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Jane Curry, M.B.A.

Student ID: 000104377

Health Studies

Graduate School

Cardiac Device Algorithms for Optimal Outcomes in Patients with Sick Sinus Syndrome

An evaluation of programming and implanting practice in County Durham and Darlington Pacemaker Services

Programme of Study: Master of Science –Research

December 2012

Abstract

Sick sinus syndrome (SSS) is a relatively common chronic condition affecting the electrical conduction system of the heart. In the absence of any reversible cause of SSS, the most effective treatment is implantation of a permanent pacemaker to maintain the heart rate and conduction sequence within the normal physiological parameters. Although atrial pacing may be sufficient, in practice most patients in the UK receive dual chamber pacing.

There is considerable clinical evidence that long term ventricular pacing can have a deleterious effect on the heart function and can increase the risk of heart failure hospitalisation, especially in patients with pre-existing cardiac dysfunction.
A link between the degree of right ventricular pacing (RVP) and the development of atrial fibrillation (AF) has also been demonstrated.

Pacemaker manufacturers have therefore developed a variety of programmable modes, features and algorithms that can be utilised to reduce unnecessary RVP. These include prolongation of atrioventricular delay (AVD), with or without "search", and pacemakers that offer minimal ventricular pacing. Although there are national UK guidelines on the use of appropriate pacemaker modes at implant, there is no such guidance on appropriate programming strategies.

This research project sought to identify the implanting and programming practice in a large pacemaker service in County Durham and Darlington (CD&D) between 2006 and 2011. The records of 349 patients who were paced for SSS were studied, with a follow-up of up to 5 years. Pacemaker implantation practice was compared to national audit data. The association between programming strategies and degree of RVP was then explored.

The results from this project showed there is a lack of consistency in the historical approach to reducing right ventricular pacing by the use of particular devices and algorithms.

Devices with a minimal ventricular pace algorithm reduce the degree of RVP to as little as <4% per year, whereas algorithms that altered AVD were significantly less effective, reducing RVP to between 17% and 27% per year (years 1-3). The data were less robust in years 4 and 5 due to relative small data sizes in each algorithm grouping.

There was no observable correlation between algorithm and the amount of AF, but a significant correlation was present between the degree of RVP and AF ($p<0.05$).

Based on these findings, local guidelines for the management of sick sinus syndrome have been adapted to recommend minimal ventricular pace devices in patients with sick sinus syndrome.

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Thanks and recognition is also due to County Durham and Darlington NHS Foundation Trust for their sponsorship of this project and agreement for its initiation and development.

Finally, as ever, I owe a debt of thanks to my family who resigned themselves to another 2 years of anguish whilst I complete another academic programme and have supported me through my endeavours.
As with all my major academic and career achievements, this piece of work is dedicated to the memory of Jim Underwood MBE – my father and inspiration.

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Abbreviations

ACC…….American College of Cardiology

AF……. atrial fibrillation

AP……. atrial paced

AS…….. atrial sense

AV……... atrioventricular

AHA……American Heart Association

AVB……...atrioventricular block

AVD…….. atrioventricular delay

BAH…….. Bishop Auckland Hospital

BiV……..bi-ventricular

BPEG……... British Pacing and Electrophysiology Group

CCAD……...Central Cardiac Audit Database

CDDFT…… County Durham and Darlington Foundation Trust

CHF……... congestive heart failure

CRM…….. cardiac rhythm management

CTOP……Canadian trial of physiological pacing (trial)

DMH…….. Darlington Memorial Hospital

ECG…….. electrocardiograph

HRS……. Heart Rhythm Society

HQIP…….. Healthcare Quality Improvement Partnership

LBBB…….. left bundle branch block

LV…….. left ventricle

MOST…….. Mode Selection Trial

ms……... milliseconds

MVP…… minimal ventricular pacing

NASPE ……...North American Society of Pacing and Electrophysiology

NCAPOP……. National Clinical Audit and patient outcome Programme

NECVN…….. North East Cardio-vascular Network

NHS…… National Health Service

NICE……. National Institute of Clinical Excellence

PACE…….pacing to avoid cardiac enlargement (trial)

PASE…… pacing selection in the elderly (trial)

R/RR…… rate response

RA…… right atrium

RV …….right ventricle

RVA…….. right ventricular apex

RVOT…….. right ventricular outflow tract

SAN…… sinoatrial node

SPSS……... Statistical Packages for the Social Sciences

SSS……..sick sinus syndrome

VP…….ventricular paced

VS……ventricular sensed

UHND……. University Hospital of North Durham

Cardiac Device Algorithms for Optimal Outcomes in Patients with Sick Sinus Syndrome

Chapter 1 – Introduction to the Research Project

1.1 Motivation and Background

Cardiac pacing is an established treatment of symptomatic bradycardia (slow heart rate). Technology in this area has developed dramatically, from the fundamentals of preventing heart rates dropping below a predetermined rate, to effectively mimicking the normal cardiac conduction cycle.

There has been considerable research into the most effective pacing mode in terms of just how it mimics the normal conduction pattern and maintaining that same sequence of events (cardiac synchrony), which is closely associated with the mechanical events of the cardiac cycle (systole and diastole).

There is no clear guidance on the programming of these devices in light of emerging evidence on the haemodynamic effects of long term ventricular pacing.

The motivation for undertaking this research was to establish the most effective programming strategy in pacemakers that are implanted for one of the main cardiac conduction abnormalities – sick sinus syndrome (SSS). Research has highlighted the emerging effects of long term ventricular pacing; ensuring that the benefits of maintaining stable heart rates is not diminished by the deleterious effects of long term ventricular pacing on cardiac function, and utilising some of the technologies to reduce the amount of inappropriate pacing.

1.2 Research Environment

County Durham and Darlington NHS Foundation Trust is a secondary care organisation dealing with the acute and community health care needs of a population of around 600,000 across County Durham, Darlington, North Yorkshire, Tees Valley and South Tyneside.

There are two acute hospital sites and a number of community facilities covering a large geographical area.
The two acute hospital sites are Darlington Memorial Hospital (DMH) in the South of the County and University Hospital of North Durham (UHND) covering the Northern region of the county.
Bishop Auckland Hospital (BAH) was downgraded from an acute hospital to a community facility in 2008 and is positioned approximately mid-way between the two acute sites.
Both of the current acute hospital sites have Cardiac Angiography Units that perform coronary angiography and pacemaker implantation. These were both opened in 2004 with pacemaker implantation starting in 2006.
Around 250 primary (new) pacemaker implants are carried out per year in these units and there around 50 pacemaker replacements per year.

1.3 Research Purpose

The use of artificial pacemakers via an endocardial approach was introduced in 1958 by Seymour Furman in the USA.(Hemel and Wall 2008)

This technology revolutionised the lives of patients with conduction abnormalities leading to chronic bradycardias. SSS is one of the commonest causes of symptomatic bradycardias. There has been much debate about the most appropriate choice of device or the programmed mode. National and international guidelines on the appropriate device prescription for a cardiac rhythm disturbance were published and updated most recently in 2008. (Epstein, DiMarco et al. 2008)

Although there are clear implantation criteria available in these national and international guidelines on the type or mode of device implanted for SSS, this does not offer guidance on the use of programmable algorithms or specific device features.

There is considerable research evidence that long term right ventricular pacing (RVP) can have a deleterious effect on cardiac function, especially in patients with pre-existing cardiac functional impairment, the purpose of the research is to evaluate the current and historic implanting and programming practice in light of this evidence.

There is also evidence from the major devices trials that ventricular pacing can increase the prevalence of the development of atrial fibrillation.

This project reviewed data on all devices implanted in the 2 implanting units in County Durham and Darlington NHS Foundation Trust (CDDFT with pacemaker implantation being undertaken at University Hospital of North Durham and Darlington Memorial Hospital) and the devices that have been repatriated from other device implant centres that are followed up and programmed at the pacemaker clinics in CDDFT.

The research sought to evaluate the programming rationale in light of the degree of right ventricular pacing per year and the percentage burden of atrial fibrillation per year for patients with a primary implant reason of SSS.

It is anticipated that this will offer an evidence base for the most effective strategy for device prescription and programming in this patient population, and hence lead to departmental protocols to ensure patients receive the most appropriate device and the most effective programming regime.

1.4 Research Outline

SSS refers to an impairment of the automaticity of the sinus node, also known as sinus node dysfunction. The sinus node initiates an impulse which is then propagated across the atria and down the ventricles thus enabling the mechanical events that cause cardiac contraction and relaxation. The cause is often conduction tissue fibrosis but can be post-surgical or drug induced (Bennett 2006 p. 154).
Implantation of a pacemaker is the treatment of choice in patients with symptomatic SSS without a reversible cause.

The normal intrinsic cardiac conduction starts within a dense collection of pacemaker cells which initiate impulses and spontaneous electrical activity – this area is known as the sinoatrial node and is located in the right atrium at the junction of the superior vena cava (Ellenbogen and Wood 2008 p: 1). SSS is the term used to describe a failure of this area of specialised cells automaticity, regularity, rate or a combination of aetiologies.

Pacemakers seek to mimic part or all of the electrical conduction system of the heart ensuring activation of the mechanical events of normal atrial and ventricular systole and diastole. **Chapter 2** provides a clinical overview of the electrical cardiac conduction system and some of the major conduction abnormalities that would warrant permanent pacing. **Chapter 3** gives a basic overview of pacemaker components and function.

Physiological or atrial based pacing is the mode of recommendation for patients with a primary indication of SSS.

In pure SSS a single chamber atrial pacemaker provides right atrial pacing; the right atrium is the chamber from which sensing takes place and the mode of operation is inhibition of artificial stimulus upon a sensed event – this mode of device is called AAI (Fig.4.2.1). This type of device is indicated "*in the management of sick sinus syndrome in patients in whom, after full evaluation, there is no evidence of impaired atrioventricular conduction; in this situation, single-chamber atrial pacing is appropriate*" (National Institute for Clinical Excellence 2005)

The rationale here is that the electrical disturbance is isolated to the sinus node only and that normal conduction takes place beyond this point. The statement *"after full evaluation"* requires an assessment of the likelihood of failure of normal atrioventricular conduction to be undertaken. However there are no absolute predictors of future development of atrioventricular block (AVB) with time, given that a pacemaker lasts 7-10 years until battery depletion.

In clinical practice, patients with SSS rarely receive a single chamber atrial pacemaker in favour of a dual chamber device which has the ability to both sense and pace the right atrium and the right ventricle in a synchronous way. If we consider the UK national implanting practice it is clear that single chamber atrial pacing is rare, accounting for less than 1% of all new pacemaker implants (Cunningham 2009) . **Chapter 4** deals with the local and national context for device prescriptions and implanting behaviours

Clinical practice in the UK is to avoid the use of single chamber atrial pacemakers in patients with SSS as the primary mode of choice, despite National Institute for Clinical Excellence (NICE) recommendations.

The rationale for the deviance from recommended practice is the potential for the development of AVB in patients with SSS, which would require further premature intervention to upgrade the system to dual chamber. Research undertaken in Denmark comparing single chamber atrial pacing to single chamber ventricular pacing suggested "*The main argument for using DDD pacing is the concern, that the patients will develop symptomatic atrioventricular (AV) block. In the Danish AAI/VVI trial, the risk of AV block was approximately 0.6% per year*" (DANPACE 2009).

In a prospective study looking at patients with a pacemaker indication of SSS, 225 consecutive patients with a primary pacemaker indication of SSS were randomised to either single chamber atrial paced devices or single chamber ventricular paced devices. Of the 110 patients in the pure atrial paced device cohort, four went on to develop grade 2 or grade 3 atrioventricular block. This would represent, in this small sample, a 4% incidence of atrioventricular block overall with an annual incidence of 0.6% per year (also noted in the DANPACE study). (Andersen, Nielsen et al. 1998)

It is also well established that ventricular pacing has a deleterious effect on cardiac function; right ventricular pacing has the effect of inducing an abnormal cardiac activation sequence resulting in left bundle branch block (LBBB) which can cause a degree of left ventricular remodelling. Le Clercq et al reported this remodelling as thinning of the areas of myocardium which were activated earlier than normal and a characteristic thickening of the areas which were activated later than normal. The clinical picture of such patients is one of reduced systolic function, increased hospital admissions, worsening of CHF and increased incidence of AF (Leclercq, Gras et al. 1995) . Further analysis of research data relating to the effects of long term RV pacing is provided in **Chapter 5.**

The National Pacemaker and ICD (implantable cardiac defibrillator) Database managed by Central Cardiac Audit Database (CCAD) (Cunningham 2009), shows that the majority of devices implanted in the UK in 2009 are dual chamber devices with or without rate responsive functionality. SSS is also shown to be the commonest primary indication for pacemaker implantation running at 27%, yet it is a contradiction that less than 1% of patients receive a pure single chamber atrial based pacemaker.

There have been multiple randomised clinical trials examining the various prescribed pacemaker modes and their outcomes in terms of mortality, quality of life, incidence of atrial fibrillation and stroke. A review of the major clinical trial is detailed in **Chapter 6.**

There are more recent devices on the market that effectively operate as single chamber atrial based pacemaker systems but with a back-up mode of dual chamber atrioventricular synchronous pacing – they are classed as minimal ventricular pacing devices. These devices function in such a way as to promote intrinsic atrioventricular (AV) conduction whilst only reverting to dual chamber synchronous pacing in the presence of confirmed AV block (Milasinovic1, Tscheliessnigg et al. 2008; Medtronic Incorporated 2010; Sorin Group 2012). However the recent implanting information from CCAD (more recently taken over by the National Institute for Cardiovascular Outcomes and Research) describes a less than 0.5% rate for these devices. This may in part be explained by the cost of these devices, or implanting centres may use dual chamber synchronous devices and programme the atrioventricular delay longer than is physiological in order to promote normal AV conduction. Another explanation may be miscoding of the device into CCAD.

In **Chapter 7** an appraisal of the programming strategies available to reduce RVP was undertaken along with analysis of existing evidence of the efficacy of these pacing strategies.

The practice within the pacemaker services in CDDFT is to implant a mixture of dual chamber synchronous pacemakers and minimal ventricular pacing devices for patients with an indication of SSS. Current practice is somewhat ad hoc with a mixture of dual chamber devices with atrioventricular delay ‘programmed long’, and /or the addition of a ‘search algorithm’ which automatically extend the atrioventricular delay to encourage normal conduction, or minimal ventricular pace devices.

The rationale of extending AV delay relates to the period of time the atrial impulse is delayed before conduction down to the ventricles, the physiological importance of this is to allow optimal ventricular filling prior to systole. Artificially extending this delay can be non-physiological. The physiological effects of these algorithms needs further review and this is also included in **Chapter 7**.

1.5 Ethics Considerations

Ethical approval has been received from both the host NHS organisation sponsoring the research and the academic institution overseeing the project.

A full summary of the research proposal and protocol was also submitted to County Durham and Darlington NHS Foundation Trust Research Department, which recommended a full submission via the Integrated Research Application System. The research project was approved on 18th October 2011 by the Research Review Board Chair of County Durham and Darlington NHS Foundation Trust. (Appendix 1)

As part of the standard requirement for those undertaking research projects the author attended and completed a course entitled an Introduction to Good Clinical Practice (GCP) – A practical guide to ethical and scientific quality standards in clinical research, presented by National Institute for Health Research on 31st August 2011. (Appendix 2).

A full summary of the research proposal and protocol was submitted to Durham University for ethical consideration in June 2011. As this project does not require the enrolment of participants it did not therefore require a full committee review by the School of Medicine and Health Ethics Sub-Committee. Ethical approval was granted by Chair's action on 30th June 2011. (Appendix 3)

1.6 Research Methodologies

- The author of this thesis has in excess of 20 years clinical experience of implantable cardiac device management and completed both nationally (Heart Rhythm UK) and internationally (International Board of Heart Rhythm Examinations) accredited cardiac device specialist examinations. Much of that technical and clinical knowledge has been applied to the development of this project.
- Review of current literature related to device prescription, inspecting national and international recommendations and the clinical evidence base.
- Review of research into the effect of ventricular pacing on cardiac function, incidence of arrhythmias, related hospitalisations and quality of life.

- Review of the research data and randomised clinical trials detailing outcomes in patients with differing pacing modes.
- Appraisal of the pacemaker algorithms of the companies providing devices for ventricular pace avoidance including minimal ventricular pacing, MVP™, SafeR™ and AV delay search algorithms.
- An audit of all pacemakers implanted in CDDFT since the service commenced in June 2006, covering a period to June 2011 (5 years), and all repatriated patients from other implanting centres. This audit shows how the local implanting services mirror the national picture in-line with the CCAD reports. The percentage of patients implanted with a primary indication of SSS, and the types and modes of devices implanted was identified. The data further shows the efficacy of the differing algorithms for ventricular pace avoidance to identify the optimal clinical outcome in terms incidence of atrial fibrillation and the overall percentage of ventricular pacing.

1.7 Research Objectives

Identify the demographical data on the pacemaker population in County Durham and Darlington. In this population, further identify the primary indication for pacing and specifically the percentages of patients with SSS and the development of AV block.

Detail the historical use of single chamber atrial base pacemaker systems, the use of dual chamber devices and minimal ventricular pace devices.

Appraise the existing evidence to support a ventricular pace avoidance strategy.

Identify evidence to support a particular implanting and programming strategy over another. Identify the mode of device and programming strategy that is most effective in producing a statistically significant reduction in RVP pacing whilst protecting AV conduction.

Obtain evidence from the pacemaker data review on any effect of differing mode strategies or algorithm programming on percentage of RV pacing and burden of atrial fibrillation.

Use data analyses to identify clinically significant differences in terms of the percentage of RV pacing of the differing algorithms, and identify the overall atrial fibrillation durations and correlate with the amount of RV pacing.

Based on the evidence, what is the most effective programming strategy in patients with SSS in terms of reduced inappropriate right ventricular pacing, and is there a correlation between this reduced right ventricular pacing and the incidence of atrial fibrillation?

1.8 Planned Project Time-Lines

The planned project time-lines were generally reached on schedule, as indicated below.

Literature review covering Chapters 1-7 including refinement of the research question took approximately 6 months from February – August 2011.

The systematic review/audit of all pacemaker implants commenced from August 2011 onwards. Data collection was be expected to last 3 months and included all 3 follow-up centres in County Durham and Darlington. The sample size was expected to be around 1500 patient records, around 400 (27% expected rate of SSS nationally from CCAD national data) likely to be patients with an indication of SSS.

The data analysis phase commenced with the development of datasets, and analysis of the data sources that added evidence to the research question. Statistical analyses and training in the use of the statistical software (Statistical Packages for the Social Sciences –SPSS 19) and data interpretation was expected to take up to 4 months.

The remainder of the final year dealt with the writing up of the thesis beyond the literature review to include data analysis and validation, assessing data against the research questions, development of conclusions and discussions based upon the evidence, appraisal of the evidence and identification of any weaknesses in the methodology and conclusions drawn

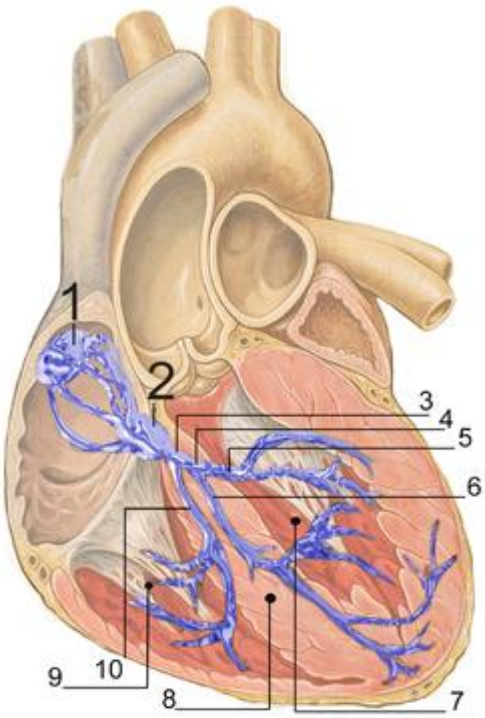
Chapter 2 – The Cardiac Electrical Conduction System

2.1. Anatomy of the Cardiac Conduction System

The American College of Cardiology (ACC), American Heart Association (AHA) and Heart Rhythm Society (HRS) updated guidelines "Device Based Therapy of Cardiac Rhythm Abnormalities"(Epstein, DiMarco et al) in 2008. This document developed clinical decision making tools based on the patients presenting symptoms and rhythm abnormalities.

Patients' symptoms and rhythms were stratified into classes for the two main cardiac conduction abnormalities, sinus node dysfunction and atrioventricular node dysfunction.

To understand the principles and concepts of cardiac pacing, a review of these electrical disturbances in relation to the anatomical sites of these abnormalities and the cardiac conduction pathways is essential. (Ellenbogen and Wood 2002 pp 1).



1. Sino-atrial node
2. Atrioventricular node
3. Bundle of His
4. Left Bundle Branch
5. Left posterior Fascicle
6. Left Anterior Fascicle
7. Left ventricle
8. Ventricular Septum
9. Right Ventricle
10. Right Bundle branch

Fig 2.1.1. Electrical conduction system of the heart (http://en.wikipedia.org/wiki/Electrical_conduction_system_of_the_heart) *permission granted under creative commons attribution.

1. Sinoatrial node (SAN): This is an area of specialised cells located at the junction of the right atrium and the superior vena cava. It has a rich blood supply and abundance of autonomic innervation. This area of specialised cells

is sometimes referred to as the “natural cardiac pacemaker” - the normal resting rate of the SAN depolarisation or impulse initiation is 60-100 beats per minute (bpm).

2. Atrioventricular node (AVN): This forms the electrical bridge between the atria and the ventricles situated within the interatrial septum. The AVN, like the sinoatrial node, is an area of highly innervated cells with a rich blood supply.

   Having received impulses from the SAN, the AVN delivers impulses to the Bundles of His. If the AVN fails to receive an impulse from the SAN, in the case of some forms of sinus node dysfunction or SSS, the AVN can initiate impulses in isolation of receipt of stimuli at a rate of 40-60 bpm. This allows for maintenance of cardiac conduction in the presence of failure of the SAN, rather like a back-up electrical generator but at a slower rate.
3. Bundle of His: Purkinje fibres, made up of specialised cardiac muscle cells, emerge from the distal area of the AV node to form the His bundle. Unlike the SA and AV nodes, the His bundle is less innervated although it still has a rich blood supply.
4. Bundle branches: an extremely complex network of interlacing Purkinje fibres make up the bundle branches. The branches form “electrical roads” into the myocardium of the ventricles with the left ventricle supplied by two branches; anterior and posterior fascicles, and the right ventricle with a single branch. The bundle branches are a source of rapid electrical conduction causing almost simultaneous ventricular activation. (Ellenbogen and Wood 2008 pp:1-4)

The electrical impulse arises in the SAN situated in the right atrium. This impulse is then propagated to the left atrium and to the AVN where it is held for a brief period of time (100-200ms) before travelling down the Bundle of His to the branches supplying the left and right ventricles. This electrical circuit stimulates the mechanical events of atrial and then ventricular depolarisation and systole. (Rogers 1999; Ellenbogen and Wood 2008 p.46)

2.2. Electrical Sequence Related to the Electrocardiogram

The electrocardiogram is a graphical representation of the electrical signals produced by the heart during a single cardiac cycle.

