOT group (mean 11, 95% CI: -1 – 23, P = 0.04). RVOT was also superior in the same areas of SF-36. This includes: physical function (mean 25, 95% CI: 8 – 41, P = 0.003), role limitation due to emotional problem (mean 38, 95% CI: 8 – 69, P= 0.014), and vitality/energy/fatigue (mean 19, 95% CI: 3 – 34, P = 0.019).

4.1.2 Bonferroni correction

In our study we performed 40 clinically significant comparisons between study groups. Therefore, the expected number of spurious significant results is 40 times 0.05 = 2. It is mandatory to be aware of attaching too much importance to a lone or few significant results among a mass of non-significant ones. It may be the one in twenty which we should get by chance alone. This is particularly important when we find that a clinical trial or epidemiological study gives no significant difference overall, but does so in a particular subset of subjects, such as in a certain age group. We can allow for this effect by the Bonferroni method. In general, as we are testing at 5% significance level, then the corrected significant level will be 0.05/number of comparisons. Therefore, in our study the corrected significant level will be 0.05/40 = 0.00125.

4.2 Study population age group and comorbidity

There are many challenges inherent in conducting clinical trials in elderly patients. One of the most frequently reported problems involves travelling to the clinic or research site. Factors such as transportation availability, complexity of directions, and the time and cost that are required in travelling, are all labelled as

possible deterrents to participation. Another problem relates to the nature of the inclusion/exclusion criteria. Also, this population is also much more likely to have, or develop during the course of the study, comorbid medical conditions that will result in their exclusion or drop out. After the recruitment phase, the next task of the investigator(s) involves the retention of the selected patients to ensure adequate monitoring and recording of the variables of interest (Cassidy, Baird, & Sheikh 2001; Macias, Ramsay, & Rowan 2007).

In this study the follow up was not performed on 5 patients (10%). Two patients, one in each study group, died with an unrelated cause. One patient in the RVOT group refused follow up, while 2 patients in the RVA group had serious adverse events (pericardial tamponade) as a result of the pacemaker implantation procedure. This is a much higher than average rate of pericardial tamponade in the RVA (2/25) group. Liverpool Heart and Chest Hospital implants an average of 1000 new pacing systems per year with an average rate of 1/500 cases of pericardial tamponade. There are 10 consultants and 6 registrars implanting at any one period in time. The high rate of this complication in the RVA group can only be explained by pure chance as it was the same implanting physicians who also implanted in the study patients. RVOT septal pacing has the theoretical advantage of avoiding pericardial effusion secondary to myocardial perforation as the pacing lead is fixed to the interventricular septum. As the rate of this complication is very low, this theoretical advantage is not yet proven in prospective randomised trials.

4.3 Poor definition of right ventricular outflow tract

Attempts to define the RVOT have been the subject of extensive debate. No universal definition of site has been agreed. The term has been used to describe a variety of pacing sites including the true outflow tract, the mid septum, and the anterior region above the apex (Mond et al. 2007). This confusion persists despite attempts to standardise the nomenclature of nonapical pacing sites (Lieberman et al. 2004). Consequently, the resultant acute and chronic studies of RVOT pacing have produced conflicting results making interpretation of the published literature difficult. Furthermore, even when the true RVOT is considered, the anatomy is complex and many studies do not distinguish between different sites within this structure (McGavigan et al. 2006), which may be important, as activation patterns and wavefront propagation will depend on the pacing site within this large area of the right ventricle.

In our study, the RVOT was only defined fluoroscopically, not electrocardiographically. When the post-implant ECGs in the RVOT group were analysed, negative or isoelectric QRS vector in lead I was seen in 43% of the RVOT implants. This ECG finding has a 90% positive predictive value for RVOT septal placement (McGavigan et al. 2006). Surprisingly, this feature has not shown any correlation with a shorter QRSd in our study. We also reviewed the CXR in the RVOT group (both PA and lateral), acquired post pacemaker implantation. The right ventricular lead was positioned in the free RVOT wall in 10 cases, in the anterior RVOT in 9 cases, and in the RVOT septum only in 2 cases. This heterogeneity in lead position might account for heterogeneity in patients' clinical response.

4.4 Cardiopulmonary exercise test data

Assuming that RVOT pacing can preserve the LV haemodynamics and therefore produce better cardiac output, this should be reflected in a better functional performance in patients receiving RVOT rather than RVA lead. The overall functional performance can be objectively assessed by measuring the peak oxygen consumption (PVO_2) on CPET. Only one of the previous studies comparing RVOT with RVA pacing has included PVO_2 as a study outcome (Victor et al. 1999). In this study 16 patients with chronic atrial tachyarrhythmia and complete AV block were included. LVEF was > 40% in 10 and < 40% in 6. Patients were implanted with a standard DDDR pacemaker connected to two ventricular leads. A screw-in lead was placed at the RVOT and connected to the atrial port. A second lead was positioned at the RVA and connected to the ventricular port. Right ventricular outflow tract and RVA pacing was achieved by programming either the AAIR or the VVIR mode respectively. Four months later patients were randomised so as to undergo either RVOT or RVA pacing for three months according to a blind crossover protocol. Apart from the pacing mode, programming remained unchanged throughout the study. At the end of each period, NYHA class, LVEF, exercise time and PVO_2 were assessed. No significant difference was observed between the two modes for all the parameters analysed. These results were observed in all patients globally, in patients with LVEF > 40% as in those with LVEF < 40%. It is possible in this study that the presence of two ventricular leads has affected the right ventricular haemodynamics by inducing tricuspid regurgitation especially in those with LVEF < 40%. It is also important to be aware that this study was not powered to differentiate between patients with LVEF < 40% and those with LVEF > 40%.

In our study, CPET was performed on 21 patients at the baseline (12 RVA and 9 RVOT) and on 34 patients at the follow up (17 in each study group). We were not able to detect any significant improvement in exercise time or PVO_2 (primary endpoint) in either arm or any differences between the study groups. The relatively small number of patients completing cardiopulmonary exercise test at baseline was very disappointing to the investigators. The initial inclusion criteria included only patients with AF who were listed for ablation of the AV node and pacemaker implantation. Due to initial slow recruitment, the inclusion criteria had to be expanded to include other patients who were in need of permanent RV pacing, such as patients with chronic AV block. Unfortunately, PVO_2 was not measured at baseline in such cases because CPET is a relative contraindication in this group and that a significant proportion of the study population was elderly with functional limitation due to a non cardiac cause limiting their ability to ride on the cycle ergometer. This undoubtedly contributed to the fact that no significant difference in the primary end point was demonstrated.

The predictive value of PVO_2 is accurate only when exercise capacity is limited by heart failure. Factors that can prematurely terminate the test should be excluded, including significant peripheral muscular deconditioning, peripheral arterial disease, arthritis, angina pectoris, or low patient motivation. All tests should be performed under standard conditions. It is possible that our study missed a real difference between the study groups in terms of PVO_2 because of the relatively small study sample or the relatively short follow-up that was insufficient to permit LV remodelling.