This signal can be detected from the body surface using electrodes attached to an electrocardiogram recorder or monitor.(Julian, Cowan et al. 1998 p: 11)

The initial electrical deflection is the P wave and this represents the spread of electrical activation through the atria. (Topol and Califf 1998 p: 1550)

The PR interval represents the time taken for the impulse to propagate over the atria, AV node and His bundle.

The QRS complex represents the spread of depolarisation through both ventricles.

Finally the T wave represents ventricular repolarisation. (Julian, Cowan et al. 1998 p:14)

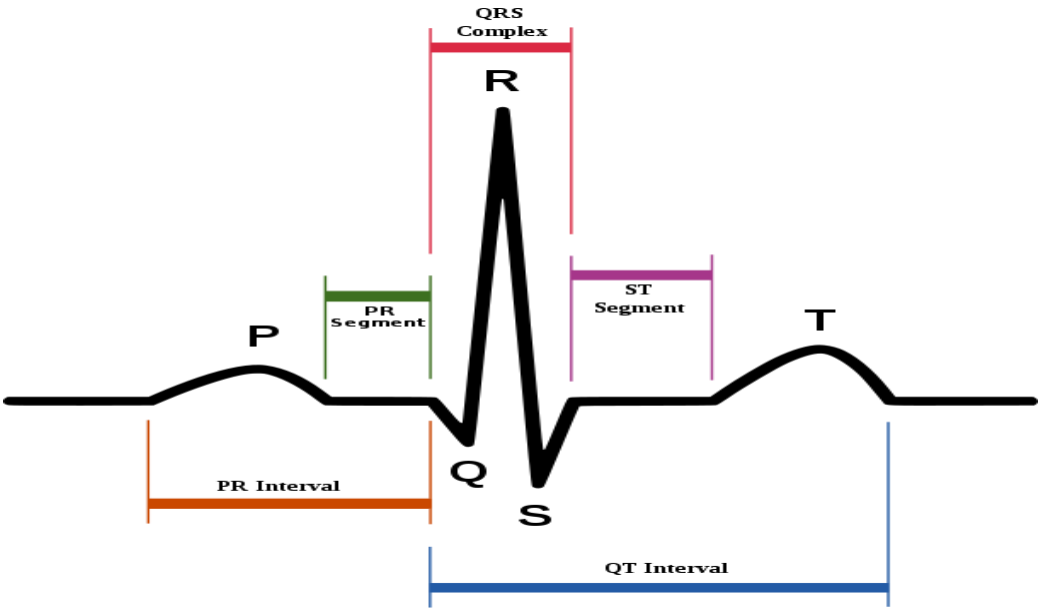


Fig 2.2.1 Electrocardiagram Components

http://en.wikipedia.org/w/index.php?title=File:SinusRhythmLabels.svg&page=1, (with permission)

2.3. Electrical Mechanical Sequence

The electrical sequence is the precursor to the mechanical events that allow the heart to contract and relax (National Heart Lung and Blood Institute 2011)

Atrial depolarisation starts from the SAN and conducts radially through the atria taking about 0.1 seconds. This spread of electrical activity forms the P wave on the surface ECG and causes atrial contraction, pushing blood into the lower pressure ventricular chambers.

Conduction in the AV node is slower, allowing for optimal ventricular filling; as the atria begin to relax, a spread of electrical depolarisation from the His Bundle at the top of the ventricular septum spreads rapidly down the bundle branches to the Purkinje fibres and all parts of the ventricles in approximately 0.08 -0.1 seconds. This spread of electrical activity forms the QRS complex on the surface ECG and causes ventricular contraction (systole).

The final part of the electrical cycle is repolarisation of the cardiac cells corresponding to ventricular relaxation (diastole) and the T wave deflection on the surface ECG.(Barret, K.E. 2010)

2.4. Cardiac Conduction Abnormalities

Sinus node dysfunction relates to a malfunction of the SAN. This can result in failure to initiate an impulse, intermittently or persistently, or at a rate slower than physiologically appropriate. This can manifest as sinus bradycardia, sino-atrial block, sinus arrest and bradycardia-tachycardia syndrome (atrial flutter, fibrillation and paroxysmal atrial tachycardias).

In the absence of a preceding impulse from the sinus node, the cardiac conduction system has a “back-up” electrical escape function which is initiated by specialised tissue located in the atrioventricular node, allowing for continuation of ventricular depolarisation and consequential ventricular systole. This rhythm it at a slower rate, typically around 40-50 beats per minute and lacks any chronotropic regulation (autonomic heart rate control).(Camm and Fei 1996; Bennett 2006 pp:16-18)

SSS is an umbrella term used to describe all the rhythm abnormalities detailed that manifest themselves as a result of a failure or malfunction of the SAN. As a result of this syndrome there are a large variety of symptoms from vague headaches, palpitations and chest pains to blackouts, dizziness and nausea.

Atrioventricular block describes an impairment of the signal between the atria and the ventricles and comprise 3 types:

First degree AV block – delay in the impulse travelling from the atria to the ventricles in excess of 200ms.

Second degree AV block – gradual lengthening delay in the impulse between the atria and the ventricles until one of the impulses is blocked (Mobitz type I). Further development of AV block results in every alternate atrial impulse being conducted to the ventricles – a 2:1 association of atrial impulses to every ventricular response (Mobitz type II)

Third degree AV block – no association between the electrical impulses of the atria (SA node) and the ventricular conduction, hence the ventricular escape "back-up" conduction circuit produces ventricular depolarisation. (Bennett 2006 pp: 141-146)

2.5. Indications for Cardiac Pacing

The implantation of a permanent cardiac pacemaker is an important decision and should be based on solid clinical evidence.

This is an operative procedure involving the placement of electrodes and leads into the heart. Once placed the reversal of this lead placement or removal attract significant clinical risks (further discussion on implant process in Section 3.4).

The American Heart Association (AHA) in joint consultation with the American College of Cardiology (ACC) first developed implantation criteria in 1984 which was most recently updated in 2008 (Epstein, DiMarco et al 2008).

These guidelines must be seen in the context of the patients' presentation and the ever evolving technological and clinical science advancement (see Section 4.1 Prescription guidelines).

The AHA and ACC developed a classification matrix depending on the clinical presentation, symptoms, type of rhythm disturbance and the clinical evidence base.

Permanent pacemaker implantation is undertaken in the absence of any reversible cause of the bradycardia.

2.5.1. Temporary Cardiac Pacing

Temporary pacing therapy is used when the bradycardia is considered secondary to an acute event: commonly this would be an acute myocardial infarction. This involves either a temporary or permanent impairment to the conduction system due to ischemia of the SAN tissues or AVN tissue following coronary artery occlusion. This may

reverse with reperfusion and should be monitored after the acute event to assess if normal SAN or AVN activity resumes.

Other potential reversible causes of bradyarrhythmias includes neurological deficits affecting the carotid sinus which regulates the brains control of heart rate, some infections which can cause transient bradyarrhythmias such as Lymes disease, endocarditis or myocarditis and certain medications can cause or precipitate cardiac conduction problems.(Ellenbogen and Wood 2002 pp: 41)

Temporary cardiac pacing can be external or intracardiac. External pacing or transcutaneous pacing, uses large electrodes placed on the patients' chest delivering around 0.1 Joules of energy to the chest surface – although not necessarily painful, prolonged external pacing can become uncomfortable.

Intracardiac temporary pacing requires the placement of an electrode to either the epicardial or endocardial heart muscle surface in much the same way as permanent cardiac pacing (see Section 3.4), this electrode is attached via an electrical conducting lead to an external, battery operated pulse generator capable of delivering varying electrical outputs depending on the degree of energy required to pace the heart and at varying rates depending on the levels of support the heart requires.

2.5.2. Permanent Cardiac Pacing

A permanent pacemaker has leads with electrodes placed into the heart with the pulse generator inserted in the subcutaneous tissue of the upper left or right chest, in the pre-pectoral region for adults.

The implantation of a permanent pacemaker system has a strong and well established evidence base in terms of its efficacy (Vardas, Auricchio et al. 2007) and in absence of any reversible cause it remains the treatment of choice in symptomatic bradyarrhythmias. (Pacemaker implantation Section 3.4)

Chapter 3 – The Cardiac Pacemaker

3.1. Cardiac Pacing Concepts

The first totally implantable pacing system was utilised by Senning in 1958: since then the use of pacemakers has seen a rapid clinical and technological evolution. (Topol and Califf 1998)

The fundamental effect of cardiac pacing is to promote and maintain, as near as possible, the normal electrical conduction of the intrinsic cardiac electrical circuit. This is achieved by the placement of electrodes, generally inside the heart, that can stimulate the cardiac tissue.

These electrodes are connected by leads to a small pulse generator which is placed under the subcutaneous tissue of the chest wall. The pulse generator delivers electrical stimuli via the leads to the heart at appropriate intervals, such that it mimics the normal intrinsic electrical sequence.

The artificial stimulus causes depolarisation of the excitable cardiac tissues at the interface of the electrode. Commonly there is an electrode in the right atrium and another in the right ventricle. In dual chamber synchronous pacing the atrial artificial stimulus causes atrial depolarisation, there then follows a brief delay of around 150-200ms, mimicking the time taken for the impulse to spread across the atria and reach the AV node. This period of time is followed by an artificial ventricular stimulus which causes ventricular depolarisation. (Ellenbogen and Wood 2002 pp: 299-303; Ellenbogen and Wood 2008 p: 299)

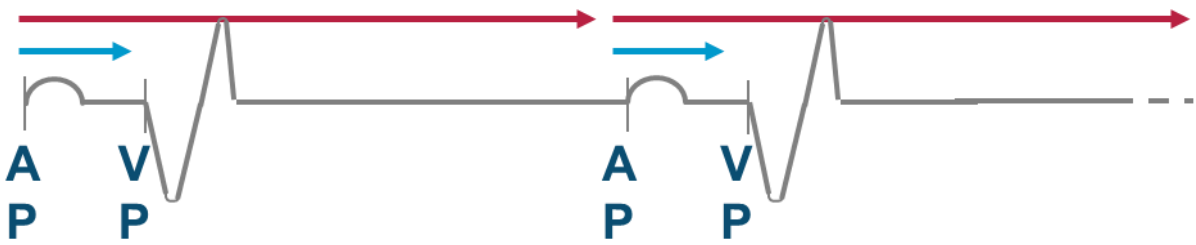


Fig 3.1.1 ECG Representation of Synchronous Atrioventricular Pacing

AP=atrial pace, VP= ventricular pace. Red arrow=pacing rate, blue arrow=AV delay.

(Medtronic Inc. CorePace (2008) educational multimedia power point presentations-permission granted).

The electrical representation of pacing can be seen above. AP causes a sharp upward deflection which is the electrical stimulus from the pacemaker, producing atrial depolarisation which is represented by the P wave. The **blue** arrow shows the brief timing delay (AV delay) programmed into the pacemaker allowing for the depolarisation to spread across the atria to the AV node and His Bundle (PR interval in the normal intrinsic cardiac conduction), before the second sharp deflection from the pacemaker stimulus, VP, causing depolarisation of the ventricles. The overall timing, shown by the **red** arrow, dictates the heart rate, the time from AP to AP. This is nominally programmed at 60 pacemaker pulses per minutes to mimic the general resting heart rate of 60 beats per minute.

Fig. 3.1.1 represents the fundamental concept of atrioventricular synchronous pacing: further discussion follows detailing how and when the pacemaker operates.

3.2. Cardiac Pacemaker Function

A modern day cardiac pacemaker has a number of discrete operating functions:

- The ability to stimulate myocardium such that "*an artificial pacing stimulus excites cardiac tissue by the creation of an electrical field at the interface of the stimulating electrode and the underlying myocardium"* (Ellenbogen and Wood 2008 p: 46)
- **Pacing:** This electrical stimulus causes action potentials propagating away from the site of the stimulus. The source of this electrical stimulus is the power source in the pacemaker and the delivery of this stimulus is via a conduction lead to the point of delivery at the tissue electrode interface of the myocardium.
- **Sensing:** This same electrode/myocardium interface needs to be able to detect native intra-cardiac electrical signals in order to prevent the delivery of an artificial stimulus.
- **Timing:** A timing circuit comprises a series of "clocks" that operate depending on the input (sensed intrinsic cardiac signal) and output circuitry (pacing- artificial electrical stimulus). The device also has timing intervals for refractory periods, blanking periods and atrioventricular delays. These periods

allow for the requirements of repolarisation at a cellular level and the physiological requirements of mechanical cardiac actions.

There are also rate limiting circuits to deliver pacing stimuli up to a maximum rate and a safety mechanism to prevent pacemaker "runaway", an effect that can allow pacemakers to follow apparent intrinsic sensed events at higher than physiological rates.

These timings essentially mimic the physiological delays in the electrical conduction pathways that allow for atrial filling, atrial systole, ventricular filling and ventricular systole. Blanking periods mimic refractory periods allowing for the cardiac cells to repolarise.

3.2.1. Pacemaker Components

- **Communication:** Telemetry coil – this allows for interrogation of the device via an external programmer. It can also allow for external interaction with the device such as reprogramming features – rate, intervals and algorithms. The device has a degree of storage memory allowing for rhythm information with intracardiac ECG's to be stored for scrutiny by clinicians.
- **Power source**: a lithium iodine chemical battery to power the internal electrical components and the cardiac stimulation.
- **Rate adaptive sensors**: the sinus node augments the heart rate in response to biological need and under the influence of the autonomic nervous system (chronotropic response). In the presence of impaired sinus node function this augmentation of heart rate is disturbed. Much of the need for heart rate response is initiated by exercise or exertion. Within pacemakers small sensors are built in -these detect movement or vibration and increase the pacing rate accordingly. There are other more physiological sensors that detect breathing rate and can blend with movement sensors to provide more sensitive rate augmentation. This function is known as rate response and often denoted by the letter R after the pacing mode, e.g. DDDR.

  (Camm and Fei 1996; Ellenbogen and Wood 2008 pp:102-109)

Fig 3.2.1 – Permanent Pacemaker (scale is approximately 110% of actual)

Medtronic, Inc- CorePace training slides with permission (May 2011)

3.3. Pacemaker leads

The pacemaker leads generally have a greater clinical longevity than the pacemaker. On average the pacemaker battery life is 7-10 years. The battery is within the pacemaker which is a hermetically sealed system, the whole pacemaker is replaced as the battery starts to deplete.

This involves removing the electrical pin end of the pacemaker lead(s) from the pacemaker via small grub screws which fix the leads into the header of the pacemaker completing the electrical circuit.

The leads remain in the heart, with a new pacemaker attached with a further 7-10 year battery life expectancy.

The leads inside the heart become fibrosed within the muscle tissue of the heart, this makes it not only very difficult to remove leads but potentially dangerous with a 0.8% risk of death and 1.9% risk of major complication (Ellenbogen and Wood 2008 pp:265)

Due to the generally elderly population of pacemaker patients, the original leads are expected to last the existing lifetime of the patients, however pacemaker implants in the younger patient carry a significant increase in the likelihood of requiring new leads at some point in their pacemaker management;

Pacemaker leads have the following components:

- **The electrode:** this is the distal part of the lead that is in contact with the cardiac tissue. The fixing method of the electrode to the cardiac tissue may take a number of different forms such as silicone tines which passively anchor to the cardiac muscle / atrial tissue or small retractable screws which actively fix the electrode to the cardiac tissue. The interface of the electrode at the tissue is important in ensuring as small a current density is ensured over a large surface area. This can be achieved with porous tips with edges and ridges of high current density.
- **The conductor:** this refers to the wires inside the lead that connect the pacemaker, sited just below the clavicle, to the electrode in the heart, allowing the conduction of electrical stimuli produced in the pacemaker to the cardiac tissue. The conductor is made up of a nickel alloy (good conducting properties and less prone to corrosion) formed in multiple strands coiled along the length of the wire. In a unipolar lead this is a single coil conductor, in a bipolar lead this is a dual coil conductor. The characteristics of the conductor must allow for flexing and movement at a rate of 60-70 beats per minute minimum for the lifetime of the lead (on average 15-25 years).
- **Insulation:** this is the material covering the conductor coils from the point of insertion into the pacemaker through to the electrode at the cardiac muscle interface. The material used as the insulator can be either silicone or polyurethane: more recent lead designs use a blend of both materials. The insulator protects the conductor and ensures no current drain into the surrounding tissues.
- **Connectors:** these are the pins that insert into the head of the pacemaker completing the electrical circuit. These are now standard lead connectors such that one manufacturer's leads will fit into another manufacturer's pacemaker. (Ellenbogen and Wood 2008 pp:78-96)

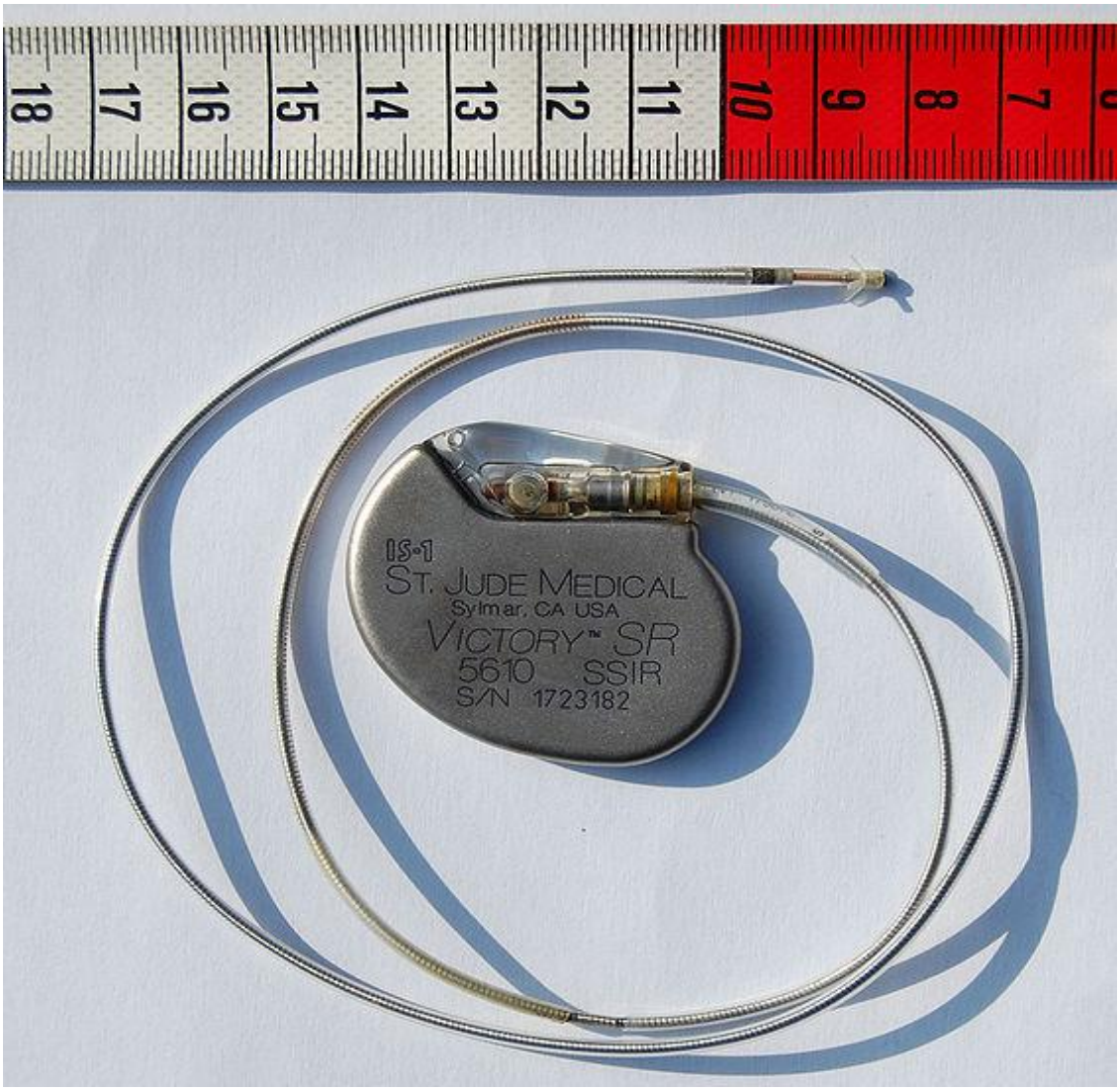


Fig 3.3.1 Permanent pacemaker and Passive Fixation Lead – black rounded tip at end of lead is the electrode, small thin tines above the electrode are the fixing mechanism anchoring the electrode to the trabeculae of the heart muscle. Coils can be seen of the conductor and this is covered by a see-through silicone insulator. The circuit is completed by the electrical pin which fits into the header, which is also see through, at the top of the pacemaker. There is a small circle of silicone at the distal pin in the header – this is the point of insertion for a small screw-driver to fix the connector pin in place. http://en.wikipedia.org/wiki/File:St_Jude_Medical_pacemaker_with_ruler.jpg (with permission)

3.4. Pacemaker Implantation

The implantation procedure is undertaken in either an operating theatre or more commonly in a cardiac angiography unit, with sufficient air changes required for a sterile procedure.

There must be either a fixed or mobile image intensifier (x-ray machine) as the lead insertion and placement must be performed under fluoroscopy.
The patients' electrocardiogram (ECG) must be monitored to confirm that the artificial electrical stimulus is capturing the heart tissue and resulting in a paced rhythm on the surface ECG.
The procedure is carried out by an implanting physician, generally a consultant cardiologist or specialist registrar in cardiology, under sterile conditions.
The pre-pectoral region of the chest wall is prepared (below the collar bone), usually on the left hand side unless the patient is left handed. A local anaesthetic is administered; general anaesthesia is not usually indicated in adults for first implants.
An incision in the area of the subclavian or more superiorly the cephalic vein is made, and either a direct cut-down to the vein or a needle is used to access the vein (Seldinger technique) (Chiariello 1978).
The pacemaker lead is inserted into the vein and visually guided, with the aid of fluoroscopy, to the right atrium via the superior vena cava.
If two leads are to be inserted, the ventricular lead is often inserted first via the tricuspid valve between the right atrium and the right ventricle and generally placed into the apex of the right ventricle.

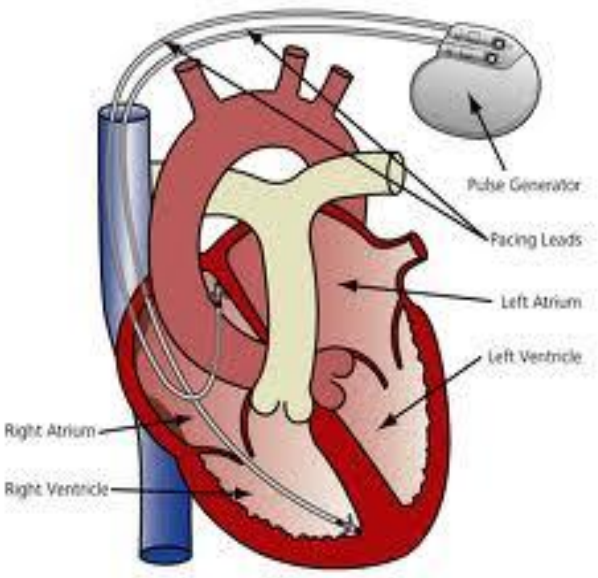


Fig 3.4.1 Implantation of Permanent Pacemaker
(www.understandingatrialfibrillation.com) *permission sought 2011 and 2012 – site unobtainable.

The atrial lead is then inserted via the subclavian or cephalic vein and visually guided into the right atrium where it is placed into the right atrial appendage (a small redundant fold in the RA). Due to the lack of dense muscle or trabeculation to passively anchor the lead in the atrium, operators tend to prefer an active screw mechanism that is deployed out of the distal electrode of the lead.

A pocket is manually separated in the pre-pectoral region between the muscle and the sub-cutaneous tissue to house the pacemaker. The leads are then tested to assess the size of the signal detected via the leads and the degree of energy required in order to stimulate the heart muscle.

- Sensing test: this test assesses the size of the signal from electrode at the end of the lead. This is called the intra-cardiac signal, and it relates to the intrinsic cardiac stimulus that is detected at the electrode interface. This signal is important; all pacemakers respond to the detection of an intrinsic signal by inhibiting the need for an artificial stimulus from the pacemaker.
  The optimal ventricular signal should be 3-30 millivolts at implant, and the atrial signal 1-6millivolts (Ellenbogen and Wood 2008 pp:70)
- Stimulation threshold test: "*cardiac pacing involves the delivery of a polarizing electrical impulse from an electrode in contact with the myocardium with the generation of an electrical field of sufficient intensity to induce a propagating wave of cardiac action potentials"* (Winfree 1990). This statement from A.T.Winfree offers the fundamental principles of cardiac artificial stimulation and the importance of the stimulation threshold test. At implant, the clinical team needs to assess the minimal amount of energy required to initiate the propagation of the electrical wave of action potential that will precede the mechanical event of systole. This needs to be sufficient to initiate the action potential but not so large as to drain the battery of the device shortly after implant. Ideally, this is <1.0 volt over a fixed pulse duration of 0.5milliseconds. (Ellenbogen and Wood 2008 p:49)

Once satisfactory electrical parameters are confirmed, the leads are sutured above the venous entry to the chest muscle, the connector pins are inserted into the pacemaker

header and screwed into contact, and the pacemaker is placed into the pocket in the pre-pectoral region of the chest. The wound is then sutured and dressed.

Chapter 4 – Pacemaker Prescription

4.1. Prescription Guidelines

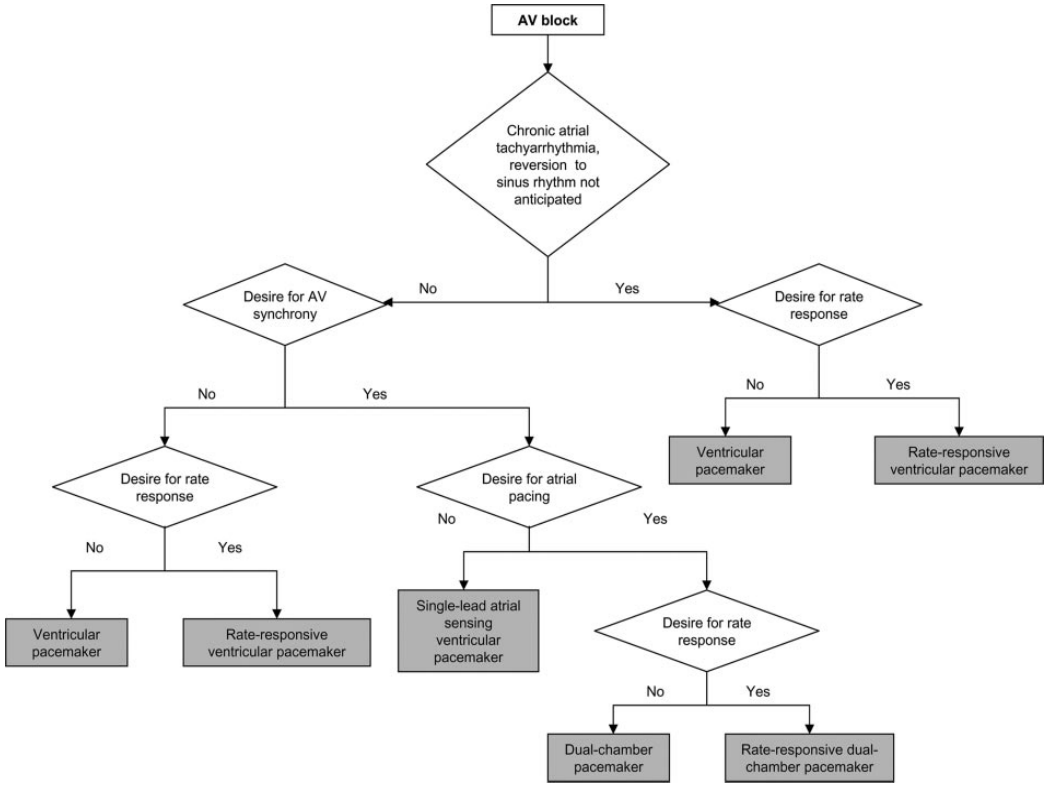
As previously described ACC/AHA/HRS updated 'The Guidelines for Device Based Cardiac Rhythm Abnormalities' in 2008. The decision to pace is based on the evidence base and ranking depending on that weight of evidence such that data derived from multiple randomised control trials involving large numbers of individuals is ranked at Level A. Data derived from a limited number of trials and comparatively small number of patients or from observational data was ranked a Level B, Level C was designated for evidence based on consensus of experts being the primary source of evidence. (Epstein, DiMarco et al. 2008)

Furthermore the indication for cardiac device therapy was classified depending on a benefit versus risk ratio.

Symptomatic bradycardia refers to a documented bradyarrhythmia that has a direct correlation to symptoms such as transient dizzy spells, syncope or pre-syncope.

There are International Guidelines "A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines"(Epstein, DiMarco et al. 2008) that give classifications of conduction abnormalities and symptomology together with an evidence base to assist clinicians in identifying patients requiring pacing.

The following schematics offer clinicians a decision making tool to assist in device prescription.



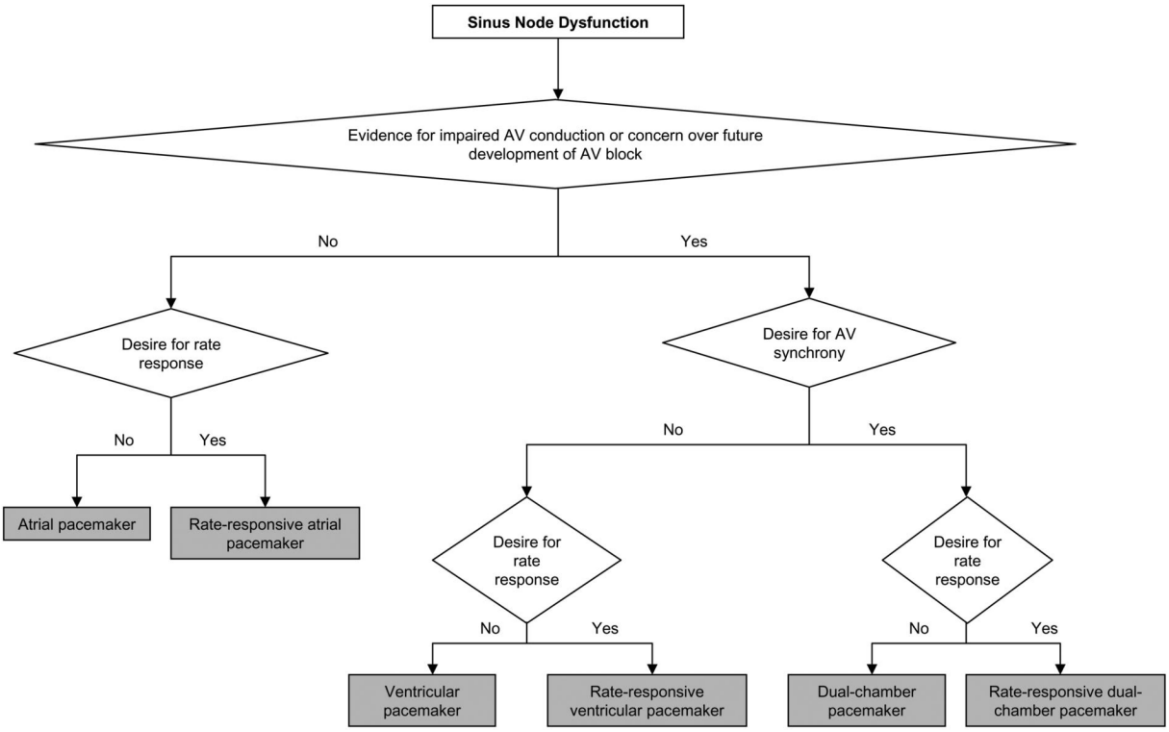


Fig. 4.1.1&2 – Decision Tool for Permanent Pacemaker Implantation (Epstein, DiMarco et al. 2008) with permission Nov 2012

National Institute for Clinical Excellence has also published guidelines for England and Wales. These recommendations further emphasise the need for maintenance of cardiac conduction physiology:

"Dual-chamber pacing is recommended for the management of symptomatic bradycardia due to sick sinus syndrome, atrioventricular block, or a combination of sick sinus syndrome and atrioventricular block, except:

• *in the management of sick sinus syndrome in patients in whom, after full evaluation, there is no evidence of impaired atrioventricular conduction; in this situation, single-chamber atrial pacing is appropriate*

• *in the management of atrioventricular block in patients with continuous atrial fibrillation; in this situation, single-chamber ventricular pacing is appropriate*

• *in the management of atrioventricular block (atrioventricular block alone, or in combination with sick sinus syndrome), when patient-specific factors, such as frailty or the presence of comorbidities, influence the balance of risks and benefits in favour of single-chamber ventricular pacing"* (National Institute for Clinical Excellence 2005)

4.2. Pacemaker Selection

Having assessed the need for treatment of a bradyarrhythmia requiring permanent pacemaker implantation, decisions must then be made as to the type of device. This decision must be taken prior to the procedure as this will influence site, access and number of leads required.

For the purposes of treating bradyarrhythmias only, the decision is generally between a single or a dual chamber device i.e. a pacemaker with a single lead having an electrode in either the atrium or the ventricle, or a pacemaker with electrodes in both the atrium and ventricle.

There is both a cost and procedural benefit from implanting a pacemaker with a single electrode: less hardware hence less cost, requires single transvenous access and hence less potential for procedural and post procedural risks.

As already stated there is much evidence supporting physiological pacing, such that the pacemaker function mimics that of the native conduction system – sinus rhythm.(Lamas, Lee et al. 2002; Newman 2003; National Institute for Clinical Excellence 2005). This maintenance of normal cardiac conduction ensures

atrioventricular synchrony, physiological pacing increasing cardiac output both during exercise and at rest regardless of the status of the left ventricular function.

The British Pacing and Electrophysiology Group (BPEG), together with North American Society of Pacing and Electrophysiology (NASPE), developed a generic code called the NBG(**N**ASPE/**B**PEG **G**eneric) code in 1987. (Bernstein 2000)
This code offers single letter annotation to the chamber of the heart paced, chamber of the heart from which sensing can take place, the type of response of the device to those paced/sensed events, the availability of further programmable features and finally any tachycardia therapy.

Function I	**Function II**	**Function III**	**Function IV**	**Function V**
Chamber(s) Paced	**Chamber(s) Sensed**	**Mode of response**	**Programmable functions**	**Antitachycardiac functions**
V=Ventricle	**V=Ventricle**	**T=Triggered**	**R=Rate response**	**O=None**
A=Atrium	**A=Atrium**	**I=Inhibited**	**C=Communicating**	**P=Paced**
D=Dual (A&V)	**D=Dual (A&V)**	**D=Dual-** (Triggered and inhibited)	**M=Multiprogrammable**	**S=Shocks**
O=None	**O-None**	**O=None**	**P=Simple programmable**	**D=Dual (P&S)**
			O=None	

Table 4.2.1 – Modified from the 1987 NASPE/BPEG Generic (NBG) Pacemaker Code (Bernstein 2000)

When considering the two main bradyarrhythmias requiring permanent pacemaker implantation, SSS/sinus node dysfunction and atrioventricular block, then the above annotations would translate as follows:

- SSS relates to the failure of the sinus node to initiate an impulse either permanently or intermittently. The pacemaker requirement would be to electrically mimic sinus node electrical activation thus starting the normal conduction pathway down to the ventricles.

In this case the chamber paced would be the atrium – **A,** the chamber from which sensed activity would be required (when the sinus node dysfunction is intermittent) would also be atrium – **A** and the mode of response would be inhibition i.e. if the

pacemaker detects a sensed event from the atrium then this would inhibit a pacing stimulus.

If there was the requirement, as is often the case, for rate modulation during activity, the rate response would be a required device feature, giving an overall mode of operation of **AAIR.**

- Atrio-ventricular block, as previously described, is a problem with the signal from the atria reaching the ventricles, this impulse from the sinus node may be delayed, intermittent or completely unable to conduct.

In this case the chamber not receiving any impulse from the sinus node is the ventricle and hence the chamber paced would be ventricle – **V,** the chamber sensed would be both atria and ventricles –**D**. In order to synchronise ventricular stimulation following atrial depolarisation the pacemaker must sense that atrial signal to set an appropriate time or atrioventricular delay (<200ms) before pacing the ventricle, and therefore the mode of response in order to maintain AV synchrony would be both triggered (i.e. a sensed atrial event would trigger a ventricular paced event) and inhibited – **D.** Again, the need for rate modulation would need to be assessed: if this feature is incorporated then the overall operating mode would be **VDDR.**

In clinical practice, atrial sensing can most reliably be achieved by having an electrode permanently fixed in the atrium. The electrode can either sense of pace, the option of having the atrial electrode capability of pacing would generally result in programming the device **DDD** or **DDDR** – thus giving both atrial and ventricular sensing and pacing support.

Given this methodology of deriving pacemaker mode of operation, the decision of which type of pacemaker and mode to implant should be relatively straightforward. Clinical practice shows a somewhat different picture for type of device. Although much of this could be explained away by the prevalence of mixed conduction disturbances, this does not fully justify the picture, certainly in the United Kingdom.

The next section considers the national pacemaker implanting practice and gives clinical insight and justification into the types of pacemakers prescribed.

4.3. Pacemaker Prescription - The National and Local Context.

All cardiac devices implanted in England and Wales are reported to the Central Cardiac Audit Database (National Institute for Cardiovascular Outcomes Research since 2011). This national audit is part of the National Clinical Audit & Patient Outcome Programme (NCAPOP), which is managed by the Healthcare Quality Improvement Partnership (HQIP).

This data is shared nationally with the commissioners of cardiac device therapy in the Primary Care Trusts and the individual implanting centres via the regional Cardio-Vascular Networks. Its purpose is to ensure that evidence-based practice is delivered equitably across all implanting centres in England and Wales.

The data on implant rates are further compared to international practice and measured against National Institute for Clinical Excellence recommendations for cardiac device implant rates.

One of the key reporting markers is the use of physiological pacemakers. It states in the most recent report covering national data submissions for 2009:

In practice we define physiological pacing as atrial-based pacing, i.e. any pacing mode which senses or paces the right atrium. These modes will include:

- *Atrial pacing (whether rate responsive or not modes AAI and AAIR)*
- *Dual chamber pacing (whether rate responsive or not modes DDD and DDDR)*
- *Non-P synchronous pacing with dual chamber sensing (modes DDI and DDIR)*
- *Managed ventricular pacing modes (MVP, AAI⇔DDD, AAIR⇔DDDR, AAIsafeR)*

Atrial based pacing does NOT include:

- *Ventricular inhibited pacing (VVI mode)*
- *Ventricular inhibited pacing with rate response (VVIR mode)*

(CRM National Clinical Audit 2009 (Cunningham 2009))

The Cardiac Rhythm Management (CRM) National Clinical Audit classes physiological pacing as "*cardiac pacing in which the pacemaker senses or stimulates cardiac activity such that it emulates as closely as possible the normally conducted*

sinus rhythm" it further suggests *"the physiological contribution of the atria should not be ignored"*. (CRM National Clinical Audit (Cunningham 2009))

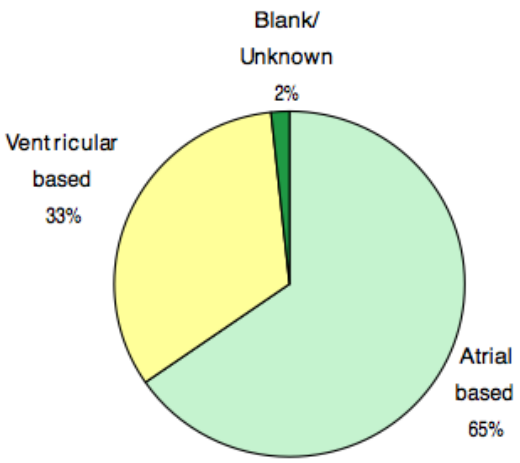
These requirements, although not mandated, are recognised as the preferred physiological criteria to be fulfilled when offering permanent cardiac pacemaker as a treatment for symptomatic bradycardia,

During the initial review of data for this research thesis the most up to date implant data was 2009, however the 2010 data was released in late 2011. Both sets of data have been included as 2009 gave greater detail of implanting rationale, whereas the 2010 featured greater levels of detail of advanced device data not covered in this project.

It is worth noting that there is debate regarding the accuracy of the coding data showing the maximal programmable capabilities of devices as this is an area where CCAD completion is inconsistent.

When the data was analysed for the implantation practice for England and Wales in 2009, it shows a total of thirteen pacing modes were adopted at implant – these modes are the maximum possible mode of the implanted device, not necessarily what the device was programmed to at discharge.

Atrial based modes		
DDDR	19559	53.05%
DDD	4122	11.18%
AAIR	182	0.49%
DDI	46	0.12%
AAI	43	0.12%
DDIR	29	0.08%
AAI>DDD	15	0.04%
AAIR>DDDR	9	0.02%
AAIsafeR	5	0.01%
Ventricular based modes		
VVIR	10836	29.39%
VVI	1248	3.38%
VDD	119	0.32%
VDDR	7	0.02%



So physiological pacing is used in the majority of patients.

Fig 4.3.1. CRM National Clinical Audit 2009 (Cunningham 2009)

By examining the audit returns of all implanting sites in England and Wales the following ECG (electrocardiograph) indications were reported for new permanent pacemaker implants by CCAD for 2009:

Complete heart block – 22.1%
Incomplete heart block – 21.7%
AF with bradycardia – 23.4%
Sick sinus syndrome – 26.1%
Other – 6.7%

Analysis of the modes implanted and pacing indications, when compared to AHA/ACC/HRS guidelines as the basis for these decisions, allows the following conclusions to be drawn:
The vast majority of patients implanted in 2009 had rate response as a feature (as detailed in Section 3.2.1. - this programmable feature modulates the pacing rate depending on the detection of activity). This is normally a feature associated with sinus node dysfunction or chronotropic incompetence.
If we consider the atrial based systems, 44% of patients had impaired atrio-ventricular conduction (complete and incomplete AV block).
AF with bradycardia, providing the AF is chronic, has no synchronous atrial activity, the atrial rates exceed 300 bpm and natively conducts irregularly. Pacing is indicated when the conduction to the ventricles is chronically slow due to AV block or bradycardia as a result of necessary drug therapy. 23.4% of patients had an indication of AF with bradycardia for which the only pacing mode is VVI +/- R, however 33% received ventricular based devices. This would suggest a non-physiological prescription of VVI/R for 10% of new implants.
The most staggering conclusion is that 26% of patients had an indication of sick sinus syndrome but <1% received pure atrial pacing devices only (AAI) and less than 1% received new minimal ventricular pacing devices (AAI⇔ DDD).

The CRM National data is further broken down into regional data, offering audit of individual implanting centres within a Cardio-Vascular Network or Strategic health Authority.

The data below are taken from Clinical Audit of Heart Rhythm Device Implantation 2009 for the North of England Cardiovascular Network. Further research took place within the Network: it is useful to measure implanting practice within this locality area and how it matches the national picture.

North of England Cardiovascular Network

	VVI	VVIR	AAI	AAIR	DDD	DDDR	VDD	VDDR	Atrial Based Pacing
NATIONAL	3.5%	30.0%	0.1%	0.5%	11.4%	54.2%	0.3%	0.0%	66.2%
This Network	2.4%	28.4%	0.0%	0.3%	13.3%	55.5%	0.1%	0.0%	69.2%
ASH.Wansbeck General Hospital		35.1%		1.0%	8.8%	55.2%			64.9%
DAR.Darlington Memorial Hospital		31.2%		0.6%	16.8%	51.4%			68.8%
DRY.Dryburn Hospital	0.8%	18.5%			23.4%	57.3%			80.6%
FRE.Freeman Hospital		25.5%		0.3%	2.2%	72.0%			74.5%
QEG.Queen Elizabeth Hospital		21.8%			32.1%	46.2%			78.2%
SCM.James Cook Hospital	9.2%	30.0%		0.3%	19.9%	40.4%	0.3%		60.5%
SUN.Sunderland District Hospital	1.8%	22.7%			9.1%	66.4%			75.5%

Fig 4.3.2. Mode/Device Prescription – North of England Cardiovascular Network (Cunningham 2009), with permission

The NECVN mode selection for 2009 is very similar to the national mode selection data for 2009. There were 7 implanting centres in the North East of England in 2009. There are no significant outliers in terms of device use between the implanting centres in the North of England, with higher than average performance in use of atrial based systems from Dryburn Hospital (known as University Hospital of North Durham and part of this research project), performance likely influenced by lowest proportion of VVIR devices suggesting either high performance against the use of atrial based pacing or a relatively lower prevalence of atrial fibrillation with bradycardia in Durham.

Since the original literature review, the data for the implanting year of 2010 have been published. This data shows a broadly similar use of modes between the 2 years with an increase in the use of rate response, but there remains an under-utilisation of single AAI/AAIR or the newer AAIR⇔ DDDR devices (R denotes use of rate response).

Atrial based modes		
DDDR	21719	60.50%
DDD	1635	4.55%
AAIR	181	0.50%
AAI>DDD	26	0.07%
AAIR>DDDR	21	0.06%
DDI	20	0.06%
AAI	19	0.05%
DDIR	6	0.02%
AAIsafeR	2	0.01%
Ventricular based modes		
VVIR	11087	30.88%
VVI	626	1.74%
VDD	88	0.25%
VDDR	13	0.04%

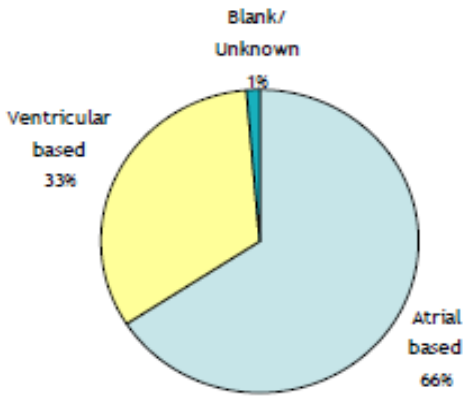


Fig 4.3.3 CRM National Clinical Audit 2010 *permission granted April 2011(Cunningham 2010),

There is little difference in implanting practice nationally between 2009 and 2010. The implantation of DDDR is up from 53.05% to 60.5%, there is very little change in the use of AAI/AAIR with both remaining <0.5%, and the use of the more novel programming mode options of AAI⇔DDD and AAIR⇔DDDR has risen minimally and still at less than 0.1%.

It is worth comparing our local Network data for 2010 to see if evidence or device development has influenced practice between years 2009 and 2010.