4.5 Quality of life data

Biventricular pacing is currently indicated in patients with heart failure. Large randomised controlled trials have demonstrated significant benefits in terms of functional capacity, QOL, hospitalisation and more recently mortality (Cleland et al.) With respect to patients undergoing pacemaker implantation for a bradycardic indication, only the ROVA study (Right ventricular Outflow Versus Apical pacing) trial (Stambler et al. 2003) has evaluated the potential impact of different pacing sites on QOL. The primary purpose of this cross-over trial was to determine whether pacemaker recipients with CHF, LV systolic dysfunction, and chronic atrial fibrillation have better quality of life (SF-36 questionnaire) during chronic pacing from the RVOT than the RVA. At 6 months, the RVOT group had higher (P = 0.01) role-emotional QOL subscale scores than the RVA group. At 9 months, there were no significant differences in QOL scores between RVOT and RVA groups. Comparing RVOT to RVA pacing within the same patient, mental health subscale scores were better (P=0.03) during RVOT pacing. The ROVA investigators concluded that in patients with CHF, LV dysfunction, and chronic AF, RVOT and dual-site RV pacing do not consistently improve QOL compared with RVA pacing.

The patients in our study were fundamentally different to those in the ROVA study in that they had preserved left ventricular function at baseline evaluation. However, all patients had either advanced AV block or uncontrolled atrial arrhythmia requiring AV node ablation. This explains the significant improvement in NYHA heart failure class and quality of life scores after implanting a permanent pacemaker regardless of the RV lead position. However,

the main purpose was to examine whether the magnitude of change in QOL was different between those patients in the RVA and RVOT groups. Minnesota LWHF scores improved significantly by 32 ± 19 in the RVOT group and by 21 ± 22 in the RVA group, P=0.041. Additionally, SF-36 health scores improved significantly more in the RVOT pacing group as compared with the RVA group. Interestingly, the between group analysis showed an insignificant difference in the change in NYHA class on intention to treat, P = 0.08. In contrast, per protocol analysis showed significant improvement in favour of RVOT pacing, P = 0.04.

Alternative studies have evaluated the effects of para-Hisian pacing compared to RVA pacing. One positive trial with relation to the QOL was reported in favour of para-Hisian pacing (Occhetta et al. 2006). In this study, permanent para-Hisian pacing in patients with chronic atrial fibrillation and narrow QRS who underwent atrioventricular (AV) node ablation was compared with RVA pacing in 16 patients. Clinical and echocardiographic data were collected at baseline and after two randomised six-month periods (with para-Hisian and conventional pacing). Para-Hisian pacing allowed an improvement in NYHA functional class (1.75 ± 0.4 vs. 2.33± 0.6 at baseline and 2.5 ± 0.4 during apical pacing, $p < 0.05$ for both), in quality-of-life score (16.2 ± 8.7 vs. 32.5 ± 15.0 at baseline, $p < 0.05$).

4.6 Echocardiography data

In our study, analysis of the whole population revealed a reduction in ejection fraction of 6.1%, $P < 0.0001$ and mitral regurgitation grade by 0.27, $P=0.007$. The changes in left ventricular ejection fraction and mitral regurgitation grade were similar in the study groups, on both intention to treat and as per protocol analyses. In addition, The CARE-HF (Cardiac Resynchronisation in Heart Failure) echo dyssynchrony criteria were similarly met in both RVA and RVOT pacing groups. In summary, both pacing sites were equally harmful in terms of LVEF, dyssynchrony and mitral regurgitation severity.

It is well known that chronic right ventricular apical pacing worsens left ventricular systolic function (Buckingham et al. 1998). Right ventricular outflow tract pacing has been introduced to avoid this complication of RVA pacing. It is assumed that a more normal ventricular activation brings out less deterioration in the LV function. Despite this theoretical advantage, various clinical reports did not show convincing data of the superiority of mid-term RVOT pacing over RVA pacing (de Cock et al. 1998; Stambler et al. 2003; Tse et al. 2002; Victor et al. 1999). Ten Cate et al assessed the acute effects of RVA and RVOT pacing on LVEF in order to determine the contribution of echocardiography for the selection of the optimum pacing site during pacemaker implantation (ten Cate et al. 2008). They studied 14 patients with a DDD-pacemaker (7 RVA, 7 RVOT) and normal LVF without other cardiac abnormalities. They concluded that both acute RVA and RVOT pacing negatively affect wall motion score, longitudinal

LV strain, and mechanical activation times, without clear differences between both pacing sites.

It is possible that RVOT superiority may become evident only if His bundle is targeted and that non-His bundle RVOT sites can induce LV dyssynchrony as much as RV apex pacing. In one acute study (Padeletti et al. 2007), 12 patients with a standard indication for electrophysiological study were evaluated. A pressure-volume catheter was positioned in the left ventricle. Pressure-volume loops were collected during atrial (AAI) and dual-chamber overdrive pacing at 82 ± 15 beats/ min after 2 minutes of haemodynamic stabilisation. Ventricular pacing catheter position was randomised between the RV apex, RV septal, and free wall portions of the outflow tract, LV free wall, and His bundle. His bundle capture was verified from surface electrocardiographic morphometry using standard criteria. LV only pacing, but not His pacing, resulted in improved stroke work and stroke volume compared with alternate site RV pacing. No changes in +dP/dt, LV end-systolic pressure, LV end-diastolic pressure, or cycle efficiency, were observed between RV pacing sites. They concluded that acute His bundle pacing did not improve LV function compared with alternate site RV pacing and may be inferior to LV pacing.

Long-term improvement in LV function after direct His bundle pacing was only seen in a small study involving 18 patients with dilated cardiomyopathy, chronic AF, and QRS <120 msec (Deshmukh et al. 2000). In their study, LVEDD reduced from 59 ± 8 mm to 52 ± 6 mm ($P < 0.01$) with an accompanying increase in left ventricular ejection fraction from 20 ± 9% to 31 ± 11% ($P < 0.01$).

4.7 Study limitations

1- The PVO_2 results could have been confounded by the fact that the mean age of the study population was 73 years and therefore participants were possibly restricted physically by other systems rather than the cardiac performance such as pulmonary or musculoskeletal pathologies.

2- The power calculation was done by referring to previous small studies with peak oxygen consumption as an endpoint. We had also to refer to other studies on cardiac resynchronisation therapy to agree on the minimum clinically significant difference in peak oxygen consumption to be able to do the power calculation of the sample size. It may be inappropriate to do such thing as cardiac synchronisation is indicated in a completely different group of patients with advanced heart failure and poor left ventricular function. We then estimated that 25 patients are needed in each study group to reach the required power of 90%.

3- As patients' recruitment was slow we had to expand the inclusion criteria to include patients with atrioventricular block. It is inappropriate to exercise such patients as they have chronotropic incompetence and therefore exercise test is a relative contraindication in such cases. Consequently, CPET was only performed in 21 patients out of the total 50. This has therefore underpowered the study and made it susceptible to type II error (no difference between the study groups was found when there is actually a difference).

4- Four patients crossed over from the RVOT group to the RVA group. This was explained by the inability to find a stable and satisfactory RVOT pacing site. However, it is possible that the relative inexperience of the implanting physician was a contributing factor. In an attempt to overcome this challenge, both intention to treat and per treatment received analyses were performed.

5- Five patients in the RVA group had previous myocardial infarction with only one in the RVOT group. Although P value was insignificant at 0.08 but this could be an important clinical factor that could affect study outcomes. It is however reassuring that the baseline LV ejection fraction was well matched between both study groups.