North of England Cardiovascular Network

	VVI	VVIR	AAI	AAIR	DDD	DDDR	VDD	VDDR	Atrial Based Pacing
NATIONAL	1.6%	31.4%	0.0%	0.5%	4.5%	61.7%	0.3%	0.0%	66.8%
This Network	0.8%	27.9%	0.1%	0.5%	6.3%	64.4%	0.0%	0.0%	71.3%
ASH.Wansbeck General Hospital		31.4%		2.3%	1.1%	65.1%			68.6%
DAR.Darlington Memorial Hospital		30.6%			8.9%	60.5%			69.4%
DRY.Dryburn Hospital		18.3%	0.9%		3.5%	77.4%			81.7%
FRE.Freeman Hospital		27.3%		0.6%	1.7%	70.5%			72.7%
QEG.Queen Elizabeth Hospital		29.3%			17.1%	53.7%			70.7%
SCM.James Cook Hospital	2.9%	24.4%		0.3%	13.1%	59.3%			72.8%
SUN.Sunderland District Hospital	2.4%	27.6%				69.9%			69.9%

Fig 4.3.4. Mode/Device Prescription – North of England Cardiovascular Network (Cunningham 2010)

The NECVN mode selection for 2010 is very similar to the national mode selection data for 2010 and also for local implanting data for 2009 but with10% increase in use of DDDR and decrease in use of DDD.
Dryburn (UHND) still remains the highest performer in the use of atrial based systems.
As previously described the ® represents the use of rate response. This increase may not necessarily represent an increased prevalence of sinus node dysfunction and chronotropic incompetence, but rather a tendency to use rate response in all presenting bradyarrhytmias to ensure that the development of chrontropic incompetence at a later stage would allow the opportunity to utilise rate response rather than having to perform a pacemaker change, a further surgical procedure, to access this feature.

The questions developing from this data required further understanding and evidence supporting the mode decisions for patients with a pacemaker indication of sick sinus syndrome, for which the mode of AAI +/- R would be the expected mode of choice (Section 4.2).

Chapter 5– Effects of Long-Term Ventricular Pacing

5.1. Electrical and Mechanical Effects of RVA Pacing

"Fifty years after its introduction, cardiac pacing for symptomatic bradycardia can look back on its impressive past. It is one of those rare medical therapies that has changed the lives of numerous patients faced with a disease with high morbidity and mortality to a prognosis which almost equals that of the normal population. Associated with a steep increase in life expectancy in the industrial world during the last half century, the number of device implants has been steadily growing and is expected to grow even further. Because of the clear benefits of cardiac pacing in patients with symptomatic bradycardia, potential harmful effects of pacing have only recently been recognised."(de Cock 2008)

This statement from a commentary by C.C.de Cock in 2008 entitled "*fifty years of pacing: the dark side of the moon*?" suggests that pacing is not a treatment without potential longer term harmful effects on heart function.

A number of recent research trials and clinical evidence has suggested that there is a correlation between long term right ventricular apical (RVA) pacing and the development and worsening of heart failure symptoms and hospitalisation (Manolis 2006).

This same commentary went on to suggest that avoiding ventricular pacing, specifically in those patients for which ventricular pacing was not the primary reason for the implant, should be established by whatever contemporary pacing procedure or programming was available.

The avoidance of ventricular pacing in atrioventricular block and atrial fibrillation with bradycardia is dependent on the degree of chronic pacing support that is required.

If the atrioventricular block is intermittent, then pacing support is only required when the signals from the sinus node intermittently fail to conduct through the AV node to the ventricles.

In pure sinus node dysfunction, there should be no need to pace the ventricle though there is evidence of conduction disease progression that can result in patients with

sinus node dysfunction going on to develop AV block, AV nodal or distal His bundle-Purkinje conduction system disease can be co-existent in up to 30% of patients (Ellenbogen and Wood 2008 pp:19).

The Danish AAI vs VVI trial noted *"the risk of AV block was approximately 0.6% per year, which is equivalent to the risk found in a larger meta analysis. This is only a little higher than the risk of AV block in the aged matched non-paced population."(DANPACE 2009)*

There have been a number of large scale trials investigating the effect of pacing the right ventricle in isolation, with or without atrioventricular synchrony.

As detailed in Section 3.4, the ventricular electrode is placed in the right ventricular apex (RVA) generally using a passive fixation mechanism pushing the electrode tip into the trabecular apex of the RV.

The pathophysiology of the detrimental effects of RV apical pacing is attributed to these abnormal electrical activation sequence and hence mechanical activation patterns of the ventricles. This results in a delay in the activation sequence, much in the same way as left bundle branch block, where the activation of the RV myocardium takes place before the LV myocardium. This delay in ventricular activation manifests as a broader QRS on the surface ECG during pacing.(Kass 2002)

This delay is characterised by early activation of the septum with the final activation being in the basal infero-posterior area of the LV.

This delayed electrical sequence results in a change in the mechanical pattern of contraction. Whereas the ventricles would contract in a simultaneous manner in normally conducted intra-cardiac signalling, the ventricular contraction becomes dyssynchronous with RV apical pacing and consequential conduction delay.

"*This abnormal contraction pattern of the regions of the LV may result in a distribution of myocardial strain/work and subsequent less effective contraction"*(Tops, Schalij et al. 2009)

A sub-study of MOST (Mode Selection Trial) showed a strong association between RV pacing and risk of heart failure hospitalisation as well as the development of atrial fibrillation in both the physiological DDD mode and single chamber VVI mode, although the risks were somewhat higher in the single chamber VVI modes .(Lamas, Lee et al. 2000)

5.2. Physiological Effect of RVA Pacing

The table below details some of the adverse effects of RV apical pacing as suggested by Tops et al – RV Apical Pacing and Dyssynchrony (Tops, Schalij et al. 2009)

Metabolism/Perfusion	Changes in regional perfusion Changes in oxygen demand
Remodelling	Asymmetrical hypertrophy Histopathological changes Ventricular dilation Functional mitral regurgitation
Haemodynamics	Decreased cardiac output Increased LV filling pressures
Mechanical Function	Changes in myocardial strain Interventricular mechanical dyssynchrony Intraventricular mechanical dyssynchrony

Table 5.1 – Acute and Long-Term Effects of RV Apical Pacing. (Tops, Schalij et al. 2009)

Mechanical cardiac dyssynchrony is associated with increased risk of cardiac mortality and morbidity in the heart failure population.

RV apical pacing can result in both interventricular (between RV and LV) mechanical dyssynchrony and intraventricular dyssynchrony (within the LV). The existence or degree of dyssychrony can be assessed using cardiac ultrasound and utilising Doppler tools that can look at delayed ejection times and late activation of LV walls.

RV apical pacing, with or without AV synchrony, reduces stroke volume and results in significant regional myocardial perfusion defects hence reducing myocardial efficiency.

These effects can lead to ventricular-remodelling, which refers to adaptations of myocardial contractility and symmetry – this can lead to atypical segmental thickening or hypertrophy, thinning and overall cardiac dilatation which in turn leads to impaired systolic and diastolic function. (Thambo, Bordachar et al. 2004; Tops, Schalij et al. 2009)

Given these potentially catastrophic effects on cardiac performance, there have been a number of large scale clinical trials looking at the effects of differing pacing mode strategies, which are discussed in the following section.

Zhang et al (2008) performed a study of 304 patients paced for acquired AV block and suggested that "*after a median follow-up of 7.8 years, permanent RV apical pacing was associated with heart failure in 26% of patients"*(Zhang, Chen et al. 2008)

Abdul Al-Hesayan et al suggested that the effects of RVA pacing on the cardiac activation sympathetic system was a possible cause of the reduction in cardiac contraction efficiency and subsequent development of cardiac functional impairment in what were previously normally functioning hearts.(Al-Hesayen and Parker 2006)

A number of studies have suggested that ventricular dyssynchrony may be present in up to 50% of patients following long term RVA pacing with a greater prevalence in those patients with underlying cardiac impairment, and that the presence of mechanical dyssynchrony is associated with LV dilation and functional impairment. It remains unclear if the dyssynchrony is an acute phenomena post RV apical pacing that ultimately leads to LV functional impairment and longer term heart failure.

It is also unclear why some patients develop dyssynchrony with RV apical pacing and some do not. The PROSPECT trial looked at echocardiographic parameters employed to predict the responders to cardiac resynchronisation therapy and suggested that some echo techniques are not sensitive enough to detect small changes in electromechanical activation.(Chung, Leon et al. 2008)

It is also worth noting that these deleterious effects on ventricular function are not universal amongst the pacemaker population.

5.3. Bi-Ventricular Pacing

In order to reduce adverse effects or prolonged right ventricular pacing due to conduction delay and resultant mechanical dyssynchrony, device technology has developed bi-ventricular pacing to allow for simultaneous left and right ventricular activation. This type of therapy requires the placement of a pacing electrode and wire into the right ventricle in the same way as normal pacemakers, with the addition of a

wire in or on the left ventricle and usually the placement of an atrial wire to ensure atrioventricular synchrony.

This procedure is technically more challenging; it can result in higher levels of complications and is considerably more expensive.(Ellenbogen and Wood 2008 pp: 65-66)

Due to the degree of evidence of the deleterious effects of RV pacing in the presence of pre-existing heart failure due to ventricular impairment, this type of therapy has been reserved for patients at the more severe end of the spectrum of mechanical heart failure.

The publication of the results of the recent PACE trial – Pacing to Avoid Cardiac Enlargement, suggested that bi-ventricular pacing is superior to RV pacing in patients with normal or preserved cardiac function, concluding that the "*Left ventricular adverse remodelling and deterioration of systolic function continues at the second year after RVA pacing. This deterioration is prevented by BiV pacing*".(Chan, Fang et al. 2011)

The impact of this research is yet to be established into mainstream clinical practice for pacing in bradycardia, with bi-ventricular pacing remaining an option for those with poor pre-existing cardiac function and symptoms of heart failure in the presence of a native broad QRS complex.

5.4. Effects of Pacing from other RV Sites

There have been a small number of trials looking at varying the RV pacing site and the effect this has on the electromechanical activation sequence and hence the presence of dyssynchrony.

Although RV apical pacing remains the stimulation site of choice in the vast majority of the pacemaker population, there are other potential RV sites for stimulation: right ventricular outflow tract (RVOT), RV septum or para-Hisian regions of the RV septum do offer theoretical electrical activation advantages over RV apical pacing. As the pacing stimulus originates from higher up in the electrical conduction system, this should result in a narrower paced QRS complex due a more simultaneous activation of RV and LV.

Direct His-bundle pacing offers the greatest effect on paced QRS complex closely mirroring the narrow complex of normal sinus rhythm and normal interventricular conduction, however this is technically very challenging. In five published studies, His-bundle pacing was only achieved in <70% of patients attempted.(Sweeney and Prinzen 2006)

The majority of studies on alternative RV pacing sites have used the septal portion of the RVOT, however the reported results of many of the randomised trials have shown equivocal differences compared to RV apical pacing.(Mera, DeLurgio et al. 1999; Nikoo, Ghaedian et al. 2011)

A number of potential explanations have been suggested for this relatively minor difference in outcome between RVOT and RVA pacing: technically it is difficult to identify the RVOT site via fluoroscopy, there were only small patient numbers and there were variations in the baseline cardiac function prior to pacing in these cohorts. It was also further noted that the most effective pacing site may vary from patient to patient, and may not always be in the outflow portion of the RV septum.

It is clear that optimum RV lead placement for improved cardiac synchronisation requires larger and longer term prospective studies to establish whether RVA, septum or RVOT pacing has the best outcomes in terms of preserving ventricular function. (Harris 2000)

It is clear that pacemaker prescription decisions are complex and multi-factorial, and that the impact of long term pacing on patient outcomes should always play a part in the decision making process. It is worth considering some of the larger and frequently quoted randomised clinical trials relating to device prescription and some of the outcomes.

Chapter 6 – Randomised Clinical Trials in Cardiac Device Mode/Prescription.

6.1. Canadian Trial of Physiological Pacing (CTOPP).

The remit of this large scale randomised clinical trial sought to compare physiological or atrial based pacing and ventricular based pacing systems.

The primary outcomes of this trial were cardiovascular death or stroke, the total cohort compromised 2568 patients with symptomatic bradycardia, of whom 1474 were randomly assigned ventricular based pacing (VVI/R) and 1094 assigned physiological pacing (AAI/R or DDD/R). (Kerr, Connolly et al. 2004)

This trial excluded those patients in chronic atrial fibrillation, patients <18 years of age or patients not expected to live beyond 1 year following implant.

As previously discussed, physiological or atrial pacing indicates a system that maintains the normal atrioventricular synchrony of the heart – such as an atrial paced and sensed pacemaker with normal atrioventricular conduction or an atrial and ventricular paced and sensed system.

A ventricular based pacing system refers to pacing and sensing from the ventricle only without any maintenance of normal atrioventricular synchrony.

The outcome of this trial reported "*no significant reduction in cardiovascular death or stroke from physiological pacing occurred during a mean follow-up period of 6.4 years"* (Kerr, Connolly et al. 2004)

The most significant outcome was a 6.4% absolute reduction in the incidence of atrial fibrillation in the atrial based cohort compared to the ventricular based cohort.

Gillis et al suggested that it is not atrial based pacing that prevents the development of atrial fibrillation but that ventricular based pacing promotes the development of atrial fibrillation.(Kerr, Connolly et al. 2004; Gillis, Kerr et al. 2005)

This association between pacing mode and the development of atrial fibrillation should be explored in relation to the mode and programming of the research cohort in County Durham and Darlington to evaluate the relationships between programmed mode/algorithm and the prevalence of atrial fibrillation.

6.2. Mode Selection Trial in Sinus Node Dysfunction – MOST

This was a 6 year randomised control trial involving 2010 participants comparing dual chamber rate responsive pacing to single chamber ventricular pacing in patients with sinus node dysfunction.(Lamas, Lee et al. 2000; Sweeney, Hellkamp et al. 2003)
The purpose of this clinical trial was to discover if dual chamber rate responsive pacing was superior to single chamber ventricular pacing in terms of adverse effects such as stroke, quality of life and function and cost effectiveness in patient with sick sinus syndrome.
The trial concluded "*in sinus-node dysfunction, dual-chamber pacing does not improve stroke-free survival, as compared with ventricular pacing. However, dual-chamber pacing reduces the risk of atrial fibrillation, reduces signs and symptoms of heart failure, and slightly improves the quality of life. Overall, dual-chamber pacing offers significant improvement as compared with ventricular pacing*"(Lamas, Lee et al. 2000; Lamas, Lee et al. 2002)
Indeed further analyses of the original MOST study by Sweeney M.O. et al on *Adverse Effect of Ventricular Pacing on Heart Failure and Atrial Fibrillation Among Patients With Normal Baseline QRS Duration in a Clinical Trial of Pacemaker Therapy for Sinus Node Dysfunction,* concluded that ventricular pacing, even with maintenance of atrioventricular synchrony, increases the risk of heart failure hospitalisation and the risk of atrial fibrillation in patients with sinus node dysfunction. (Sweeney, Hellkamp et al. 2003)

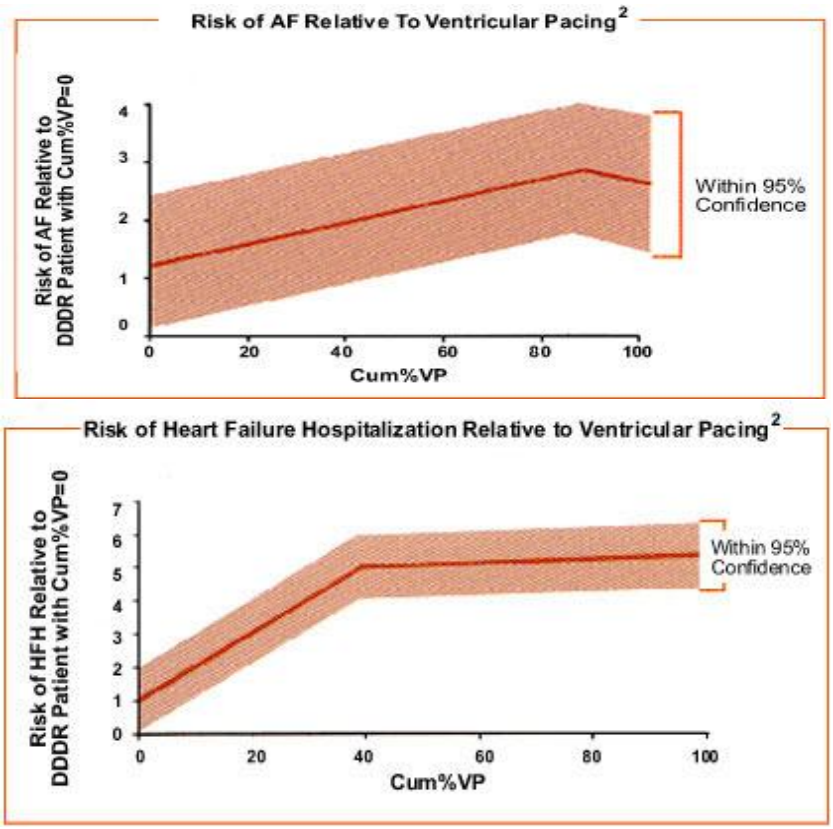


Fig 6.2.1 Risk of Heart Failure Hospitalisation due to RVP and the risk of AF due to RVP. When RVP is less than 40% for each 10% rise in RVP there is a 54% relative increase in heart failure hospitalisation, however when RVP exceeds 40% then the risk remains constant. Furthermore AF increases linearly as RVP rises. (Sweeney, Hellkamp et al. 2003) *permission for re-use granted

MOST offers further evidence of the deleterious effects of RV pacing, and in addition suggests that the maintenance of atrioventricular synchrony does improve outcomes and reduces the incidence of atrial fibrillation. It does not, however, compare single chamber atrial pacing to dual chamber pacing which are the prescribed modes for pacing in sick sinus syndrome. Single chamber ventricular pacing in SSS is not recommended by NICE or AHA/HRS guidelines for device prescription in SSS.

6.3. Pacemaker Selection in the Elderly - PASE

This study again looked at the comparison of single chamber ventricular pacing compared to dual chamber synchronous pacing in the elderly population investigating clinical outcomes.

407 patients were investigated in a single blinded randomised trial over a 30 month period.

This study also further confirmed improved clinical outcomes in patients with dual chamber synchronous devices over single chamber ventricular devices, especially in those patients with sinus node dysfunction.(Lamas, Orav et al. 1998)

6.4. Single-Chamber versus Dual-Chamber Pacing for High-Grade Atrioventricular Block - UKPACE

This study, also relating to mode selection, was specifically for patients with implant aetiology of atrioventricular block.

The study enrolled 2021 patients with new implants for atrioventricular block and compared the use of single chamber ventricular pacing with dual chamber synchronous pacing.

The results of this trial indicated no statistical difference between the two pacing strategies in terms of rates of atrial fibrillation, heart failure, stroke or other thromboembolic events.

This was a rather different outcome to other major trials in terms of clinical benefits and all-cause mortality, however this trial only considered patients requiring pacing for atrioventricular block.(Toff, Camm et al. 2005)

These major trials have all given influence to the national and international guidelines on device and mode prescription, and given evidence for the development of device algorithms and programming rationale.(Tse and Lau 2006)

6.5. Trials Specifically Investigating Mode Selection in Sick Sinus Syndrome

Kristensen et al compared single chamber atrial pacing and dual chamber rate responsive pacing in 177 patients with sick sinus syndrome, in a trial looking for the incidence of atrial fibrillation and thromboembolism between the two main modes. This trial also considered dual chamber pacing with atrioventricular delay either ‘short’ or ‘long’.

The conclusions of this trial stated that the outcome in terms of burden of atrial fibrillation was significantly reduced in AAIR with an incidence of 7.4% compared to 23.3% in dual chamber with AV delay ‘short’ and 17.5% in dual chamber AV delay ‘long’.

This result could well be explained in the terms of degree of ventricular pacing such that in AAIR there would be no ventricular pacing, but in DDDR with short AV delay there was 94% ventricular pacing and 14% in the AV delay long group.(Kristensen, Nielsen et al. 2004).
This trial was curtailed early due to the commencement of the DANPACE trial.

DANPACE looked specifically at comparing the outcomes in terms or mortality, heart failure, incidence of paroxysmal and chronic atrial fibrillation and rate of re-operation in a randomised population of 1415 patients with sick sinus syndrome randomly assigning either atrial paced and sensed systems- AAIR and dual chamber rate responsive systems-DDDR.(DANPACE 2009)
The conclusions suggest that there is no statistically significant difference between the two modes in terms of all-cause mortality (primary end point), and no statistically significant differences in the incidence of heart failure and chronic atrial fibrillation and stroke (secondary end points). However there was a statistically significant difference in the incidence of paroxysmal atrial fibrillation with AAIR having less paroxysms (p-value 0.042), and difference in the requirement for re-operation in favour of DDDR (p-value <0.001).
The DANPACE investigators went on to conclude that due to the need for re-operation, dual chamber rate responsive pacemakers (DDDR) should be the mode of choice for patients with sick sinus syndrome.(Nielsen 2010)

Anderson HR et al conducted a randomised prospective trial of 225 consecutive patients with sinus node dysfunction who were randomised to either atrial or ventricular pacing. These patients were followed up over a 5 year period. It concluded that "*patients with sick-sinus syndrome should be treated with atrial pacing rather than ventricular pacing because atrial pacing is associated with lower frequencies of atrial fibrillation, thromboembolic complications, and a low risk of atrioventricular block"(Andersen, Thuesen et al. 1994).*

6.6. Conclusions from Major Pacemaker Mode Trials

It is clear from the review of major trials into the efficacy of pacemaker mode decisions that considerable research has been undertaken into comparing single chamber ventricular pace devices to synchronous dual chamber pacing.

Although the evidence is not compelling in favour of dual chamber devices in terms of all-cause mortality, there is consistent evidence for the reduction of the burden of atrial fibrillation with dual chamber synchronous pacemakers.

According to National Institute for Health and Clinical Excellence*" atrial fibrillation is the most common sustained arrhythmia and if left untreated is a significant risk factor for stroke and other morbidities* (National Institute for Health and Clinical Excellence CG/36- 2006)

MOST was the only major trial looking at mode selection in patients with sick sinus syndrome: conclusions suggested dual chamber superiority over single chamber ventricular pacing in terms of reduced atrial fibrillation burden and heart failure hospitalisation.

There are fewer trials comparing single chamber atrial pacing to dual chamber pacing in sick sinus syndrome with DANPACE by far the largest and most cited research. Its conclusions support the use of dual chamber devices mainly because of the prevalence of re-operation. This is likely due to the development of atrioventricular block requiring ventricular pacing at a later stage, but as described below, there is conflicting evidence on development of atrioventricular block in the SSS population. This research seems to confirm the underlying implanting practice of the UK, where patients with sick sinus syndrome are rarely implanted with single chamber atrial systems in favour of dual chamber systems with the rationale relating to the small risk of re-operation to implant a ventricular lead due to the development of atrioventricular block.