6- The RVOT group had more patients with persistent atrial fibrillation compared to the RVA group (RVOT/RVA = 7/4). This meant that dual chamber pacing was used more in the RVA group.

7- The RVOT lead was positioned on fluoroscopy only and no specific part of the RVOT was targeted. This may possibly explain the fact that on retrospective review of the chest X rays, the right ventricular lead was positioned in the free wall in 10 cases, in the anterior wall in 9 cases, and in the septum in 2 cases only. This heterogeneity in RVOT lead position may also explain the fact that QRS duration was similar in both study groups. It is also worth mentioning that when the post-implant ECGs in the RVOT group were analysed, negative or isoelectric QRS vector in lead I was seen in 9 out of 21of the RVOT implants which was suggested to correlate with septal pacing. Therefore, in our study there was no

clear correlation between fluoroscopy and ECG signs of septal pacing. This can possibly be explained by the fact that previous studies were conducted on different group of patients with variable characteristics.

8- Echocardiographic variables were similar in both study groups. It is possible that negative LV remodelling and therefore LV ejection fraction could take years to significantly change, especially that the baseline LVEF was 59% in the study population. Another possible confounder is that the intra-observer variability is well described in the assessment of LV function via echocardiography.

9- With regard to LV dyssynchrony assessment, we used simple criteria that were previously used in trying to select heart failure patients for biventricular pacemaker implantation. It is possible that as our patients were of completely different characteristics and that the majority have normal or near normal LV function that these dyssynchrony criteria is not applicable. Actually, even in the field of selecting patients for cardiac resynchronisation therapy, a recent multi-centre trial (PROSPECT) showed that there is no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines.

10- The main positive finding in our study is the QOL difference between the study groups. Although QOL is a relatively soft and subjective endpoint, it might be more relevant to this age group of patients than the echocardiogram parameters which are usually seen as harder endpoints. In addition, NYHA functional class was estimated by the investigator at baseline and follow-up

instead of an evaluation by an independent investigator. In an attempt to avoid bias, baseline investigations were done before randomisation while follow-up investigations were performed by investigators with no access to the allocated/ received treatment. The investigator is also at risk of subjectively deciding on NYHA class as all clinicians are aware of borderline cases where it is difficult to decide whether it is NYHA class II or III. There is also significant inter and intra observer variability which becomes more relevant when subjects are unable to read the questionnaire and the researcher had to read these questions loud. This becomes even more relevant in elderly patients who are hard of hearing.

11- Although the use of SF-36 appears to be the most validated among generic questionnaires because of its psychometric characteristics, the MLWHF questionnaire has only been used in patients with heart failure to measure their response to either medical or device intervention. This clearly does not apply to our study patients as they were mainly patients with good LV function and in NYHA class II.

12- Pacemaker implantation in patients with advanced AV block and in those who had "ablate and pace" for uncontrolled AF will clearly have a significant positive impact on their QOL scores. Therefore, detecting possibly a smaller impact secondary to the position of the RV lead will be confounded by the larger improvement secondary to giving them a pacemaker.

CHAPTER FIVE

Conclusion & Recommendations

The right ventricular apex has been the default pacing site since 1959 with many patients surviving with 20-30 year old follow-up assessments. However several trials have suggested that right ventricular pacing can cause deleterious consequences such as left ventricular dilatation and negative remodelling. Other randomised controlled trials have demonstrated that a high percentage of right ventricular apical pacing was strongly predictive of higher incidence of adverse clinical outcomes such as heart failure hospitalisation, atrial fibrillation, thromboembolic complications, and even death. It is unclear whether it is pacing the right ventricle or the right ventricular apex that is the actual problem. It was therefore recommended that pacing the right ventricle should be minimised. However, programming strategies are not relevant in patients with advanced atrioventricular block or patients who have undergone atrioventricular node ablation who require permanent ventricular pacing. This has led to evaluation of alternative right ventricular pacing sites in order to achieve a more "physiological" pattern of ventricular activation. The most studied of these sites has been the right ventricular outflow tract.

Within the limitations of our study, RVOT pacing, at 6 months, was not superior to RVA in terms of PVO_2. In contrast, RVOT pacing offered a more significant improvement in health-related quality of life scores. Both RVA and RVOT pacing comparably worsened echocardiogram parameters. Our study therefore adds to the limited evidence that is available in relation to SSP. It provides further support for the emerging benefits of RVOT compared to RVA pacing.

We recommend conducting a better designed trial by only including patients post AV node ablation. This would permit all patients to be evaluated in terms of our primary outcome measure. The study should also allow us to calculate sample size for both: patients with preserved or impaired LV systolic function. The chance of cross over can be minimised by training junior doctors on how to implant the lead into the right ventricular out flow tract and familiarising them with the different fluoroscopic projections and the electrocardiographic that could be specific to one particular site such as the RVOT septum. It is possible that better future tools will allow a more successful delivery of pacing leads to the targeted RVOT site.

The follow up should be at least 18 months and preferably 24 months. This would allow time for the potentially prolonged remodelling processes to take place. This is quite important as the suggested patients' cohort have a well preserved LV systolic function and therefore the longer the follow up, the more chance of finding a difference between the study groups if a real difference actually exists. Echocardiogram assessment of the LV function should be ideally done using contrast to minimise the intra- and inter-observer variability. In addition, we could utilise more sophisticated methods of assessing LV dyssynchrony including tissue Doppler techniques which may have more sensitivity in detecting signs of dyssynchronous LV contraction. The other way forward in the field of searching for a better RV pacing site, if one exists, is conducting a well designed large multi-centre trial. The primary outcome should be a clinical one such as time to hospitalisation, occurrence of atrial fibrillation, or even death. This will require a huge amount of financial support which may be

very difficult to find as the industry has no financial incentive to invest in such large study unless it involves new techniques that could make it financially viable for them.

Another very important point is that so far there has been no study of non-RV apical sites that showed a detrimental effect of these sites when compared to RV apical pacing (SSP is not inferior to RVA pacing). Actually, all previous trials revealed either a neutral outcome or were in favour of non-apical pacing site. The pacing community should also be fully aware of the publication bias as "positive" trials have more chance reaching the wider audience. Meanwhile, it would seem logical to abandon the right ventricular apex as a default pacing site and train the next generation of junior implanters to target non-apical site so they would be better equipped for a possible future change in practice.

5.1 General lessons learnt by the researcher

Dedication

I have learnt that a prolonged period in research should not be undertaken lightly. The difference from a structured training program is disconcerting. You initially feel lost in the whole process. There is so much new to learn but there appears to be so much time. Having spent considerable time on background reading and under taking statistics courses I became engrossed with producing a review article which would form the basis of my introduction. I had not appreciated the importance of fully understanding the nuances of methodology and the difficulty

of performing high quality clinical research. I was to find myself frustrated with the clinical services, colleagues and ultimately myself. The initial difficulty in recruiting patients was to be dwarfed by the difficulty in collecting complete data for each and every patient. This really came to light during analysis where I found myself reliant on the help of others once more. I spent many long hours trying to understand statistics and even more hours writing up late at night. This was to the detriment of my wife and young family without whose understanding I could not have completed my thesis. I have found my period in research extremely challenging but ultimately very rewarding. Without regular meetings with my supervisor and occasional kind and understanding advice I would have struggled.

Methodology

The most important thing that I have leant about research is that the methodology must be appropriate and feasible. An understanding of the background is vital in order to formulate a hypothesis which will have relevance to clinical practice. Whilst it is possible to define a patient population exactly, it is not always possible to find such patients in clinical practice. Whilst it is also easy to define a clear and objective endpoint, it is not always possible to measure this in all your patients. This can create enormous frustration and place stress on a researcher. One has to be true to both best clinical practice in the interest of the patient and best research practice in the interest of the project. This can create conflict and I found this difficult to cope with. I was helped by senior colleagues and

supervisors alike. When planning future clinical research I will consider very carefully the clinical framework within which I will have to adapt.

Time Management

Time in research initially seemed ample although there was much to do and learn. However, once recruitment started I was initially excited and invigorated but soon found myself torn between recruiting new patients and fitting in follow ups. There did not seem to be enough time in the day. I was always disappointed to find I had missed a potential patient especially if I had been busy with something else. Once data analysis started I then had to make deadlines for abstract submission, the process of which was more testing than producing the work itself. I was often asked to cover clinical sessions for colleagues. This was initially fine but later had to be declined. I found it difficult to step back from clinical work especially procedure sessions as I was concerned that I would de-skill. Fortunately I have not but I have had to work extremely hard to write up having returned to a full time clinical job. This was not an ideal situation and an extension to my time in dedicated research may have been considerably easier.

People Skills

Research has taught me to understand patients and their fears much more. The process of informed consent required detailed explanation and discussion of potential complications. I think this will help me in my future clinical practice. I also had to understand that the focus of those in clinical practice is to provide a

high quality and efficient service. This did not always help with patient recruitment for research especially if there was no potential benefit to clinical colleagues. I therefore had to learn the importance of educating colleagues, secretaries, physiologists, nurses and bed managers to inform me if a potentially appropriate patient had been listed. I also realised the benefits of making coffee and providing biscuits as bribes.

University Regulations

The rules regarding the completion of an MD thesis must be adhered to exactly and need to be read and understood at an early stage. This was low on my list of priorities but was insisted upon by my supervisors. Interim reports had to be completed in time and needed to be concise and relevant. Lessons learnt from discussions at such meetings helped mould my final project which had to be altered as it progressed. Without following the correct procedure this would not have been possible.

Data Collection

As part of my study, considerable time and effort had been put into formulating a Case Report Form for each patient. This meant that transcription of relevant research data was efficient and appropriate. Despite this it was easy to miss a single piece of vital information which was time consuming to remedy. Hospital notes can vanish for weeks at a time. I had to be meticulous in collecting complete data at every patient visit. Where it was not possible to collect some

data on clinical grounds there was considerable impact on the statistical analysis for individual endpoints. This reinforces my opinion that all research is only as good as the methodology.

Statistical Analysis

Having completed several statistical courses and digested a book I felt I had a rudimentary understanding of the topic and would be able to analyse my data in a reasonable manner. However on my initial attempt it was clear that data does not always follow the rules. I am most grateful for the advice and time of those with experience in statistical analysis of clinical data. It was easy to produce copious amounts of p values but understanding which was appropriate and relevant was more of a challenge. I feel that I know and understand the results from my study in great detail which can only come from taking ownership of the analysis. I have learnt that parametric tests are often preferred because they are more robust and they have greater power efficiency, in other words, they have greater power relative to the sample size. In addition, a significant violation of the assumption of normality can seriously increase the chances of committing either a Type I or II error. Finally, it is mandatory to be aware of attaching too much importance to a lone or few significant results among a mass of non-significant ones. This can be avoided by adjusting the significance level using Bonferroni method.

Writing up

In the early stages of my research I was asked to write a review article by my supervisor. This meant I had to do back ground reading a produce my first ever manuscript. This helped me understand the fundamental issues to be addressed in my thesis and also to place my work in the context of that already published. After several drafts and rejection from a journal I realised that this was a skill I would have to work on. I learn to persist with article writing and submission. I also learnt to adapt an article according to the requirements of an individual journal. I became more successful as time passed. The same process had to be applied to abstract submission and although rejection was always disappointing the joy of acceptance made it bearable. When it came to thesis writing however, the detail and formatting required was altogether different. Nevertheless I am proud of what I have learnt and achieved.

5.2 Study specific lessons learnt be the researcher

RVOT Definition

We should have been more specific in defining RVOT pacing by not only relying on the fluoroscopic definition but on the electrocardiographic findings as well. By doing so we can be more confident about which part of the RVOT is targeted. Implanting physicians should have been introduced to this study and formally be trained in how to reach the RVOT and more specifically perhaps the RVOT septum prior to the recruitment phase.

The Inclusion Criteria

It is possible that the inclusion criteria should not have been modified as simply by its expansion the power calculation was invalidated and this put the study at a risk of type II error. Perhaps it would have been favourable to recruit patients from other implanting centres rather than adjusting the inclusion criteria. It is also possible that the quality of life parameters would have been more relevant in our patients' age group than the peak oxygen consumption as the measurement of the later may be confounded by the multiple comorbidities encountered in such age group. Other potential confounders are: previous myocardial infarction, history of PAF and its duration, lead position on the lateral CXR which was done after pacemaker implantation, being on antiarrhythmic drugs at the time of implantation in particular amiodarone.

The Follow-up

The study follow-up should have been done at 6 months as well as 18 months to account for the possible long term left ventricular remodelling. Echocardiogram parameters should have been assessed by two independent investigators after formally assessing the inter- and intra-observer variability.

5.3 Implications for clinical practice

Although our study added to the existing evidence it remains a relatively small study with a medium-term follow up that was conducted in a single centre. It is therefore unlikely to change clinical practice. It will however encourage more device implanters to at least think about where to position the RV lead rather than targeting the RV apex at al times. The RVOT will always have the theoretical advantage that it is less likely to cause pericardial tamponade. However, the skills required for targeting the RVOT take longer to acquire with probably higher rate of failure. In my practice RVOT pacing has a 5-10% failure rate either because the site is electrically inadequate or it is impossible to fix the lead to the targeted area. It is possible that future multi-centre studies on selective site pacing will prove the superiority of RVOT lead as a default position for the RV lead. It may be more appropriate for the RV apex to be targeted in special subgroups, when the implanting physicians are at the beginning of their career, or are simply general cardiologists who were trained in the "traditional" manner. Finally, this study may help to influence the training of future generations of device implanters to incorporate RVOT pacing as a primary implant site.

Appendices

Appendix 1

The Cardiothoracic Centre – Liverpool NHS
NHS Trust
Liverpool
L14 3PE
Telephone switchboard 0151 228 1616

Participant Consent Form

Study Number: 695

Patient Identification Number for this trial (CRF No.):

Title of Project: A study evaluating the effects of Selective Site Ventricular Pacing on the haemodynamic and functional recovery of patients following atrio-ventricular nodal ablation. (SSP-1 study)

Name of Researchers: ***Dr Khaled Albouaini/ Dr Jay Wright***

	Please initial box
1. I confirm that I have read and understand the information sheet dated 14th June (version 2) for the above study and have had the opportunity to ask questions	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Clinical Trials Unit at cardiothoracic centre NHS Trust or from regulatory authorities where it is relevant to my taking part in research. I give permission for these	☐
4. I agree to take part in the above study.	☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

3 copies to be signed: 1 for patient; 1 for research files: 1 for casenotes.