It is suggested that clinical risk stratification that can be undertaken in patients with SSS to evaluate the risk of developing atrioventricular block. The use of atrioventricular Wenckebach rates have been routinely used as a predictor suggesting that an atrial paced rate of >120bpm with maintenance of a 1:1 atrial to ventricular conduction rate was a predictor of reduced risk of development of atrioventricular block. (Masumoto, Ueda et al. 2004)

However Haywood et al found that Wenckebach rates over 120bpm did not correlate well with reduced rates of development of atrioventricular block.(Haywood, Ward et al. 1990)

Anderson et al also suggested that low intraoperative Wenckebach rates were a poor predicator of the development of atrioventricular block but did suggest that these rates remained stable throughout longer term follow-up.(Andersen, Nielsen et al. 1998)
Brandt et al suggest that the use of AAI devices in SSS can be successfully applied in the absence of advanced bundle branch block, and that routine use of DDD devices in these patients is not warranted in the natural history of SSS.(Brandt, Anderson et al. 1992)
The levels of conflicting evidence for the likelihood of development of atrioventricular block in the sick sinus population seems to give credence to the implanting practice in the United Kingdom and indeed in the North East of England, as stated in Section 4.3, despite the recommendations for bradycardia pacing stated in the NICE technical appraisal document.(NICE 2005)
The overwhelming evidence of the potential for adverse effects of long term ventricular pacing on the development or worsening of heart failure, as stated in Chapter 5, has resulted in device manufacturers offering programming strategies and specific algorithms to minimise the likelihood of ventricular pacing in dual chamber systems.
The following chapter seeks to review the strategies undertaken by pacemaker companies to offer implanting and follow-up centres algorithms that will maintain atrioventricular synchrony whilst mitigating the risk of the development of AV block.

Chapter 7 – Review of Available Pacemaker Algorithms

7.1. Post Implant Programming Options

Modern pacemakers have a number of programmable features depending on the type and general sophistication of the device.

In the sinus node dysfunction population it is recommended that physiological or atrial based pacemakers are implanted (NICE 2005; Epstein, DiMarco et al. 2008). As described in the previous section, conflicting evidence exists on the use of a single chamber atrial pacemaker as the system of choice in SSS, and this is certainly in evidence from the implanting report from the National Database (Brandt, Anderson et al. 1992; Cunningham 2009; Cunningham 2010).

Modern dual chamber pacemakers have multi-programmable options to allow for adjustments depending on the implanting rationale, underlying rhythm following pacemaker implant, lead integrity and battery maintenance.

The main feature that was to be considered within this research project was the atrioventricular delay (AVD). This feature mimics the normal delay between the start of atrial systole and the start of ventricular systole: this brief delay (between 120 -210 milliseconds) allows for maximal ventricular filling prior to systolic ejection (Ellenbogen and Wood 2002 pp:303-307).

The AVD can be programmed nominal or longer than physiological. In most pacemakers the nominal (boxed or factory programmed settings) is between 150 and 170ms. The haemodynamically optimal AV delay, which corresponds to the intrinsic PR interval is 120 – 210ms at rest in the average patient with normal ventricular function. (Ellenbogen and Wood 2010 p:1).

The programming options for AV delay is dependent on the model of device implanted but this may be:

- Programming the AV delay longer than nominal i.e. greater than 150 -170ms
- Programming an AV search algorithm which extends the AVD automatically
- Programming the AVD long and adding an AV search algorithm
- Programming a mode such as managed ventricular pacing MVP™ or SafeR™

7.2. Atrioventricular Delay Programming

As previously described, lengthening the AVD will encourage or offer sufficient opportunity for normal intrinsic atrioventricular conduction in patients with sick sinus syndrome.

There are potential haemodynamic compromises of a longer than physiological AV delay, such that there is inadequate ventricular filling due to early or premature mitral valve closure, truncating the diastolic filling time and hence reduced cardiac output.(Harris 2000; Ellenbogen and Wood 2008 pp:117-9).

Long AV delays and their haemodynamic relationships can cause symptoms in patients, generally termed as pacemaker syndrome. These symptoms can include malaise, general fatigue, light-headedness and dizziness. Although pacemaker syndrome is rare, and more often associated with loss of atrioventricular synchrony commonly associated with single chamber ventricular pacing (VVI) (Ellenbogen and Wood 2008 pp:142-3); it should be considered if present with long or very long AV delays. Sulke et al found that an AV delay of 175ms offered the most appropriate timing based on symptomology and in terms of cardiac performance as assessed by echocardiography (Sulke, Chambers et al. 1992)

There are often trade-offs in terms of functionality of the device if the AV delay is hard-programmed ‘long’.

There are features within dual chamber devices that will prevent the tracking of rapid atrial arrhythmias such that, if a pathological atrial arrhythmia occurs, it will prevent the ventricular stimulation from following or tracking that rapid atrial rhythm. This is termed the maximum tracking rate. This function also limits the degree of atrioventricular delay that can be programmed due to integral programming conflicts. As a result of this safety feature preventing ‘pacemaker runaway’, the ability to track faster physiological rates is limited if the atrioventricular delay is long.

It is physiologically appropriate to have a rate responsive atrioventricular delay that mimics the normal PR interval as it shortens by 20-50ms for every 10 beat physiological increase in heart rate. This algorithm effectively works in conflict with hard programmed AV delay ‘long’ (Ellenbogen and Wood 2008 pp:305).

The ability for dual chamber pacemakers to switch modes in the presence of atrial fibrillation is an accepted requirement of these types of sophisticated devices in order

to reduce the risk of inappropriate upper rate tracking. A long atrioventricular delay reduces the window for detection of atrial fibrillation and as such can reduce the effectiveness of mode switch from dual chamber synchronous pacing to single chamber ventricular pacing in the presence of atrial fibrillation.

Nielsen et al performed a small scale trial of 38 patients programming the atrioventricular delay to 300ms. The outcomes showed that in approximately one third of patients this strategy was ineffective at reducing ventricular pacing and furthermore caused endless loop tachycardias in 5 patients due to retrograde ventricular-atrio conduction. Nielsen et al, therefore, could not recommend hard programmed long AV delays in sick sinus syndrome.(Nielson, Pederson et al 1999)

Endless loop tachycardia is a non-physiological phenomena experienced when there is ventricular to atrial conduction, this signal is then tracked and causes the pacemaker to pace at the maximum rate. There are programmable features to counteract this abnormality of function.

7.3. Atrioventricular Search Algorithms

In response to the resulting haemodynamic and device interactions of programming a long atrioventricular delay and the overwhelming evidence of the deleterious effects of unnecessary ventricular pacing, pacemaker companies developed specific algorithms to reduce the need to ventricular pace whilst maintaining atrioventricular synchrony.

Typically the device is programmed with a nominal AVD during pacing, for example 170ms, then a programmable delta value is applied, this may be a duration or a percentage value. Using the example of 170ms base AVD, if search or AV hysteresis was programmed to a value of 100ms then the device would allow the timing of the AVD to extend to 270ms to allow for intrinsic conduction.

Different manufacturers utilise slight variations in this algorithm in order to actively seek intrinsic AV conduction; there has been reported reduction in RV from 97% to 23% using these algorithms (Bastian and Fessele 2012).

The advantage of AV search allows for a more flexible and dynamic management of the AVD, with periodic AVD extension as conduction through the AV node varies. It

also will prevent the need for longer than physiological AV delays and the associated risks of endless loop tachycardias and delayed mode switching.

7.4. Atrioventricular Delay Long and AV Search

There are opportunities to programme both features, having the base AVD long and also add a degree of search. This is quite an aggressive strategy and in some devices can extend the AVD up to 400ms.

The haemodynamic consequences and programming conflicts obviously apply to this programming strategy, the benefits of maintaining atrioventricular synchrony and intrinsic conduction must be balanced against the potential for these haemodynamic consequences.(Harris 2000; Ellenbogen and Wood 2008)

7.5. Minimal Ventricular Pacing (MVP)

There are a number of device manufacturers that have produced pacemakers with specific minimal ventricular pacing algorithms. The companies use differing algorithms terms but they effectively operate in an AAI mode with a back-up mode of DDD. The specific minimal ventricular pacing devices used in CDDFT are Medtronic MVP (managed ventricular pacing) and Sorin SafeR.

Medtronic have a number of devices with this specific algorithm: the Adapta DR and the Ensura DR are two of these devices that are used in County Durham and Darlington pacemaker services.

These devices operate as atrial based pacing with a back-up of ventricular pacing in the presence of atrioventricular block AVB. When atrial conduction to the ventricles is blocked for two out of four atrial to atrial depolarisation (whether paced or sensed), then the devices switches to DDD (atrial and ventricular synchronous pacing). The device operates within the programmed AVD and after 1 minute the device checks for normal intrinsic AV conduction, if this is found the device switches back to AAI, if there is no intrinsic conduction it remains in DDD but checks every 2 minutes incrementally (2, 4, 8 etc. up to 16 hours).(Milasinovic, G. Tscheliessnigg, K. et al. 2008; Medtronic Incorporated 2010)

This mode is classed using the national coding system as AAI⇔DDD – rate response is generally used as this mode is recommended in patients with SSS, which is requires rate regulation due to chronotropic incompetence. (Bernstein 2000)

The other manufacturer of minimal ventricular pacing devices used in the CDDFT pacemaker service are Sorin SafeR™, Sorin is the manufacturer and SafeR™ is their specific algorithm. There are two devices identified in this research from Sorin that have the SafeR™ algorithm: these are the Reply DR and the Symphony DR.

The Sorin algorithms are more complex and sophisticated, switching from AAI to DDD depending on the type of atrioventricular block the device detects.

First degree AV block is tolerated up to a pre-programmed AV delay limit and will switch to DDD if there are/is:

i. Six consecutive abnormal AR/PR (atrial paced to intrinsic R wave or atrial sensed to intrinsic R wave) intervals
ii. Three blocked atrial events in the last 12 beats, or cardiac cycles
iii. Two consecutive blocked atrial events
iv. A ventricular pause of up to a programmable limits of between 2 and 4 seconds

The device remains in DDD making attempts to return to AAI providing normal AV conduction is restored.(Davy, Hoffmann et al. 2012; Sorin Group 2012)

There are circumstances for normal device function and intrinsic conduction to inappropriately cause SafeR to switch into DDD mode, most commonly early intrinsic events and extra beats falling in the refractory period.

There have been reports of patient symptoms associated with MVP algorithms, ranging from chest pain to dizziness.

A study by Murukami et al in 2010 enrolled 141 patients, randomly assigned to either AV search or MVP, reported two patients having symptoms due to the algorithms programmed (1%), one with MVP and one with AV search.(Murakami, Tsuboi et al. 2010)

The SAVE PACe trial for patients with symptomatic bradycardia due to SSS compared dual chamber pacing with AV search and MVP algorithms with primary outcome of development of AF. This study was terminated prematurely due to early achievement of the end points in terms of development of atrial fibrillation and RV

pacing differences between 99% in the DDD group to 9% in the MVP group.(Bastian and Fessele 2012)

It is clear that symptoms must be monitored and correlated to device activity to assess any negative effects of device programming. There have been some adverse reports from the use of MVP devices as reported by Murukami et al (2010), and van Mechelen and Schoonderwoerd in 2006 reported one pro-arrhythmic complication requiring external defibrillation, both cited by Bastian and Fessele 2012.

Chapter 8 – Research Objectives

8.1. Review of Key Issues from Literature

The previous sections have sought to place the topic of interest into a clinical context, and thus identifying pertinent research questions which need addressing.

There are a number of key issues that have been highlighted by the literature review:

I. Sick sinus syndrome refers to an impairment of the automaticity of the sinus node, however in many patients the electrical conduction pathways beyond the sinus node remains intact. Permanent pacemaker implantation is the treatment of choice for symptomatic patients with sinus node dysfunction, with the requirement for atrial/sinus node artificial stimulation and hence a single chamber device for atrial sensing and atrial pacing (AAI).

II. National and local data suggests the pacemaker mode of choice for patients with sick sinus syndrome is dual chamber pacing (DDD) such that there is atrial and ventricular pacing function in a synchronous way. This accounts for failure of sinus node automaticity but also conduction abnormalities below the sinus node at atrioventricular node level. This is despite evidence showing a less than 1% per year incidence of atrioventricular conduction problems.(DANPACE 2009)

III. There is considerable clinical and research evidence that right ventricular pacing, either synchronous or asynchronous, can have a deleterious effect on ventricular function which can lead to heart failure, especially in the presence of pre-existing cardiac dysfunction. There is further evidence of increase in prevalence of atrial fibrillation which in turn can increase the risk of stroke.

IV. There are pacing algorithms available as programmable options on modern pacemaker systems that can reduce, to varying extents, the amount of ventricular pacing. This can involve extending the atrioventricular delay to allow intrinsic atrioventricular nodal activation or by operating in AAI mode (atrial paced and sensed) which will automatically switch to DDD temporarily in the absence of normal atrioventricular conduction in either 2 out of 4 beats or 3 beats out of 12 (Sorin Group 2012/Medtronic Inc. 2010).

The objectives of the research were to offer evidence on current implanting practice for the population of County Durham and Darlington, assess the local pacemaker programming strategies employed and measure their effectiveness in terms of ventricular pacing avoidance and incidence of atrial fibrillation.

8.2. Development of Research Questions

Analysis of the literature review has led to the development of the following questions:

1. What is the pacemaker implanting practice for patients in County Durham and Darlington with a primary implant indication of sick sinus syndrome?
2. What, if any, algorithms are employed in these patients in an effort to reduce the amount of right ventricular pacing?
3. What is the overall percentage of right ventricular pacing achieved by device choice and programming strategy?
4. What is the overall percentage of time the patient has spent in atrial fibrillation, and is there any correlation to the RV pacing percentage or algorithm employed?

Research Question	Research Actions (question/ hypothesis)
What is the implanting practice for patients in County Durham and Darlington with SSS?	CDDFT is a single Trust with two cardiac device implanting centres. Review the patient demographics in terms of age/sex profile, implant rates, review device prescription. Validate the appropriateness of pacemaker prescriptions for patients with SSS
What, if any, algorithms are employed in the pacemakers in an effort to reduce the amount of right ventricular pacing?	Assess implanting and programming practice in light of evidence of deleterious effects of right ventricular pacing.
What is the overall percentage of right ventricular pacing achieved by device choice and programming strategy?	Explore the significance of difference between the ventricular pace avoidance algorithms. Identify which, if any, is most effective in reducing the amount of right ventricular pacing
What is the overall percentage of time the patient has spent in atrial fibrillation and is there a correlation to RV and the use of algorithms	Describe the percentage of AF and its distribution, evaluate any correlation with the degree of RVP.

Table 8.2.1 –Relevance of Research Questions to Literature Review

The purpose of the research thesis is to assess the "*cardiac device algorithms for optimal outcomes in patients with sick sinus syndrome*".

8.3. Development of the Methodology

The research questions inform the research methodology: each research question has been considered in more detail to establish and justify appropriate methodology.

I. ***What is the pacemaker implanting practice for patients in County Durham and Darlington with an aetiology of sick sinus syndrome?***

The literature review and the ACC/AHA/HRS Guidelines for Device Based Therapy: Executive Summary, details the national and international standards for cardiac pacemaker prescription in patients with sick sinus syndrome, it states "*in the management of sick sinus syndrome in patients in whom, after full evaluation, there is no evidence of impaired atrioventricular conduction; in this situation, single-chamber atrial pacing is appropriate"*.

National implantable cardiac devices audit – Clinical Audit of Cardiac Device Implantation, has consistently shown the national tendency to implant dual chamber synchronous pacemakers (DDD) for patients with sick sinus syndrome.

This audit shows that CDDFT implanting practice does mirror the national picture, with less than 1% AAI implants and 68% and 80% DDD respectively for the two implanting sites (Darlington Memorial and University Hospital of North Durham) within County Durham and Darlington NHS Foundation Trust (Cunningham 2009). The remainder of implants are single chamber ventricular based pacemakers VVI, presumably for the treatment of chronic atrial fibrillation with bradycardia. These data, however, do not give information on the modes implanted specifically for sick sinus syndrome and their capability to programme advanced algorithms that can reduce right ventricular pacing.

CDDFT commenced pacemaker implantation in 2006, prior to this patients were referred to either James Cook University Hospital in Middlesbrough or Freeman Hospital in Newcastle for pacemaker implantation.

The project looked at pacemaker data from the start of the implant services, when decisions on device prescription and programmable options were within the control of CDDFT.

The more recent device algorithms offering an atrial paced mode with a back-up of synchronous dual chamber pacing were first launched in 2003 (ELA –Symphony™). Following a takeover by the Sorin Group, the second generation devices (SafeR™) were launched in 2005. Medtronic followed on shortly after with the release of EnRhythm and Adapta devices offering managed ventricular pacing MVP™ in 2006. Prior to this time the extension of the atrioventricular delay was the only method of allowing for normal ventricular conduction and activation. This remains the method of facilitating normal ventricular intrinsic conduction in the other manufacturers of

pacemakers and also features in other models of both Medtronic and Sorin group devices.

The project, therefore, considered a 5 year period from when CDDFT commenced its own implanting service and when alternatives to AVD extension were available. Data were gathered up to a 5 year period post implantation to evaluate any degree of progression in terms of development of AV block or the long term effects on RV pacing and the development of atrial fibrillation.

The project required data to be identified and logged based on certain criteria on all patients who received their implant and/or follow-up at CDDFT:

Inclusion criteria – all patients who have permanent pacemaker implanted for primary indication of sick sinus syndrome. To include generator changes due to battery depletion.

Exclusion criterion 1 – patients with primary implant indication of anything other than sick sinus syndrome.

Exclusion criterion 2 – patients implanted at other pacemaker centres prior to CDDFT implanting service in 2006. These patients were outside of CDDFT implanting decisions and some pre-date the availability of devices with RV pace avoidance specific algorithms.

Exclusion criterion 3 – patients programmed to VVI due to onset of chronic AF soon after implant or failure to implant an atrial lead.

Exclusion criterion 4 – patients who had a mixed pathology of sick sinus syndrome and chronic AV block.

Data Requirement

- Age and sex profile, to compare any statistically significant difference in the age/sex characteristics of CDDFT pacemaker patients compared to national data.
- The make and model of device to assess implanting practice in relation to sick sinus syndrome and availability of algorithms. (Some of the older devices do not have the programmable technologies and this information was verified by the make and model).
- The programmed mode gives information on the mode selection against the international/national guidelines.

- An analysis of patients implanted for primary indication of SSS who went on to develop AV block or chronic atrial fibrillation, and relate this to published data (showing a <1% incidence of AVB per year).

II. What, if any, algorithms are employed in the pacemakers in an effort to reduce the amount of right ventricular pacing?

Data were gathered on the programmed algorithms employed by the two implanting sites in an effort to reduce the amount of RV pacing. This included an atrioventricular delay (AVD) programmed longer than physiologically normal (normal atrial to ventricular interval is less than 200 ms) or an extension/search algorithm which automatically extends the AVD to allow for intrinsic conduction, or a specific mode change that will operate in AAI mode with the ability to change to DDD in the presence of AVB (see algorithm explanation Section 7.2).

There is a differentiation between the atrial paced and atrial sensed atrioventricular delays. This is due to detection of intrinsic atrial depolarisation occurring 20-60ms after the onset of the P wave in an electrical cycle, however the detection of an artificial paced event via the pacing spike is immediate. For this reason pacemaker programming usually had a 20-60ms offset between sensed and paced AV delays (Ellenbogen and Wood 2010). The degree of AVD extension was documented, together with any automated AVD extension algorithm.

The presence of a specific and specialised mode switching algorithm for ventricular pace avoidance was documented (either MVP ™ by Medtronic or SafeR™ by Sorin).

Inclusion criteria – all patients already selected with primary indication of SSS.

Exclusion criteria – no further exclusions sought *a priori*.

Data required – details of paced and sensed AV delays, and specific pace avoidance algorithms if any. This provided information on what additional features had been employed, if any, to reduce un-necessary ventricular pacing.

III. What is the overall percentage of right ventricular pacing achieved by device choice and programming strategy?

The literature review has suggested that RV apical pacing results in an increased risk of hospitalisation due to heart failure, especially in patients with known cardiac dysfunction and increased burden of atrial fibrillation. This has resulted in

technological developments of pacing strategies to avoid un-necessary ventricular pacing. These technologies have predominantly been incorporated into devices that extend AV delays or have specific algorithms that operate in AAI with the potential to switch to DDD in the presence of atrio-ventricular block.

Inclusion criteria – all patients already included with primary indication of SSS.

Exclusion criteria – no further exclusions expected.

Data required – the percentage of RV pacing documented and averaged per year up to a 5 year period depending on the implant date. The percentage of atrial pacing was also assessed as this has a potential impact on ventricular pace burden with increased atrial sensor driven rate. This aspect of the data was not, however, analysed as there was no evidence in the literature on the influence of atrial pacing on the percentage of ventricular pacing.

IV. What is the overall percentage of time the patient has spent in atrial fibrillation?

Many of the large randomised clinical trials reviewed in Chapter 6 detailed the higher incidence of atrial fibrillation in the pacemaker population, specifically those with a high percentage of right ventricular apical pacing. Atrial fibrillation is associated with increased hospitalisation (See Fig: 6.2.1), reduction in cardiac output and cardiac performance due to the lack of atrial transport, asynchronous cardiac activation and increased risk of stroke.

Inclusion criteria - all patients already included with primary indication of SSS.

Exclusion criteria – no further exclusions sought *a priori*.

Data required – the percentage of atrial fibrillation documented and averaged per year up to a 5 year period depending on the implant date.

8.4. Research Methodology

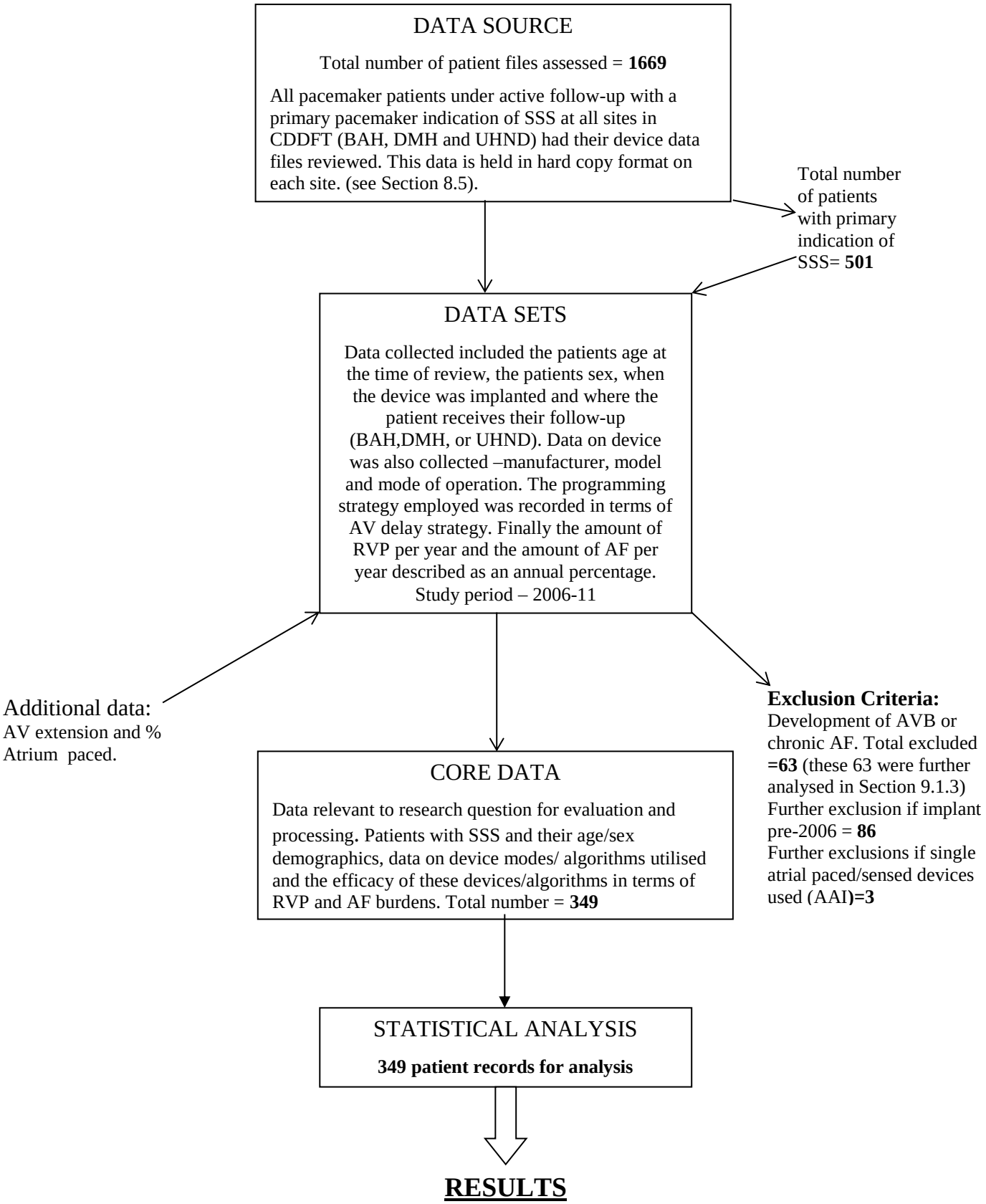


Fig. 8.4 Data processing schema

8.5. Data Source and Management

This was a retrospective analysis of existing patient data.