Appendix 2

The Cardiothoracic Centre – Liverpool NHS

NHS Trust

Patient Information Sheet

Thomas Drive,
Liverpool, L14 3PE

Centre Number:

Study Number: 695

1. Study title

A study evaluating the effects of Selective Site Pacing on the haemodynamic and functional recovery of patients requiring permanent right ventricular pacing (SSP-1 study)

2. Invitation paragraph

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

3. What is the purpose of the study?

The heart's "natural" pacemaker is called the sinoatrial (SA) node or sinus node which is a small mass of specialized cells in the top of the heart's right atrium (upper chamber) that makes the electrical impulses that cause the heart to beat. A chamber of the heart contracts when an electrical impulse moves across it and for the heart to beat properly, the signal must travel down a specific path to reach the ventricles, the heart's lower (pumping) chambers. The natural pacemaker may be defective, causing the heartbeat to be too fast, too slow or irregular or the hearts' own electrical pathways may also be blocked. An "artificial pacemaker" which is a small, battery-operated device that helps the heart to beat in a regular rhythm can be prescribed.

Traditionally pacemaker implantation has been achieved by the secure positioning of electrical leads at the top of the right atrial appendage (RAA) and at the tip of the right ventricle commonly described as right ventricular apex (RVA). Although this type of pacing maintains a regular heart beat and rhythm it results in the abnormal contraction in the left ventricle which may place the patient at increased risk of heart failure. Other sites such as the area around the opening of the right ventricle commonly described as the right ventricular outflow tract (RVOT) have been considered. However, other investigations evaluating alternative pacing sites have provided conflicting results and no firm conclusions have been drawn. We therefore propose for the first time to study the impact of

the traditional RVA pacing as compared to RVOT pacing on the improvement of patient's exercise capacity and cardiac function during exercise in a population of patients with similar disease background that require constant ventricular pacing.

4. Why have I been chosen?

You have been chosen because you have either

- Irregular heart beat which require treatment with an ablation procedure of the atrio-ventricular node and the implantation of a permanent pacemaker.
- Slow heart that requires implantation of a permanent pacemaker.

The study will aim to enrol 80 patients at the Liverpool cardiothoracic centre.

5. Do I have to take part?

It is up to you to decide whether or not to take part. You have been given this information sheet to help you make a decision. If you do decide to take part you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care and medical treatment you receive.

6. What will happen to me if I take part?

If you decide to take part you will have a pacemaker implanted with the right ventricular lead placed either in the RVA or RVOT position. A computer programme will determine your allocation to either group. This method of allocation has been shown to be the most reliable and fair way of comparing two different treatments. With this randomisation procedure 50% of patients will be chosen for RVA pacing and 50% will be chosen for RVOT pacing. Patients will be assessed twice, at 6 months and 18 months. All other aspects of the procedure and subsequent care will follow our routine practice for pacemaker implantation.

Participation in this study will involve the performance of an echocardiogram (heart ultrasound scan) and exercise test (if appropriate) before implantation and at 6 and 18 months after the procedure to evaluate how the pacemaker is affecting your heart function and your physical fitness. You will also be asked to fill out some forms assessing your quality of life. We will also collect some limited information about your health after the pacemaker implantation from your medical records. This information will be kept strictly confidential.

7. What do I have to do?

If you decide to take part there will be no changes to your routine clinical care after your pacemaker implantation. There will be no particular lifestyle or dietary restrictions over and above those advised for pacemaker patients. Similarly there are no extra restrictions concerning driving or sport over and above those advised for patients who have had a pacemaker implant.

8. What is the procedure that is being tested?

The procedure being tested is whether elective implantation of RVOT pacemaker position is better than the traditional RVA position.

9. What are the alternatives for diagnosis or treatment?

If you were not taking part in the study you would also receive either RVA or RVOT position pacemaker, but this will be decided by the implanting doctor. The echocardiogram and exercise test will not be done routinely.

10. What are the side effects of any treatment received when taking part?

The possible side effects are those common to **all patients** undergoing pacemaker implantation procedure. You will be assigned a study nurse or doctor whom you can contact in case you have any concerns or questions about the study.

11. What are the possible disadvantages and risks of taking part?

The possible disadvantages and risks of taking part are common to all patients undergoing any permanent pacemaker implantation procedure. **There is no greater** risk from implantation of the pacemaker lead at the RVOT compared to the RVA.

12. What are the possible benefits of taking part?

The possible benefits of having a pacemaker inserted at the RVOT position as compared to the traditional RVA position is a possible reduction in the risk of developing heart failure. However it is not possible to say definitively whether it is better to have a pacemaker inserted at the RVOT position as compared to the traditional RVA position at the present time. By taking part you may help us to decide the best position in the future for treating patients requiring permanent pacemaker implantation.

13. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. However if some, as yet unknown, significant new information came to light that had a bearing on the study and your participation, this would be considered by the committee of experts who oversee the conduct of all the studies conducted at cardiothoracic Centre and you will be informed of the outcome.

14. What happens when the research study stops?

When the study is completed you will not be required to continue with any study procedures and your care will continue as usual.

15. What if something goes wrong?

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action as in all NHS care. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

16. Will my taking part in this study be kept confidential?

If you consent to take part in the research, members of staff at the Clinical Trials Unit of the Cardiothoracic Centre may inspect your medical records to ensure that the data is accurate for the purpose of analysing the results. Your records may also be looked at by people from the regulatory authorities or other NHS staff to check that the study is being carried out correctly.

All information that is collected about you during the course of the research will be kept strictly confidential.

17. What will happen to the results of the research study?
When the study is completed and the data analysed a manuscript will be submitted for publication. You will also able to request a copy of any publications of the results from this study. The results will be presented at medical conferences and published in medical journals. Your identity will not be divulged in any presentation, publication or report.

18. Who is organising and funding the research?
The project is funded by the Liverpool Cardiothoracic NHS Trust and charitable funds. A Steering Committee of experts in heart disease and research methodology will oversee the conduct of the study. The study will be co-ordinated by the Clinical Trials Unit, Liverpool Cardiothoracic NHS Trust. Your doctor is not being paid for you to participate in the SSP-1 pacemaker study although some funding is provided for staff to help run the study at your hospital.

19. Who has reviewed the study?
National ethics approval has been obtained for this study and your hospital's Ethics Committee have reviewed the study.

20. Contact for Further Information
Thank you for taking time to read this patient information sheet. If you decide to take part we will ask you to sign a consent form. You will be given a copy of the signed consent form and the patient information sheet.

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions potential recruits may want to ask. You may obtain copies from CERES, PO Box 1365, London N16 0BW.

The doctors and nurses involved in this study will be pleased to discuss any questions or concerns you may have. If you do have any questions or concerns about the study please contact:

Principal Investigator: Dr D Jay Wright
Tel: 0151 293 2457 (sec)
Email: David.Wright@ctc.nhs.uk
Local Study Co-ordinator: **Dr Khaled Albouaini**
Tel: 0151 2281616, mobile 07815107165
Email: khaled.albouaini@ctc.nhs.uk

Thank you very much.

Appendix 3

The Cardiothoracic Centre – Liverpool NHS

NHS Trust

	PATIENT DETAILS		
1	Date of screening	(dd/mm/yyyy) __ __ / __ __ / __ __ __ __	
2	Patient's name	Initials :	
3	D.O.B. / Gender	__ __ / __ __ / __ __	Male/Female
4	Hospital / Unit number		
5	Address: House no./Street		
6	City		
7	Postal code		
8	Country		
9	Telephone number		
10	NHS number		
11	Consultant in charge	DMT [ ]	JEPW [ ]
	DETAILS OF RELATIVE OR FRIEND NOT AT THE SAME ADDRESS		
12	Relative's or friend's name		
13	Address: House no./Street		
14	City		
15	Postal code		
16	Country		
17	Telephone number		
	DETAILS OF G.P.		
18	GP name		
19	Surgery name		
20	Address: Street		
21	City		
22	Postal code		
23	Country		
24	Telephone number		

BASELINE CHARACTERISTICS					
MEDICAL HISTORY					
25	Has the patient been listed for ablation	Yes [ ]		No [ ]	
26	Hypertension treated with drugs	Yes [ ]		No [ ]	
27	Hyperlipidemia treated with drugs	Yes [ ]		No [ ]	
28	Diabetes	Yes [ ]		No [ ]	
29	Smoking status	Yes [ ]		No [ ]	
30	COPD requiring treatment	Yes [ ]		No [ ]	
31	Asthma requiring treatment	Yes [ ]		No [ ]	
32	Documented Peripheral Arterial	Yes [ ]		No [ ]	
33	Any previous mediastinal	Yes [ ]		No [ ]	
34	Prior CVA, if yes date (mm/yyyy)	Yes [ ]	__ __ / __ __ __ __	No [ ]	
35	Prior MI, if yes date (mm/yyyy)	Yes [ ]	__ __ / __ __ __ __	No [ ]	
36	Prior PTCA ± stent, if yes date	Yes [ ]	__ __ / __ __ __ __	No [ ]	
37	Other cardiovascular intervention, if yes date (mm/yyyy)	Yes [ ]	__ __ / __ __ __ __	No [ ]	
38	If yes, specify type of intervention	CABG [ ]		Valve surgery [ ]	
39	Congestive Heart failure, if yes date (mm/yyyy)	Yes [ ]	__ __ / __ __ __ __	No [ ]	
40	Physical disability preventing exercise test	Yes [ ]		No [ ]	
CLINICAL EXAMINATION					
41	Height (cm) / Weight (kg)	__ __ __.__ cm		__ __ __.__ kg	
42	BMI				
43	Ethnic origin				
44	NYHA class	I	II	III	IV

	MEDICATIONS AT BASELINE			
45	Aspirin	Yes [ ]		No [ ]
46	Clopidogrel	Yes [ ]		No [ ]
47	If either above is **yes**, days before intervention that they were stopped	No. of days =		
48	Warfarin	Yes [ ]		No [ ]
49	Other anticoagulant	Yes [ ]		No [ ]
50	If yes, please specify	Phenindione [ ]		Sinthrome [ ]
51	Beta-blockers	Yes [ ]		No [ ]
52	Calcium-channel antagonists	Yes [ ]		No [ ]
53	Nitrates	Yes [ ]		No [ ]
54	Potassium channel activators	Yes [ ]		No [ ]
55	Lipid lowering agent (tick all that apply)	Statins [ ]	Other [ ]	No [ ]
56	ACE inhibitors	Yes [ ]		No [ ]
57	Angiotensin-II antagonists	Yes [ ]		No [ ]
58	Diuretics	Yes [ ]		No [ ]
59	Digoxin	Yes [ ]		No [ ]
60	Amiodarone	Yes [ ]		No [ ]
61	Any other anti-arrythmic medication	Flecainide [ ]	Propafanone [ ]	NA [ ]

ELIGIBILITY CRITERIA

Inclusion Criteria

62	Atrial fibrillation	Yes [ ]	No [ ] **stop**
63	Atrial flutter	Yes [ ]	No [ ] **stop**

If any NO, <u>stop</u> - patient <u>should not</u> be randomised

Exclusion Criteria

64	Indication for implantation of ICD	Yes [ ] ***stop***	No [ ]
65	Indication for biventricular pacemaker implant	Yes [ ] ***stop***	No [ ]

66	Evidence of left or right bundle branch block	Yes [ ] ***stop***	No [ ]
67	QRS > 120 ms	Yes [ ] ***stop***	No [ ]
68	Inability to comply with follow-up procedures	Yes [ ] ***stop***	No [ ]
69	Exercise limitation due to pathological process i.e. angina, respiratory, neurological or rheumatological	Yes [ ] ***stop***	No [ ]
70	Significant valvular heart disease including indwelling	Yes [ ] ***stop***	No [ ]
71	Current or recent participation in any other clinical investigation	Yes [ ] ***stop***	No [ ]
72	Life expectancy less than 2	Yes [ ] ***stop***	No [ ]
73	Ventricular septal defect	Yes [ ] ***stop***	No [ ]
74	Undergone CABG or PTCA within last 3 months	Yes [ ] ***stop***	No [ ]
75	Planned angioplasty/cardiac surgery	Yes [ ] ***stop***	No [ ]
If any YES, <u>stop</u> - patient <u>should not</u> be randomised			
	CONSENT		
76	Has patient been fully informed and received a patient information sheet	Yes [ ]	No [ ]
77	Date of consent (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __	
78	Name of person obtaining consent		
79	Present in casenotes and site file	Yes [ ]	No [ ]

	QUALITY OF LIFE QUESTIONNAIRE 1 - MINNESOTA SCORE				
80	Questionnaire completed	Yes [ ]	Date __ __ / __ __ / __	Score	No [ ]
81	If no, reason				
	QUALITY OF LIFE QUESTIONNAIRE 2 - SHORT FORM-36 HEALTH SURVEY				
82	Questionnaire completed	Yes [ ]	Date __ __ / __ __ / __	Score	No [ ]
83	If no, reason				

BASELINE INVESTIGATIONS				
ECG				
84	ECG recorded, if yes date (dd/mm/yyyy)	Yes [ ]	__ __ / __ __ / __ __ __ __	No [ ]

85	If yes, rhythm	Sinus [ ]	AF [ ]	Paced [ ]
86	If no ECG, give reason			
ECHOCARDIOGRAM				
87	Ventricular function measured	Yes [ ]	No [ ]	
88	Date (dd/mm/yyyy)	__/__/_____		
89	Ejection fraction (%)			
90	Evidence of mitral regurgitation	Yes [ ]	No [ ]	
91	Mitral Regurgitation	Vena Contracta [ ]	Dp/Dt [ ]	PISA [ ]
92	Evidence of aortic valve disease	Yes [ ]	No [ ]	
93	Atrio-ventricular Dysynchrony APE > 140ms	Yes [ ]	No [ ]	
94	Interventricular delay (APE – PPE) > 40 ms	Yes [ ]	No [ ]	
95	Intraventricular dysynchrony D_1>D_2	Yes [ ]	No [ ]	
96	LVOT VT1 (cm)			
CARDIOPULMONARY EXERCISE TEST				
97	Date of test (dd/mm/yyyy	__/__/_____		
98	Heart rate at rest (bpm)			
99	Blood pressure at rest (mm/Hg)			
100	VE/VO_2 at 1 litre VO_2 (litres)			
101	VE (ventilation equivalent) minute ventilation (litres per min.)			
102	RER (respiratory exchange ratio) attained			
103	Peak VO_2 (ml/kg/min.)			
104	End tidal PCO2 <3 (hyperventilation) (mm/Hg)			
105	CO (cardiac output) at rest (litres per min.)			
106	CO on exercise (litres per min.)			
107	CPO (cardiac power output) at rest (watts)			
108	CPO on exercise (watts)			
109	Cardiac reserve (litres)			