All required data was gathered from patient pacemaker implantation and follow-up files which are held in secure cabinets in the Cardiac and Pulmonary Investigation Units at the hospital site where the patient receives their regular pacemaker follow-up – BAH, DMH or UHND. These files contain all the relevant implant details together with a clinical record of each clinic visit since the original implant.

Each data field was populated on the Excel spread sheet (see Table 8.5.1), and stored to an encrypted mobile media and processed using CDDFT computers at each of the sites. Compliance with CDDFT information governance requirements in terms of maintenance of patient data confidentiality was ensured throughout the data gathering, processing and analysis.

In order to analyse the SSS population and their response to device mode and programming strategy, they were assessed over a period of time. The decision on type or mode of device is made at the time of original implant, generally final programming strategy is decided at their post implant check (at CDDFT this at 1-2 months post implant), and reviewed at 6 months. Patients are then followed up annually to monitor pacing status, pacemaker lead integrity and battery drain, further programming and device alterations may be undertaken depending on patient and device status at each clinic follow-up.

It was estimated that there would be 1700 active patient data files from activity profiles (held on hospital clinic management system), with approximately 30% of implants for a primary indication of SSS suggested in the regional and national implant data (Section 4.3). There was an expected 5-10% exclusion rate due to chronic AF, forced ventricular pacing due to chronic AVB and lead displacement resulting in single chamber pacing (4% AVB rate suggested in DANPACE trial).

Data was collected over a 5 year period to evaluate any change in pacing outcomes overtime due to the development of AVB or AF, a common arrhythmia especially in the aging population.(Wyndham 2000), however evidence from the literature review suggests that it is more common in the presence of patients with RVP. (Lamas, Lee et al 2000)

The data was stored in a numerical form onto an Excel spread sheet to aid statistical analysis using Statistical Packages for the Social Sciences (SPSS 19) software.

Study ID	Site	Sex	Age	Year of In	Device model	Mode prog	AVD Pace	AVD Sens	Algorithm	Yr1% RV F	Yr1 % A P	Yr1 % AF
Example												
B001	**BAH**	M	76	2009	Sensia DR	DDDR	250	220	AV Search	25	76	5
D002	**DMH**	F	83	2011	Ensura DR	AAIR<=>DR			MVP	9	90	0
U003	**UHND**	F	73	2007	Altrua DR	DDDR	220	200	AVD long	30	55	0

Table 8.5.1 Examples of dataset Excel spread sheet, year 1 only shown.

Chapter 9 – Data Analysis and Results

The previous methodology section dealt with the formulation of the research questions, this section covers the associated methods of analysis using the core data set as illustrated in Section 8.4.

The demographic data and implanting practices of the implant and follow-up centres in CDDFT is useful in assessing any deviance from recommendations and ensuring that outcomes, against the key question of *cardiac device algorithms for optimal outcomes in patients with sick sinus syndrome,* can be applied more widely if appropriate.

The analysis now addresses the following key research questions:

i. What is the most effective programmable algorithm or programming strategy to avoid ventricular pacing in patients with pure SSS?
ii. Is there a correlation between the percentage of RVP and programming strategies and the burden of atrial fibrillation?

Preliminary analysis of the data in relation to the study population was undertaken to identify any unexpected features of each variable in terms of their distribution.

In the North of England Cardiovascular Network population 11% were over the age of 70 years of age, and this population received 76% of the pacemakers. Furthermore there is a dominance of males receiving pacemakers over females.(Cunningham 2009)

Analysis of the core data gave the age and sex distribution described in Section 9.4, this data was derived using descriptive statistics from IBM SPSS version 19 and reference book (Gray and Kinnear 2012)

9.1. Core Data Set

(As described by diagram in Section 8.4)

All patients currently under active follow-up at any of the hospital sites within County Durham and Darlington:

Bishop Auckland Hospital: 435

Darlington Memorial Hospital: 550

University Hospital of North Durham: 684

Total number of patients reviewed: **1669**

9.1.1. Exclusion of Pacemaker Indications other than SSS

Of the total pacemaker patients undergoing active follow-up at any of the hospital sites, the total number of implants for a primary pacemaker indication of sick sinus syndrome:

Bishop Auckland Hospital (BAH): 119 (29%)

Darlington Memorial Hospital (DMH): 172 (31%)

University Hospital of North Durham (UHND): 210 (31%)

Total number of patients with SSS - **501**

Percentage of patients with primary indication of sick sinus syndrome at implant = **30.3%**

9.1.2. Exclusion Due to Development of AVB or AF

It is recognised that some patients with primary implant indication of SSS go on to develop chronic atrial fibrillation and or chronic atrioventricular block. It is difficult to surmise whether this is compounded by permanent pacing or if this is due to the original implant rationale being of a mixed pathology. There is a type of SSS (brady/tachy) that is characterised by the presence of atrial tachy-arrhythmias and sinus arrest: as such these patients display paroxysms of atrial tachy-arrhythmias which may develop into chronic or sustained atrial tachy-arrhythmias such as atrial fibrillation. Furthermore patients with SSS as their primary indication for pacemaker implantation may have more advanced disease of the conduction system involving the conduction down to the ventricles, thus developing atrioventricular block in addition to the primary pathology of SSS. A mixed pathology is not by any means uncommon. Although data have been collected and analysed on these patients in terms of the time from implant to onset of sustained atrial fibrillation or atrioventricular block, they were excluded from the dataset if they had developed these conduction disturbances chronically within their first year of follow-up, with an exclusion rationale of original mixed pathology.

Patients were excluded due to development of AVB and/or AF, development of these abnormalities requires the AVD to be programmed to a more a physiologically normal delay (<200ms) and in the presence of chronic AF, single chamber ventricular paced and sensed (VVI) is generally indicated.

Exclusion		No. Patients	Percent
Valid	AV Block	26	41.3
	A.F.	36	57.1
	Both	1	1.6
	Total	63	100.0

Table 9.1.2 Exclusions due to AV block and/or atrial fibrillation

The above data describes patients implanted and followed-up in CDDFT who were excluded from the study due to the early onset of chronic atrial fibrillation or atrioventricular block. The occurrence of chronic atrial fibrillation dominates at 57%, whilst the development of atrioventricular block, as determined by no R wave following either sensed or paced atrial event at maximum programmable atrioventricular delay (first degree atrioventricular block), or chronic underlying second or third degree atrioventricular block, was evident in 41% of patients.
This gives an incidence of AVB development of 5% overall, compares quite closely to the 4% AVB development noted in the DANPACE study (DANPACE 2009).
7% incidence of AF noted in the SSS study cohort.

9.1.3. Time from Implant to Exclusion due to AVB or AF

Further analysis was undertaken to establish when the development of atrioventricular block or atrial fibrillation occurred in patients whose dominant implant rationale was sick sinus syndrome. This analysis took information from the immediate post implant pacemaker function tests and cardiac rhythm assessment, this occurs in the routine pacemaker checks scheduled at 1 month, 6 months and 1 year. The rhythm disturbance was confirmed as chronic if it was maintained beyond 6 months from onset.

Occurrence of Patients with Atrial Fibrillation and/or Atrio-Ventricular Block

Time since implant	AVB	AF	Both
1 month F/U	15	22	1
6 month F/U	7	0	0
1 year F/U	14	4	0

Note: Both=1 compromised AVB at 1 month and AF at 1 year of follow-up.

Table 9.1.3 Time from Implant to development of AVB and/or AF

This data indicates that AF or AVB was observed and noted from the first month of implant in the largest number of patients: this suggests the existence of these conduction disturbances in addition to sick sinus syndrome at the time of implant. These data also highlights existing evidence that atrial tachy-arrhythmias are often a feature of sick sinus syndrome and that often disease of one part of the conduction system may affect other parts of the conduction pathway beyond the sinus node.

9.1.4. Total Number of Patients with Pure SSS in Study

Total number of patients with pure sick sinus syndrome as defined at 1 year of original implant:

Bishop Auckland Hospital: 113

Darlington Memorial Hospital: 143

University Hospital of North Durham: 182

Total: **438**

9.1.5. Exclusions of Implants outside of CDDFT

Patients whose original implant and programming decisions were made by other pacemaker services were removed from the dataset; this essentially excluded patients repatriated from other hospitals prior to 2006 when CDDFT services commenced.

The purpose of this research is to review CDDFT implanting and programming practices in order to appraise decisions in relation to mode and algorithm in the reduction of right ventricular pacing and development of atrial fibrillation. The device choice and programming strategy of other implanting centres may influence the patient longer term outcomes. Much of the research evidence from the larger randomised clinical trials (MOST, CTOP, DAVID) was undertaken, circa 2005. The broad availability of specific devices and algorithms to facilitate reduced RV pacing has been from 2003 -2005 - the review of implants from 2006 will allow for greater inclusion of these specific features.

9.1.6. Final Core Study Data

This gave a final data source sampling size of:

Bishop Auckland Hospital: 78

Darlington Memorial Hospital: 121

University Hospital of North Durham: 153

Total sample size to evaluate cardiac device algorithms for optimal outcomes in patients with SSS was: **352**

Of these patients, 3 were implanted with single chamber atrial paced and sensed devices (AAI), for which there is no ventricular pace functionality. Although an appropriate mode for sick sinus syndrome, these devices have no necessity for ventricular pace avoidance and cannot offer information on the burden of AF.

The exclusion process gave a final data size of **349** patients.

It is important to note that this final data size only applies to patients within 1 year of implant, at each year thereafter the number decreases as the time from implant extends:

Year 1 = 349 (yrs 2010 -2011)

Year 2 = 285 (yrs 2009 – 2010)

Year 3 = 190 (yrs 2008 -2009)

Year 4 = 116 (yrs 2007 – 2008)

Year 5 = 59 (yrs 2006-2007)

The research was conducted on these 349 patients to develop conclusions against the research questions detailed in Chapter 8, understanding that these 349 patients would not all be present in the analysis in the subsequent years.

Note: All patients implanted at either UHND or DMH for a primary indication of sick sinus syndrome were implanted with an atrial based system as recommended in NICE guidance. (National Institute for Clinical Excellence 2005)

9.2. Null Hypothesis

It is these 349 patients that were analysed in order to test the null hypothesis – "there is no difference in the degree of right ventricular pacing or the incidence of atrial fibrillation between the investigated pacemaker models and programming strategies in patients with sick sinus syndrome".

9.3 Sex and Age Distribution of the Study Population

		No. Patients	Percent
Valid	Male	164	47.0
	Female	185	53.0
	Total	349	100.0

Table 9.3.1 – Sex distribution of study dataset

The data shows that, unlike the regional implanting data from CCAD, there is a higher percentage of female pacemaker patients in the study dataset. The dataset relates only to patients with SSS and is subject to all the exclusions detailed in Section 9.1. This may not be representative of the whole population of pacemaker patients currently under active follow-up in CDDFT (1669 patients).

Further analysis of the sex distribution was undertaken to see if there was any significant difference in the sex distribution to the follow-up hospital site.

Hospital Site		Sex		Total
		Male	Female	
Site	DMH	60 (36.6%)	60 (32.4%)	120
	BAH	32 (19.5%)	44 (23.8%)	76
	UHND	72 (43.9%)	81 (43.8%)	153
Total		164 (100%)	185 (100%)	349

Table 9.3.2 Sex distribution of study population to hospital site – percentage in brackets.

The data in Table 9.3.2 shows that the sex distribution is equal at Darlington Memorial Hospital, but a slightly higher female study population at both Bishop Auckland Hospital and University Hospital of North Durham.

Age Distribution of the Study Population:

Pacemakers are often regarded as a procedure occurring in the elderly population, and this generally held belief is supported by the national and regional data.

Most pacemakers are implanted due to diseases of the conduction system, which is predominantly a disease of the elderly. (Cunningham 2009)

Case Summaries

Age (in years)

N	Mean	Median	Std. Deviation	Minimum	Maximum	Std. Error of Mean
349	77.2	79.00	10.5	26	99	0.561

Table. 9.3.3 Age range of the study population

The mean age of 77 years of age is comparable with the national data (mean age of 76 years – CCAD 2009) for all cause pacemakers.

The range is broad at 26 to 99 years of age but a review of the age distribution below shows age ranges for the majority of the study population. This is also displayed for follow-up site to identify any differences in distribution to follow-up site.

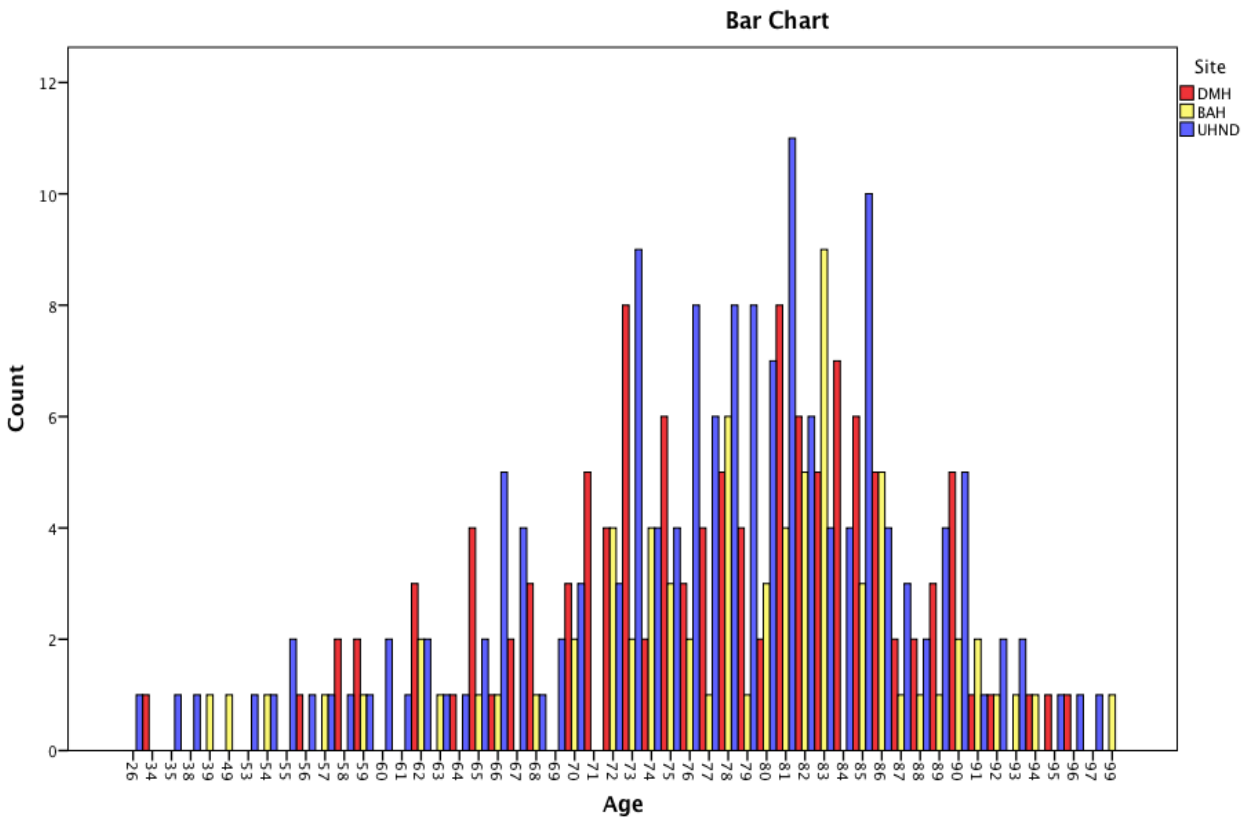


Fig 9.3.1 Graphical representation of age distribution and hospital site of study population.

The distribution is negatively skewed towards the higher age ranges with the greater density between 70 and 90 years of age. The distribution is similar across the follow-up sites.

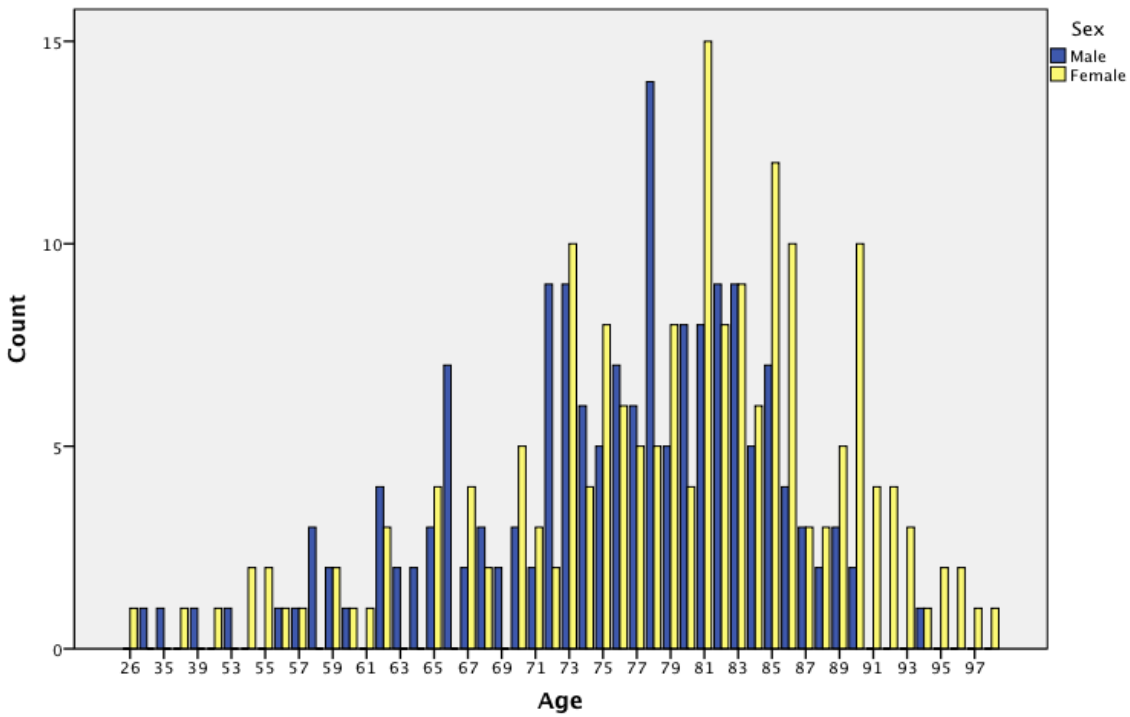


Fig 9.3.2 Graphical representation of age and sex distribution of study population.

The graph in 9.3.2 shows the age range for each sex, showing females dominating over males in the higher age ranges. This trend may relate to the higher numbers of females than males in the study and may also reflect the general historical trend of female life expectancy exceeding that of males, although this gap is closing. (Office of National Statistics 2012)

9.4. Cardiac Device Distribution for Implanting Centre and Follow-up Site

As previously described, pacemaker implantation occurs at either two sites in County Durham and Darlington: there is an implanting centre at Darlington Memorial Hospital and another at University Hospital of North Durham.

There are a number of cardiac device makes and models available on the international market. Table 9.4.1 details of the makes of devices implanted in the study population for the treatment of SSS.

There were 5 manufacturers of pacemakers within the core dataset. Within each manufacturer there was a number of differing pacemaker models, reflecting progressive technological processes, such as innovations of electronics and micro-technologies, as well as emerging research data, improving these devices.

Implantable cardiac devices represent a highly competitive market, and as such cost cannot be excluded as an influence on the device prescription decision making.

The Table 9.4.1 describes the models of devices in the core dataset in relation to the manufacturer.

Medtronic provides the largest number of devices under a variety of different models for CDDFT, with Boston Scientific having the second largest share followed by Sorin Group and finally St Jude Medical.

Section 9.5 describes the various algorithms available and their operation and shows that Medtronic and Sorin Group are the only manufacturers of devices with minimal ventricular pacing algorithms (see Section 7.5).

Device model * Manufacturer Crosstabulation

Count

		Manufacturer					Total
		Medtronic	St Jude Medical	Boston Scientific	Sorin Group	Vitatron (Medtronic)	
Device model	Adapta DR	20	0	0	0	0	20
	Altrua DR	0	0	69	0	0	69
	Enpulse DR	1	0	0	0	0	1
	Ensura DR	17	0	0	0	0	17
	Esprit DR	0	0	0	1	0	1
	Identity D	0	1	0	0	0	1
	Identity DR	0	37	0	0	0	37
	Insignia DR	0	0	20	0	0	20
	Integrity DR	0	1	0	0	0	1
	Kappa DR	6	0	0	0	0	6
	Reply SafeR	0	0	0	49	0	49
	Selection DR	0	0	0	0	1	1
	Sensia D	1	0	0	0	0	1
	Sensia DR	75	1	0	0	0	76
	Sigma D	1	0	0	0	0	1
	Symphony	0	0	0	14	0	14
	T70DR	0	0	0	0	19	19
	Verity DR	0	4	0	0	0	4
	Versa DR	3	0	0	0	0	3
	Victory DR	0	5	0	0	0	5
	Zephyr DR	0	3	0	0	0	3
Total		124	52	89	64	20	349

Table. 9.4.1 Device Distribution -Table showing the distribution of manufacturers of the devices implanted in the study population

Medtronic has the largest market share of the pacemaker implants at 124 giving a market share of 35.5%, with Boston Scientific having 25.5%, Sorin receive 18.3% of the market and 14.9% to St Jude Medical, the remaining 5.7% share of the market was with Vitatron (now owned by Medtronic).

The model of device determines the availability of programmable algorithms and features of the device.

The table below describes the device models by the site implanted.

Model	Site		Total (%)
	DMH (%)	UHND (%)	
Adapta DR	5 (2.6)	15 (9.8)	20 (5.7)
Altrua DR	35 (17.9)	34 (22.2)	69 (20)
Enpulse DR	1 (0.5)	0	1 (0.3)
Ensura DR	16 (8.2)	1 (0.7)	17 (4.9)
Esprit DR	1 (0.5)	0	1 (0.3)
Identity D	1 (0.5)	0	1 (0.3)
Identity DR	28 (14.3)	9 (5.9)	37 (10.6)
Insignia DR	17 (8.7)	3 (2)	20 (5.7)
Integrity DR	0	1 (0.6)	1 (0.3)
Kappa DR	3 (1.5)	3 (2)	6 (1.7)
Reply SafeR	48 (24.5)	1 (0.6)	49 (14)
Selection DR	0	1 (0.6)	1 (0.3)
Sensia D	1 (0.5)	0	1 (0.3)
Sensia DR	14 (7.1)	62 (40.5)	76 (21.8)
Sigma D	1 (0.5)	0	1 (0.3)
SymphonyDR	14 (7.1)	0	14 (4)
T70DR	4 (2)	15 (9.8)	19 (5.4)
Verity DR	1 (0.5)	3 (2)	4 (1.1)
Versa DR	1 (0.5)	2 (1.3)	3 (0.9)
Victory DR	4 (2)	1 (0.6)	5 (1.4)
Zephyr DR	1 (0.5)	2 (1.3)	3 (0.9)
Total	196 (100)	153 (100)	349 (100)

Table 9.4.2 Table of device models implanted for each of the two implanting sites.

There are differing implant decisions based on device model between the two sites.

It is recognised that there are operator preferences that will have an influence over the device prescribed at implant: not just by the programmable algorithms but other factors such as size, shape, cost, product familiarity and product confidence.

The data suggest a greater use of devices with AAI⇔ DDD- minimal ventricular pacing, at DMH with 62 of the Sorin SafeR™ devices (Symphony and Reply SafeR) being implanted at DMH versus 1 at UHND. Of the Medtronic devices with available AAI⇔ DDD algorithm (Adapta and Ensura DR) 21 were implanted at DMH versus 16 at UHND. This observation suggests a greater use of AAI⇔DDD devices at DMH compared to UHND. The rationale behind these decisions has not been investigated as part of this project but should be considered further in the future in light of the outcomes from the data analysis.

The most commonly used device was the Medtronic Sensia DR at 76 devices or 21.7% of the total implants. Implantation was predominantly at the UHND site with 62 devices versus 14 at DMH. This device has an AV search algorithm available.

The second most implanted device was the Boston Altrua DR with total of 69 devices, evenly split between sites of 35 at DMH and 34 at UHND. The Altrua DR also has an AV search algorithm available for programming.

As already described, there are national and international standards on device prescription in terms of mode but no such guidelines or recommendations in terms of programmable algorithms such as minimal ventricular pacing, mode switch, etc.

CCAD (now the National Institute for Clinical Outcomes Research) reviews performance on an annual basis with a mandatory requirement for all implant centres in the UK to report on implanting practice. Implanting sites are performance managed by Primary Care Trusts and Regional Cardio-vascular Networks against these standards.

There is NICE (National Institute for Clinical Excellence 2005) guidance stating that the pacing mode for patients with SSS should be atrial based i.e. dual chamber pacemaker or atrial based pacemaker (DDD or AAI). The dataset has not shown evidence of any inappropriate device model prescription from either of the implanting sites – see Chapter 4 Pacemaker prescription.

It was also noted in the regional data from CCAD in 2009 and 2010 (Fig. 4.3.2 and Fig. 4.3.4) that DDDR comprise the largest proportion of devices implanted in the North of England (Cunningham 2010). Previously, Chapter 3 described how patients with sinus node dysfunction or SSS may also exhibit a fixed heart rate when exercising – this is known as chronotropic incompetence. This abnormality manifests in fatigue and shortage of breath on exertion (Bennett 2006 pp:44-5). In these patients the addition of a sensor in the device that will increase the atrial pacing rate by

detecting movement and activity is indicated. This practice is further confirmed in Table 9.4.2 showing high volumes of devices coded DR or SafeR.
The recognised additional coding for these types of devices is ® as stated in the pacemaker, defibrillator and lead codes (Bernstein 2000).

9.4.1. Distribution of Device Models by Site of Follow-up

Programming decisions are made at the follow-up visits. The table below shows the distribution of the implanted pacemaker models to the follow-up site.

Device model * Site Crosstabulation

Count

Device model	Follow-up Site			Total
	DMH	BAH	UHND	
Adapta DR	4	1	15	20
Altrua DR	21	14	34	69
Enpulse DR	1	0	0	1
Ensura DR	12	4	1	17
Esprit DR	1	0	0	1
Identity D	0	1	0	1
Identity DR	18	10	9	37
Insignia DR	10	7	3	20
Integrity DR	0	0	1	1
Kappa DR	1	2	3	6
Reply SafeR	28	20	1	49
Selection DR	0	0	1	1
Sensia D	1	0	0	1
Sensia DR	7	7	62	76
Sigma D	1	0	0	1
Symphony DR	8	6	0	14
T70DR	3	1	15	19
Verity DR	0	1	3	4
Versa DR	1	0	2	3
Victory DR	2	2	1	5
Zephyr DR	1	0	2	3
Total	120	76	153	349

Table 9.4.3 showing the distribution of the implanted models to the follow-up sites.

9.5. Programmed Device Mode and Algorithms

The availability of algorithms to minimise the amount of right ventricular pacing are available in most of the devices within the core dataset. The decision on when and how to programme these algorithms is left to the discretion of the clinician or cardiac physiologist engaged in the follow-up of the device.

The device features available, such as algorithms or features to reduce ventricular pacing, are dependent on the device make and model.

The table below (9.5.1) shows the main programmable features and specific algorithms available for each of the models of pacemaker implanted in the study population, also included in the table is further detail on the degree of extension (ms) that can be added to the AV delay (see also Chapter 7), and the two main minimal ventricular pace algorithms (MVP™ and SafeR™).

Table: 9.5.1 Table describing the features and algorithms available in the devices used in the study that can reduce the need for ventricular pacing

Device Model	Manufacturer	Paced AV Delay (ms)	Sensed AV Delay (ms)	AV Search (ms)	SafeR AAIR-DR	MVP AAIR-DR
Adapta DR	Medtronic	30 – 350	30 – 350	Yes(+10 – 25)	No	Yes
Altrua DR	Boston	10 – 300	10 - 100 less than PAV	Yes (+10-100%)	No	No
Enpulse DR	Medtronic	30 – 350	30 – 350	Yes (+10 – 250)	No	No
Ensura DR	Medtronic	30 – 350	30 – 350	No	No	Yes
Esprit DR	Sorin	30 – 250	0 - 125 <PAV	Yes (10 – 345)	No	No
Identity D	St Jude	25 – 350	150 – 250	Yes (+120 -110)	No	No
Identity DR	St Jude	25 – 350	150 – 250	Yes (+120 - 110)	No	No
Insignia DR	Boston	20 – 300	10 - 100 <PAV	Yes (10 - 100%)	No	No
Integrity DR	St Jude	25 – 350	25 – 325	Yes (10 – 120)	No	No
Kappa DR	Medtronic	30 – 350	30 – 350	Yes (+10 – 100)	No	No
Reply SafeR	Sorin	30 – 250	0 - 125 <PAV	No	Yes	No
Selection DR	Vitatron	80 – 300	45 – 260	Yes (+60 – 120)	No	No
Sensia D	Medtronic	30 – 350	30 - 350	Yes +10 - 250	No	No
Sensia DR	Medtronic	30 – 350	30 – 350	Yes +10 -250	No	No
Sigma D	Medtronic	30 – 350	30 – 350	No	No	No
Symphony DR	Sorin	30 – 250	0 - 125 <PAV	No	Yes	No
T70DR	Vitatron	80 – 300	45 – 260	Yes +60 - 120	No	No
Verity DR	St Jude	25 – 350	25 – 325	Yes +10 - 120	No	No
Versa DR	Medtronic	30 – 350	30 – 350	Yes +10 - 250	No	No
Victory DR	St Jude	25 – 350	70 – 170	Yes +200 - -110	No	No
Zephyr DR	St Jude	25 – 350	70 – 170	Yes +200 - -110	No	No

To use an example from above, the Sensia DR was the most popular device used, if a paced AVD of 200ms and sensed AVD of 170ms were programmed, plus search of 150ms. The device would extend the AVD out to 350 ms after an atrial paced event to search for intrinsic conduction and extend AVD to 320 ms after a sensed atrial event. This delay will remain extended for a number of pre-programmed cycles before reverting to the programmed shorter AVD if no intrinsic conduction is established.

The device will search again after a period of time or number of cycles, again the period of time and number of cycles is individually programmable.

9.6. Age and Sex Influences on the use of Devices and Algorithm

In order to ensure that the use and efficacy of the differing device modes and algorithms were not influenced by other factors such as the age or sex of the patients, analysis of the algorithms and the age and sex characteristics was statistically assessed.

Non-parametric tests using Kruskal-Wallis comparing each of the 5 programming strategies/algorithms with the sex distribution for the null hypothesis of "*the categories defined by sex=male and females occur with probabilities of 0.5 and 0.5*" The table below summarises the retention or rejection of this null hypothesis.

Algorithm	Retain Null Hypothesis	Reject Null Hypothesis
No Algorithm	✓	×
AVD Long	✓	×
AV Search	✓	×
AV Search+Long	✓	×
MVP	✓	×

Table 9.6.1 Summary of hypothesis testing for significant differences in the sex distribution for each algorithm

The analysis of sex distribution in each algorithm group suggested that the distribution was not significantly different between males and females for each algorithm group.

Further descriptive statistics were used for the age distributions for algorithm categories and displayed as Box plots.

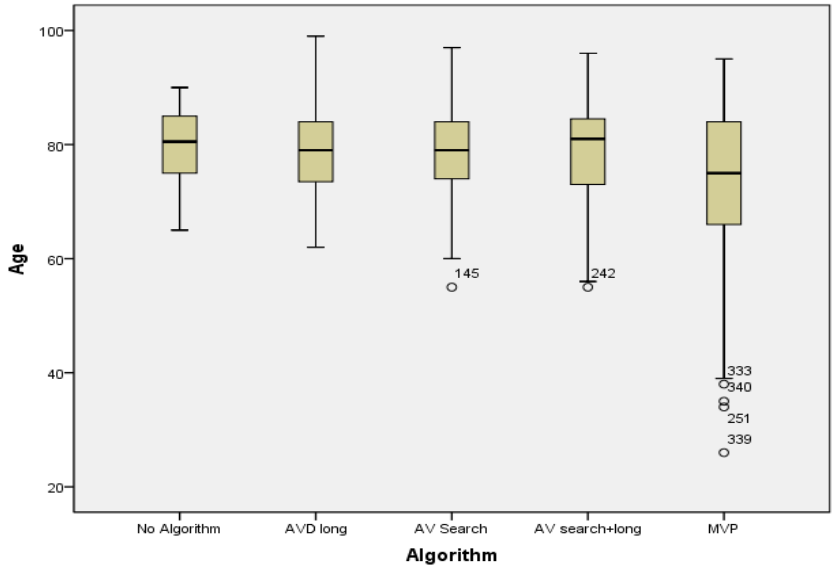


Fig 9.6.1 Box plots showing the distribution of age for each algorithm

The median values are similar across the categories of algorithms but a wider distribution of age ranges is seen in MVP group, which is also the largest single group in year 1. There needs to be further testing to identify any statistically significant differences in the age ranges between the algorithm groups.

The Kruskal-Wallis test was used to test the hypothesis that the age distribution was the same across all categories of algorithm. The summary below shows that the null hypothesis was retained.

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Age is the same across categories of Algorithm.	Independent-Samples Kruskal-Wallis Test	.128	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table 9.6.2 Hypothesis testing summary of age distribution across the algorithms

The analysis of the sex and age distributions between the algorithms in the study population was not statistically different, therefore further analysis of the effects of these algorithms on the amount of RV pacing and consequent effects on the degree of AF, was not likely to be skewed by influences of the patient's age or sex.

9.7. Analysis of the Efficacy of Programmable Device Features in Reducing RV Pacing

Chapter 5 described the potential effects of right ventricular apical pacing. The key question posed in this research is "what is the most effective programmable algorithm or programming strategy to avoid ventricular pacing in patients with pure sick sinus syndrome?"

The annual amount of right ventricular pacing was collected for each follow-up year and described as a percentage of the overall pacing detected in the ventricle.

The baseline for comparison was patients in which no specific programming was undertaken to reduce the amount of right ventricular pacing 'no algorithm'. The total number of patients in the study for which no alterations to standard programming were made to reduce the likelihood of right ventricular pacing was 14.

Chapter 7 described the available pacemaker algorithms with specific detail on the atrioventricular delay. There are effectively 5 programmable features although MVP and SafeR™ can be considered as the same algorithm, operating in effectively the same way but with slight differences in the AVB criteria.

The table below shows the algorithms utilised at each of the follow-up centres.

Site of Follow-up and Algorithm Utilised

Count

Hospital follow-up Site		Algorithm						Total
		No Algorithm (%)	AVD Long (%)	AV Search (%)	AVD long+search (%)	MVP (%)	SafeR (%)	(%)
Site	DMH	4 (28.6)	27 (48.2)	2 (2.4)	35 (36.5)	16 (43.2)	36 (57.1)	120 (34.4)
	BAH	3 (21.4)	15 (26.8)	6 (7.2)	21 (21.9)	5 (13.5)	26 (41.2)	76 (21.8)
	UHND	7 (50)	14 (25)	75 (90.4)	40 (41.6)	16 (43.3)	1 (1.7)	153 (43.8)
Total		14	56	83	96	37	63	349

Table: 9.7.1 Device algorithms employed by each follow-up centre (No algorithm=no specific changes made to nominal atrio-ventricular delay, AVD Long=atrio-ventricular delay programmed longer than physiological i.e. >200ms, AV Search=specific automatic algorithm that extends atrio-ventricular delay to a max programmed searching for intrinsic conduction, AVD long+search=longer starting atrio-ventricular delay with added search, MVP™=managed ventricular pacing is a specific Medtronic algorithm which operates only in the atrium but switches to both atrial and ventricular pacing if atrio-ventricular block occurs, SafeR™ =specific Sorin algorithm which operates only in the atrium but switches to both atrial and ventricular pacing if atrio-ventricular block occurs.

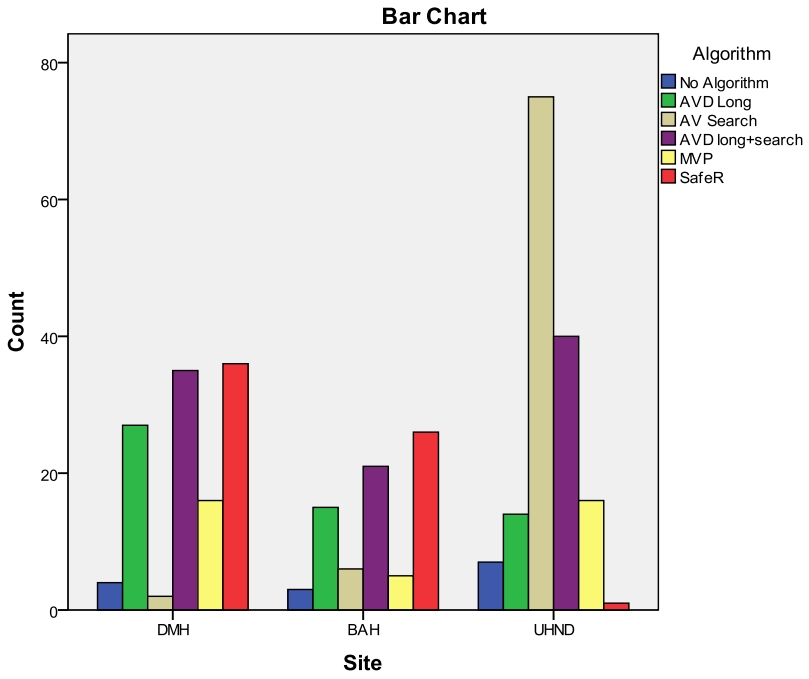


Fig 9.7.1 Bar chart representation of device algorithm distribution for each follow-up site

DMH=Darlington Memorial Hospital, BAH=Bishop Auckland Hospital, UHND=University Hospital for North Durham

This graph shows a dominance of AV search algorithm at UHND site with a fairly even split between AV long + search and MVP at BAH and DMH. This suggests a more proactive or aggressive approach to reducing RVA pacing at BAH and DMH. SafeR is the dominant MVP device at BAH/DMH with Medtronic MVP device preferred at UHND.

It can be concluded that there is a lack of consistency in the use of algorithms between BAH/DMH and UHND – being generally similar between BAH and DMH.

This can be explained by the same staff covering the clinics at BAH and DMH with different staff covering UHND.

This finding underlines the need to identify an evidence based approach to programming devices in an effort to reduce the degree of RV pacing which can be consistently applied across the services in CDDFT.

9.8. Overall Distribution of Right Ventricular Pacing

Data Distribution

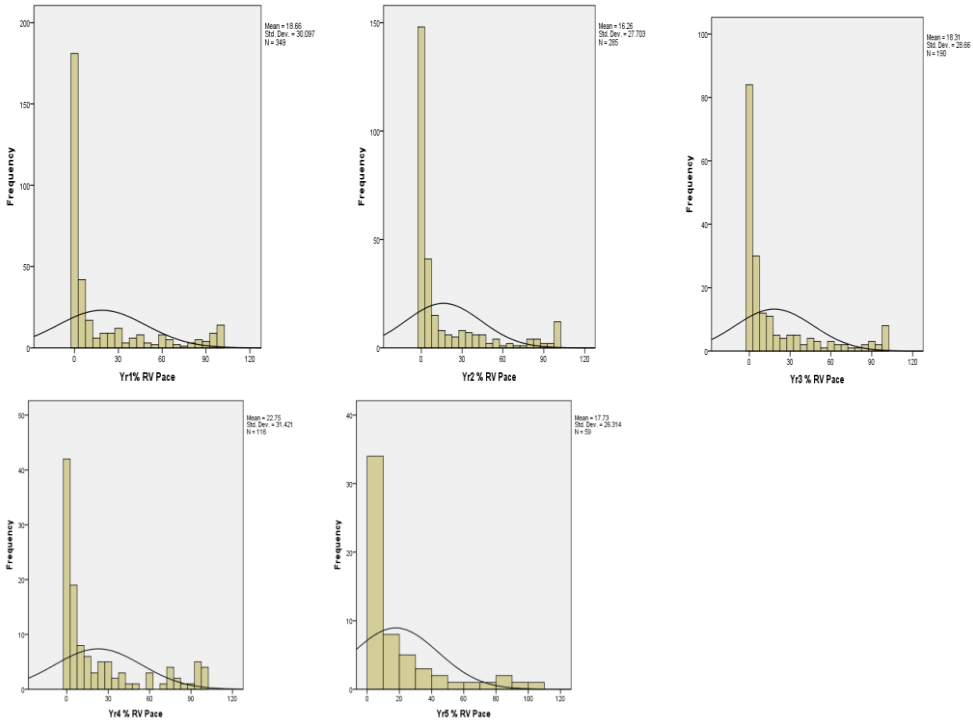


Fig 9.8.1 – Distribution curves for the percentage of right ventricular pacing in each year group.

The following observations were made from the RV pacing % distribution curves:

- Severely non-normal positively skewed distribution
- Approximately 50% of the readings are tied values at zero
- Non-parametric statistical methods of analysis would need to be undertaken
- Analysis of variance would be inappropriate as the assumptions behind ANOVA would be violated. The residual errors would be highly systematic and not random.

9.8.1. Mean RV Pacing (Percentage) Achieved by Algorithm

A series of case summaries was used to look at the distribution of mean annual right ventricular pacing percentage for each algorithm and for each year from implant.

i. Year 1 % RV Pace

Algorithm	N	Mean	Median	Minimum	Maximum
No algorithm	14	78.1	93.5	0	100
Long AVD	56	27.4	9.0	0	100
AV Search	83	21.7	4.0	0	100
Long AVD+AV search	96	19.5	4.5	0	100
MVP	36	2.9	.0	0	59
SafeR	64	1.6	.0	0	38
Total (n=)	349				

ii. Year 2 % RV Pace

Algorithm	N	Mean	Median	Minimum	Maximum
No algorithm	11	59.0	91.00	0	100
Long AVD	41	21.8	7.00	0	100
AV Search	71	19.8	3.00	0	100
Long AVD+AV search	84	17.3	5.00	0	100
MVP	26	2.7	.00	0	23
SafeR	52	3.1	.00	0	49
Total (n=)	285				

iii. Year 3 % RV Pace

Algorithm	N	Mean	Median	Minimum	Maximum
No algorithm	7	46.0	33.0	3	99
Long AVD	31	20.0	5.0	0	98
AV Search	61	22.1	4.0	0	100
Long AVD+AV search	56	19.1	5.0	0	100
MVP	15	2.4	.0	0	26
SafeR	20	3.9	.0	0	50
Total (n=)	190				

iv. Year 4 % RV Pace

Algorithm	N	Mean	Median	Minimum	Maximum
No Algorithm	6	42.50	28.50	7	100
Long AV Delay	23	22.13	12.00	0	96
AV Search	42	27.55	4.00	0	100
Long AVD + Search	33	19.52	9.00	0	95
MVP	6	2.00	.00	0	9
SafeR	6	10.33	.50	0	58
Total	116	22.75	6.00	0	100

v. Year 5 % RV Pace

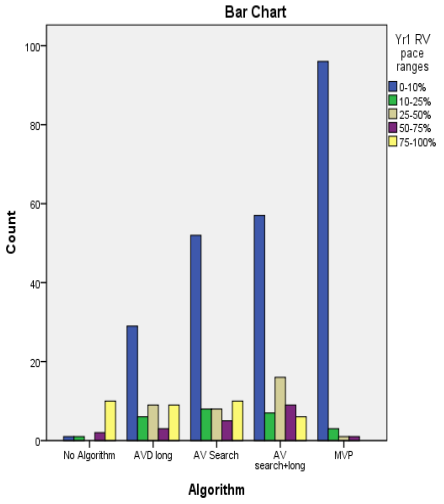
Algorithm	N	Mean	Median	Minimum	Maximum
No Algorithm	4	29.25	15.50	0	86
Long AV Delay	14	24.36	8.50	0	100
AV Search	19	10.89	2.00	0	76
Long AVD+Search	18	16.72	11.50	0	63
MVP	4	20.00	.00	0	80
Total	59	17.73	6.00	0	100

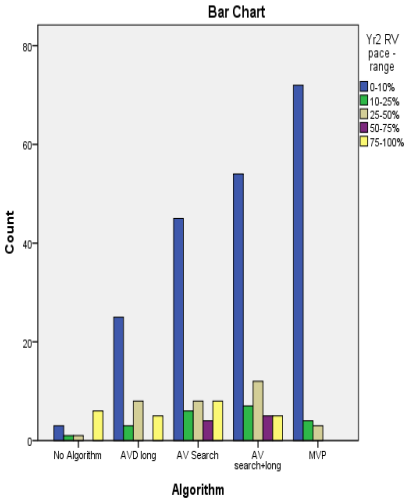
Tables 9.8.1 (i-v) Yr1-Yr5, mean annual RV pace percentage for each programmed algorithm

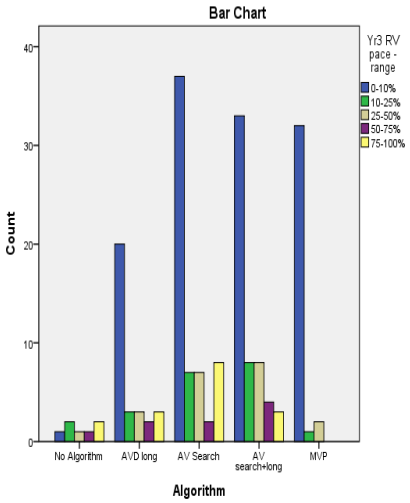
Observations from the Case Summaries

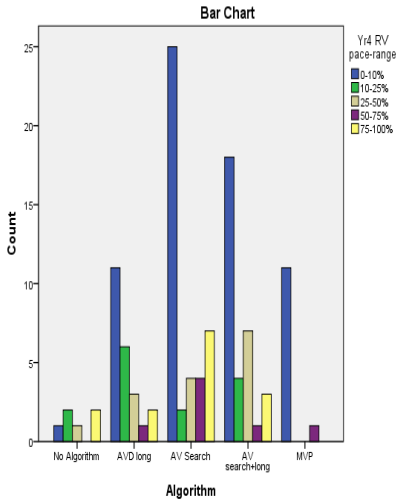
- Year 1 has the largest sample size with the full 349 dataset included in the analysis, the most RV pacing was observed in the “no algorithm” data with mean of 78% with the least mean RV pacing noted in MVP and SafeR algorithms with 2.9% and 1.6% respectively.
- The statistics are less robust due to the smaller core data size in years 4 and 5.
- Given that MVP and SafeR algorithms effectively operate in the same way by functioning in the atrium with a back-up mode to pace the ventricle when

atrioventricular block exists and there is little difference in their efficacy in terms of percentage of RV pacing, further analysis was on the basis of these two devices operating using the same algorithm. They were jointly coded as MVP giving the following visual distribution when grouped into mean RV pacing percentage bandings.