RANDOMISATION

For randomisation please call the following number during UK office hours (09.00-17.00 hrs.) 0151 293 2291 or 0151 293 2292

110	Date of randomisation (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __	
111	Randomisation code		
112	Name of person obtaining randomisation		
113	Proposed date of pacemaker implantation (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __	
114	Treatment allocation	RVA [ ]	RVOT [ ]

PACEMAKER IMPLANTATION					
Details of the procedure					
115	Date of admission (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __			
116	Date of the procedure (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __			
117	Single lead device	Yes [ ]		No [ ]	
118	Device type	VVI [ ]	VVIR [ ]	DDD [ ]	DDDR [ ]
119	Serial number				
120	Lead type	Active [ ]		Passive [ ]	
121	Lead number				
122	Total procedure time	(mins).			
123	AV nodal ablation	Yes [ ]	No [ ]	NA [ ]	
124	Programming :Base response rate	Yes [ ]		No [ ]	
125	Upper response rate	Yes [ ]		No [ ]	
126	Hysteresis	Yes [ ]		No [ ]	
PROCEDURAL COMPLICATONS					
127	Death	Yes [ ]	Date __ __ / __ __ / __ __ __ __		No [ ]
128	VT requiring cardioversion	Yes [ ]		No [ ]	
129	Transfusion requirement	Yes [ ]		No [ ]	
130	Cardiac arrest requiring CPR	Yes [ ]		No [ ]	
131	Haematoma requiring evacuation	Yes [ ]		No [ ]	
132	Lead displacement	Yes [ ]		No [ ]	
133	Pneumothorax	Yes [ ]		No [ ]	
INVESTIGATOR'S DECLARATION					
I declare that the information presented in the Case Record Form (page 7) accurately reflects the procedural details/complications within the medical records.					
134	Name of person completing form (capitals)				
135	Signature of person completing form				
136	Date form completed (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __			

FOLLOW UP AT 6 MONTHS FOLLOWING PROCEDURE					
	QUALITY OF LIFE QUESTIONNAIRE 1 - MINNESOTA SCORE				
1	Questionnaire completed	Yes [ ]	Date __ __ / __ __ / __ __	Score	No [ ]
2	If no, reason				
	QUALITY OF LIFE QUESTIONNAIRE 2 - SHORT FORM-36 HEALTH SURVEY				
3	Questionnaire completed	Yes [ ]	Date __ __ / __ __ / __ __	Score	No [ ]
4	If no, reason				
	MEDICATIONS				
5	Aspirin	Yes [ ]		No [ ]	
6	Clopidogrel	Yes [ ]		No [ ]	
7	If either above is **yes**, days before intervention that they were stopped	No. of days =			
8	Warfarin	Yes [ ]		No [ ]	
9	Other anticoagulant	Yes [ ]		No [ ]	
10	If yes, please specify	Phenindione [ ]		Sinthrome [ ]	
11	Beta-blockers	Yes [ ]		No [ ]	
12	Calcium-channel antagonists	Yes [ ]		No [ ]	
13	Nitrates	Yes [ ]		No [ ]	
14	Potassium channel activators	Yes [ ]		No [ ]	
15	Lipid lowering agent (tick all that	Statins [ ]	Other [ ]	No [ ]	
16	ACE inhibitors	Yes [ ]		No [ ]	
17	Angiotensin-II antagonists	Yes [ ]		No [ ]	
18	Diuretics	Yes [ ]		No [ ]	
19	Digoxin	Yes [ ]		No [ ]	
20	Amiodarone	Yes [ ]		No [ ]	
21	Any other anti-arrythmic medication	Flecainide [ ]	Propafanone [ ]	NA [ ]	

INVESTIGATIONS				
ECG				
22	ECG recorded, if yes date (dd/mm/yyyy)	Yes [ ]	__/__/_____	No [ ]
23	If yes, rhythm	Sinus [ ]	AF [ ]	Paced [ ]
24	If no ECG, give reason			
ECHOCARDIOGRAM				
25	Ventricular function measured	Yes [ ]	No [ ]	
26	Date measured (dd/mm/yyyy	__/__/_____		
27	Ejection fraction (%)			
28	Evidence of mitral regurgitation	Yes [ ]	No [ ]	
29	Mitral Regurgitation	Vena Contracta [ ]	Dp/Dt [ ]	PISA [ ]
30	Evidence of aortic valve disease	Yes [ ]	No [ ]	
31	Atrio-ventricular Dysynchrony APE > 140ms	Yes [ ]	No [ ]	
32	Interventricular delay (APE – PPE) > 40 ms	Yes [ ]	No [ ]	
33	Intraventricular dysynchrony D_1>D_2	Yes [ ]	No [ ]	
34	LVOT VT1 (cm)			
CARDIOPULMONARY EXERCISE TEST				
35	Date of test (dd/mm/yyyy	__/__/_____		
36	Heart rate at rest (bpm)			
37	Blood pressure at rest (mm/Hg)			
38	VE/VO_2 at 1 litre VO_2 (litres)			
39	VE (ventilation equivalent) minute ventilation (litres per min.)			
40	RER (respiratory exchange ratio) attained			
41	Peak VO_2 (ml/kg/min.)			
42	End tidal PCO2 <3 (hyperventilation) (mm/Hg)			
43	CO (cardiac output) at rest (litres per min.)			
44	CO on exercise (litres per min.)			
45	CPO (cardiac power output) at rest (watts)			
46	CPO on exercise (watts)			

INVESTIGATOR'S DECLARATION		
I declare that the information presented in the Case Record Form (pages 8 to 9) accurately reflects the medical records, including the results of tests and evaluations performed on the dates specified.		
48	Name of person completing form (capitals)	
49	Signature of person completing form	
50	Date form completed (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __

SERIOUS ADVERSE EVENTS at 6 MONTH FOLLOW UP				
51	Death	Yes [ ]	Date __ __ / __ __ / __ __ __ __	No [ ]
52	Lead displacement	Yes [ ]	No [ ]	
53	Haematoma	Yes [ ]	No [ ]	
54	Infection	Yes [ ]	No [ ]	
55	Admission to hospital with heart failure	Yes [ ]	No [ ]	
56	SAE reported by (name)			
57	Date reported (dd/mm/yyyy)	__ __ / __ __ / __ __ __ __		

Appendix 4

Minnesota Living With Heart Failure™ Questionnaire

These questions concern how your heart failure (heart condition) has prevented you from living as you wanted during the last month. The items listed below describe different ways some people are affected. If you are sure an item does not apply to you or is not related to your heart failure, then circle 0 (No) and go on to the next item. If an item does apply to you, then circle the number rating how much it prevented you from living as you wanted.

Visit date: ___ ___ /___ ___ /___ ___

Baseline ☐ 6 months ☐ 18 months ☐

Did your heart failure prevent you from living as you wanted during the last month by:		No				Very Little		Very Much	
1.	Causing swelling in your ankles, legs, etc.?	0	1	2	3	4	5		
2.	Making you sit or lie down to rest during the day?	0	1	2	3	4	5		
3.	Making your walking about or climbing stairs difficult?	0	1	2	3	4	5		
4.	Making your working around the house or yard difficult?	0	1	2	3	4	5		
5.	Making your going places away from home difficult?	0	1	2	3	4	5		
6.	Making your sleeping well at night difficult?	0	1	2	3	4	5		
7.	Making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5		
8.	Making your working to earn a living difficult?	0	1	2	3	4	5		
9.	Making your recreational past times, sports or hobbies difficult?	0	1	2	3	4	5		
10.	Making your sexual activities difficult?	0	1	2	3	4	5		
11.	Making you eat less of the foods you like?	0	1	2	3	4	5		
12.	Making you short of breath?	0	1	2	3	4	5		
13.	Making you tired, fatigued, or low on energy?	0	1	2	3	4	5		
14.	Making you stay in a hospital?	0	1	2	3	4	5		
15.	Costing you money for medical care?	0	1	2	3	4	5		
16.	Giving you side effects from medication?	0	1	2	3	4	5		
17.	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5		
18.	Making you feel a loss of self-control in your life?	0	1	2	3	4	5		
19.	Making you worry?	0	1	2	3	4	5		
20.	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5		
21.	Making you feel depressed?	0	1	2	3	4	5		
	Sub totals :								
	TOTAL SCORE :								

Appendix 5

Short Form-36 (SF-36) Health Survey

Overview

The Short-Form-36 (SF-36) Health Survey was developed by Dr John Ware and was derived from the Rand Corporation's Medical Outcomes Study (MOS). It is used as a general survey of health status and an outcome measure in clinical practice. It can also be used together with disease-specific instruments for patient evaluation. The survey may be self-administered or may be completed by an interviewer.

Instructions for self-administration:

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. **In general would you say your health is?**

   - Excellent [1]
   - Very good [2]
   - Good [3]
   - Fair [4]
   - Poor [5]

2. **Compared to one year ago how would you rate your health in general now?**

   - Much better now than one year ago [1]
   - Somewhat better now than one year ago [2]
   - About the same now as one year ago [3]
   - Somewhat worse now than one year ago [4]
   - Much worse now than one year ago [5]

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities?

If, so how much?

Responses

- Yes limited a lot [1]
- Yes limited a little [2]
- No not limited at all [3]

a. Vigorous activities such as running lifting heavy objects participating in strenuous sports. [1] [2] [3]

b. Moderate activities such as moving a table pushing a vacuum cleaner bowling or playing golf. [1].... [2]....[3]....

c. Lifting or carrying groceries. [1] ....[2]....[3]....

d. Climbing several flights of stairs. [1].... [2]....[3]....

e. Climbing one flight of stairs. [1]....[2].... [3]....

f. Bending kneeling or stooping. 1]....[2].... [3]....

g. Walking more than one mile. [1].... [2]....[3]....

h. Walking several blocks. [1]....[2].... [3]....

i. Bathing or dressing yourself. [1].... [2]....[3].....

4. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Responses

- Yes [1]
- No [2]

a. Cut down on the amount of time you spent on work or other activities. [1]....[2]....

b. Accomplished less than you would like. [1]....[2]....

c. Were limited in the kind of work or other activities. [1]....[2]....

d. Had difficulty performing the work or other activities (for example it took extra effort). [1]....[2]....

5. During the past 4 weeks have you had any of the following problems with your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

Responses

- Yes [1]
- No [2]

a. Cut down on the amount of time you spent on work or other activities. [1]....[2]....

b. Accomplished less than you would like. [1]....[2]....

c. Didn't do work or other activities as carefully as usual. [1]....[2]....

6. During the past 4 weeks to what extent has your physical health or emotional problems interfered with your normal social activities with family friends, neighbours or groups?

- Not at all [1]
- Slightly [2]
- Moderately [3]
- Quite a bit [4]
- Extremely [5]

7. How much bodily pain have you had during the past 4 weeks?

- None [1]
- Very mild [2]
- Mild [3]
- Moderate [4]
- Severe [5]
- Very severe [6]

8. During the past 4 weeks how much did pain interfere with your normal work (including both work outside the home and housework)?

- Not at all [1]
- A little bit [2]
- Moderately [3]
- Quite a bit [4]
- Extremely [5]

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

***Responses*:**

- All of the time [1]
- Most of the time [2]
- A good bit of the time [3]
- Some of the time [4]
- A little of the time [5]
- None of the time [6]

a. Did you feel full of pep?
[1]...[2]...[3]...[4]...[5]...[6]

b. Have you been a very nervous person?
[1]...[2]...[3]...[4]...[5]...[6]

c. Have you felt so down in the dumps that nothing could cheer you up?

[1]...[2]...[3]...[4]...[5]...[6]

d. Have you felt calm and peaceful?
[1]...[2]...[3]...[4]...[5]...[6]

e. Did you have a lot of energy?
[1]...[2]...[3]...[4]...[5]...[6]

f. Have you felt downhearted and blue?
[1]...[2]...[3]...[4]...[5]...[6]

g. Did you feel worn out?
[1]...[2]...[3]...[4]...[5]...[6]

h. Have you been a happy person?
[1]...[2]...[3]...[4]...[5]...[6]

i. Did you feel tired?
[1]...[2]...[3]...[4]...[5]...[6]

10. During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends relatives etc.)?

- All of the time [1]
- Most of the time [2]
- Some of the time [3]
- A little of the time [4]
- None of the time [5]

11. How TRUE or FALSE is each of the following statements for you?

Responses

- Definitely true [1]
- Mostly true [2]
- Don't know [3]
- Mostly false [4]
- Definitely false [5]

a. I seem to get sick a little easier than other people.
[1]...[2]...[3]...[4]...[5]...

b. I am as healthy as anybody I know.
[1]...[2]...[3]...[4]...[5]...

c. I expect my health to get worse.
[1]...[2]...[3]...[4]...[5]...

d. My health is excellent.
[1]...[2]...[3]...[4]...[5]...

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.

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ABSTRACTS

Albouaini K, Alkarmi A, Matata B, McGee M, Modi S, Barker D, Chenzbraun A, Rao A, Gammage M, Wright D J. Selective Site Pacing and Effects on Haemodynamics and Functional Recovery in Patients Requiring Permanent Right Ventricular Pacing. *Heart Rhythm Congress, Birmingham, UK, 2009*

Albouaini K, Alkarmi A, Matata B, McGee M, Mudawi T, Andron M, Pyatt J, Rao A, Gammage M, Wright D J. Effects of Selective Site Pacing On the Haemodynamics and Functional Recovery in Patients Requiring Permanent Right Ventricular Pacing. *American Heart Association's Scientific Sessions, Florida, 2009*

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