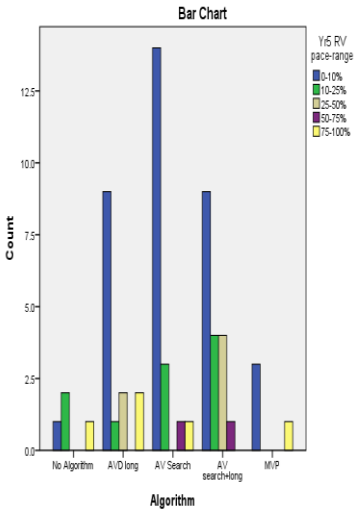
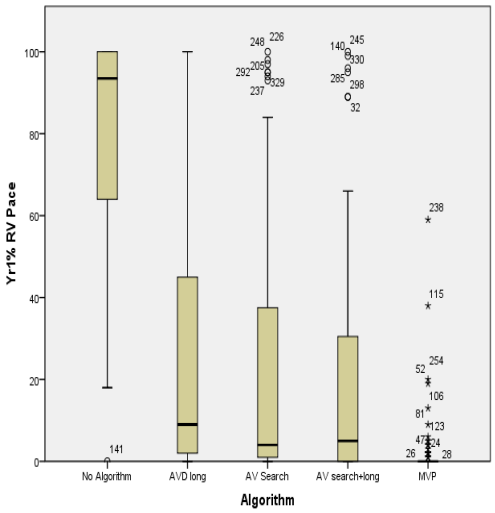
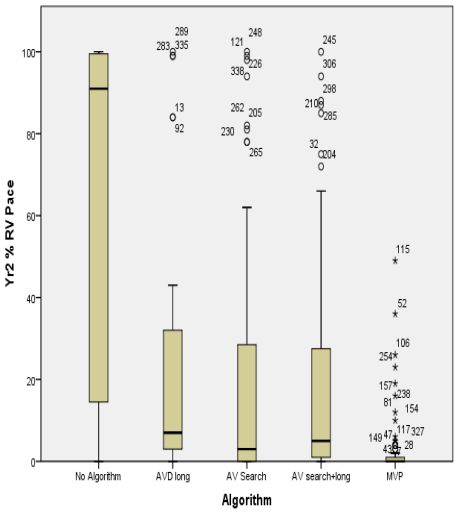


Fig. 9.8.2 – Graphs showing the percentage of RV pacing grouped into %age bandings. All showing dominance in the 0-10% (with exception of no algorithm), with a less uniform distribution in years 3-5 where there are more devices with AV algorithms compared to MVP devices

9.8.2. Distribution of RV Pacing by Algorithm using Box Plots





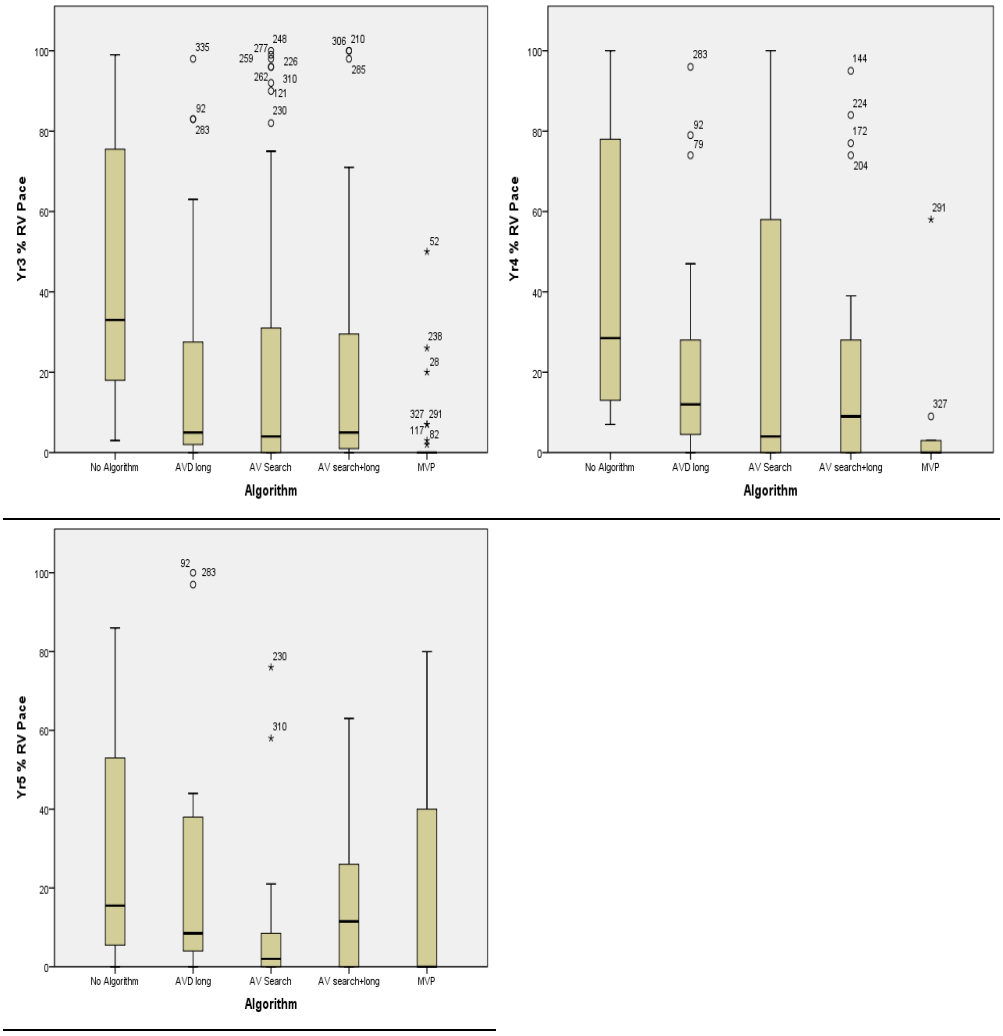


Fig 9.8.3 Box plots – non-parametric properties of the distribution of RV pacing for each year paced.

The above Box plots describe the medians of the data for each algorithm denoted by the horizontal line in the shaded box (note median line n MVP at zero – see case summary reports in Tables 9.8.1). The data in the box is the middle 50% of the data with the upper and lower quartiles above and below the horizontal line of the shaded box. The top of the shaded box and the horizontal line of the vertical line, or whisker, shows the top 25% and the lower vertical line, or whisker, below the tinted box shows the bottom 25% values.(Field 2009 pp:101)

There are a number of outliers (numbers next to small circles) in the data.

Years 1-3 show little variation in the median RV pacing between AVD long, AV Search and AVD long+search with greater differences between the control (no algorithm)and all algorithms, and MVP and all algorithms.

Further analysis is required to explore statistical significance of the differences between the algorithms, especially between AVD long, AV search and AV long+ search.

9.8.3. Statistical Significance in the Percentage of RV Pacing Between Algorithms.

The RVP annual percentage data has a non-Normal distribution, non-parametric testing was used and as there was a number of independent groups (algorithms), Kruskal-Wallis test was used to identify statistical differences between the algorithms. Due to the non-Normal distribution of the data, Krsukal-Wallis works on the basis of ranked data. Ordering the data from the lowest score to the highest and ranking the data on the basis of that score; it is these ranks that are analysed.

This type of statistic has a Chi-squared distribution with a value for the degrees of freedom being 1 less than the number of groups.

The outputs below from the SPSS programme give a significance value which is $p<0.05$ and a confidence interval on this p value is also calculated.

Ranks

	Algorithm	N	Mean Rank
Yr1% RV Pace	No Algorithm	14	306
	AVD long	56	222
	AV Search	83	199
	AV search+long	95	191
	MVP	101	96
	Total	349	

Kruskal-Wallis Test Yr1

			Yr1% RV Pace
Chi-Square			110.748
Df			4
Asymp. Sig.			<0.001
Monte Carlo Sig.	Sig.		<0.001
	99% Confidence Interval	Lower Bound	<0.001
		Upper Bound	<0.001

Table: 9.8.2 Kruskal-Wallis test showing summary of ranked data for each algorithm and test for significance between the variables, Year 1.

The computations associated with this statistical analysis, using the Exact method, are often extremely large and the SPSS system generates, like other statistical packages, sample tables for easier computation without substantially affecting the p value. This has been checked by repeating the analysis with different starting seeds.

This test shows that 1 or more of the programmed algorithms has a significant effect on the percentage of RV pacing in year 1 ($p<0.05$). Further post hoc testing (Mann-Whitney), which was adjusted for multiple testing thereafter, identified the statistical significance at individual algorithm level.

Further testing was performed for years 2-5 to see if the statistical significance remains the comparable over time, including post hoc tests.

a)

Kruskal-Wallis Year 2

			Yr2 % RV Pace
Chi-Square			62.871
Df			4
Asymp. Sig.			<0.001
Monte Carlo Sig.	Sig.		<0.001
	99% Confidence Interval	Lower Bound	<0.001
		Upper Bound	<0.001

b)

Kruskal-Wallis Year 3

			Yr3 % RV Pace
Chi-Square			38.065
Df			4
Asymp. Sig.			<0.001
Monte Carlo Sig.	Sig.		<0.001
	99% Confidence Interval	Lower Bound	<0.001
		Upper Bound	<0.001

c)

Kruskal-Wallis Year 4

			Yr4 % RV Pace
Chi-Square			13.150
Df			4
Asymp. Sig.			0.011
Monte Carlo Sig.	Sig.		0.008
	99% Confidence Interval	Lower Bound	0.006
		Upper Bound	0.010

d)

Kruskal-Wallis Year 5

			Yr5 % RV Pace
Chi-Square			4.850
Df			4
Asymp. Sig.			.303
Monte Carlo Sig.	Sig.		.309
	99% Confidence Interval	Lower Bound	.297
		Upper Bound	.321

Table: 9.8.2 a,b,c,d. Kruskal-Wallis tests for Years 2-5 testing significance of algorithms on RV pacing.

These tables show that there is a statistically significant relationship between the programmed algorithm and the degree of right ventricular pacing (percentage per year) with significance of p=<0.01. This is evident in every subsequent year except year 5 where the trend is non-significant, probably reflecting the small sample size (n=59).

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Yr1% RV Pace is the same across categories of Algorithm.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.
2	The distribution of Yr2 % RV Pace is the same across categories of Algorithm.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.
3	The distribution of Yr3 % RV Pace is the same across categories of Algorithm.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.
4	The distribution of Yr4 % RV Pace is the same across categories of Algorithm.	Independent-Samples Kruskal-Wallis Test	.011	Reject the null hypothesis.
5	The distribution of Yr5 % RV Pace is the same across categories of Algorithm.	Independent-Samples Kruskal-Wallis Test	.303	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table 9.8.3 Summary of Kruskal-Wallis tests for each year analysed looking for statistical significance against the null hypothesis of " no significant difference in the degree of RV pacing between algorithms". (Note SPSS output gives significance as .000 which approximates to p <0.001)

The data analysis using Kruskal-Wallis test shows a significant difference between the pacing algorithms chosen and percentage of right ventricular pacing for each year 1-4.

It can be deducted from the descriptive statistics in 9.8.1 and the case summary tables, that MVP and SafeR were associated with the lowest mean percentage of RV pacing in years 1-4 with the data becoming less valid in year 5.

The Kruskal-Wallis test shows statistical differences between all the algorithms in year 1-4, however there is a need for further analysis to demonstrate if there is statistical significance between each algorithm.

This analysis required post hoc procedures on the Kruskal-Wallis test, to look at each algorithm against each of the other to look for statistical significance for each pairing. The post hoc procedure used is the Mann-Whitney test which compares two independent conditions (Field 2009 pp:540) and the p-value adjusted for multiple testing (p-value)/(n!/((n-1)!*2!) for n groups being compared. For 5 groups this would be 0.05/(5.4.3.2.1/(3.2.1*2.1))=0.005.

9.8.4. Post Hoc Testing of Combinations of Algorithms Pairs Testing for Statistical Significance

The non-parametric testing suggested that there is a statistically significant relationship between algorithm and percentage of RV pacing, however it lacked any specificity.

Post hoc testing (Mann-Whitney) was used to identify the relationships between each algorithm and for each year.

As this involved more tests on the data, a decrease to the p value to 0.005 was used as the marker of statistical significance (see explanation above).

Mann-Whitney paired comparisons were performed for each subsequent year and displayed, as a summary, in the matrix below.

In years 1-3 there was statistically significant differences observed between “no algorithm” and all other algorithms and between MVP and all other algorithms. In year 4 there was a statistically significant difference between MVP and “no algorithm” and AVD long and in year 5 there was no statistical significant differences between any of the pairings. (P=<0.005)

As with previous data analyses the data in years 4 and 5 have much smaller samples and data is likely to be less reliable.

The following table (9.8.4) summarises which algorithms have the most statistically significant effect on the percentage of RV pacing.

Algorithm Yr 1	No Algorithm	AV Long	AV Search	AV search+long	MVP
No Algorithm		✓	✓	✓	✓
AVD Long			×	×	✓
AV Search				×	✓
AV search+long					✓
MVP					
Algorithm Yr2	No Algorithm	AV Long	AV Search	AV search+long	MVP
No Algorithm		×	×	×	✓
AVD Long			×	×	✓
AV Search				×	✓
AV search+long					✓
MVP					
Algorithm Yr3	No Algorithm	AV Long	AV Search	AV search+long	MVP
No Algorithm		×	×	×	✓
AVD Long			×	×	✓
AV Search				×	✓
AV search+long					✓
MVP					
Algorithm Yr4	No Algorithm	AV Long	AV Search	AV search+long	MVP
No Algorithm		×	×	×	✓
AVD Long			×	×	✓
AV Search				×	×
AV search+long					×
MVP					
Algorithm Yr5	No Algorithm	AV Long	AV Search	Av search+long	MVP
No Algorithm		×	×	×	×
AVD Long			×	×	×
AV Search				×	×
AV search+long					×
MVP					

Table 9.8.4 a simplified summary of the statistical significant differences between pairs of algorithms showing the algorithms pairs for which there is statistical significance at a value of p= <0.005, Using Mann-Whitney post hoc testing.

These data visually highlight the impact of MVP and confirm significantly lower rates of RV pacing in all years except for year 5, and when compared to AV search and AV search+long in year 4, p= <0.005 (equivalent to p=0.05).

'No algorithm' shows statistical significance in its effect on RV pacing in year 1 only.

9.9. Analysis of Time Spent in Atrial Fibrillation

Many of the major trials detailed in Chapter 6 suggested that a potential complication of pacing is the development of atrial fibrillation (AF). The reported incidence of atrial fibrillation in the elderly population is 30-44%, whilst in the elderly pacemaker population it is 48% (Wyndham 2000) The key risk element in AF is thromboembolism and stroke.

The final question posed by this thesis was to identify any correlation between the degree of RV pacing or algorithm and the overall burden of atrial fibrillation (percentage per year).

The first analysis identifies the overall percentage of pacing for all of the patients for each of the years – again looking over a period of time to identify any progression with age.

What cannot be concluded from this research is the likelihood of the study population developing AF, whether or not they had a pacemaker implanted

Time Spent in AF

Statistics

		Yr1 % AF	Yr2 % AF	Yr3 % AF	Yr4 % AF	Yr5 % AF
N	Valid	348	285	190	115	57
	*Data not currently available	1	64	159	234	292
Mean		3.1	4.5	5.2	7.4	13.7
Std. Error of Mean		.636	.961	1.086	1.847	3.732
Median		.00	.00	.00	.00	.00
Std. Deviation		11.872	16.222	14.964	19.807	28.178
Minimum		0	0	0	0	0
Maximum		100	100	93	100	100

*No current data available due to time since implant.

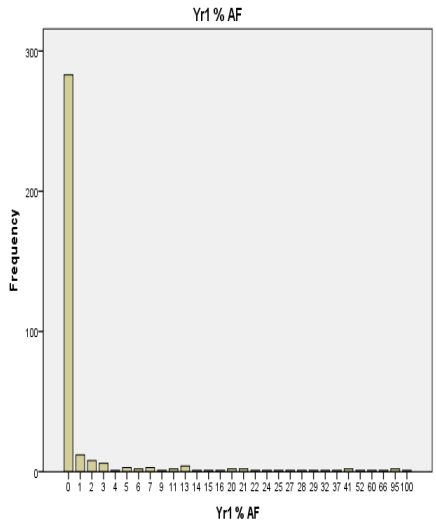
Table 9.8.5 – Descriptive summary showing the mean atrial fibrillation burden per year for all devices, as a percentage. For example a mean of 3.1% represents the mean time spent on atrial fibrillation across the dataset. Patients with 100% ventricular pacing have not been excluded if not considered chronic at time of follow-up (would be programmed VVI once 100% AF for up to 1 year – see pg 68)

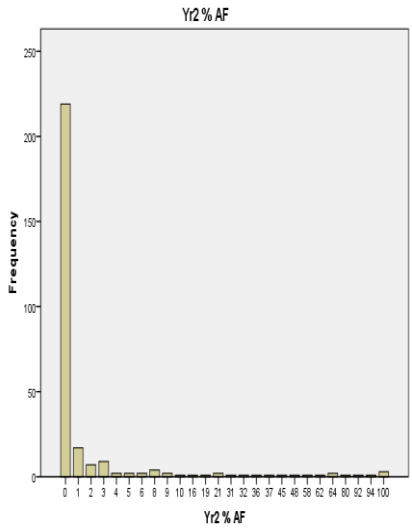
It must be noted that the distributions are non-Normal as inferred by the magnitude of the standard deviation around the mean: on the basis of Normality, much of the observations would be negative which would be incorrect demonstrating the non-normality of the data.

Although the percentage of atrial fibrillations is generally low it incrementally increases with years from original implant – or patient age. Further testing was used to establish any correlation between the burden of atrial fibrillation and percentage of RV pacing and/or algorithm.

In order to decide on the most appropriate method of statistical analysis the data distribution was evaluated.

9.9.1. Distribution of Annual Percentage of Atrial Fibrillation





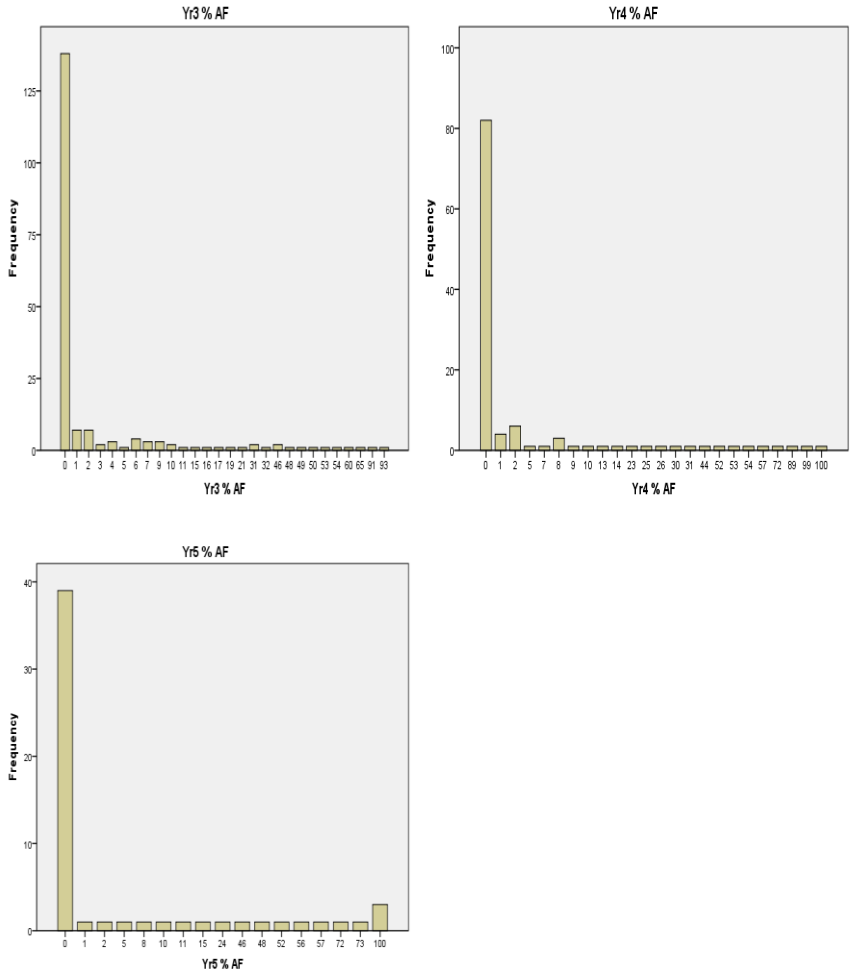


Fig 9.9.1 Yearly AF distribution for each year showing extremely non-Normal distribution.

Given the non-Normal distribution of the data for atrial fibrillation, non-parametric statistical testing was used. The question requires a correlation between the algorithm used, the percentage of RV pacing and the overall burden of atrial fibrillation (percentage per year).

Spearman's rho statistical testing was deemed as the most appropriate method based on the non-parametric nature of the data.

Spearman rho correlations were performed on RV pace percentage and AF in each of the years, the results are summarised below.

Yr1	AF%	
RV Pace%	0.003/1.000	Sig. (2 Tailed)/Correlation Coefficient
Yr2	AF%	
RV Pace%	0.006/.162	Sig. (2 Tailed)/Correlation Coefficient
Yr3	AF%	
RV Pace%	<0.001/.308	Sig. (2 Tailed)/Correlation Coefficient
Yr4	AF%	
RV Pace%	0.01/.236	Sig. (2 Tailed)/Correlation Coefficient
Yr5	AF%	
RV Pace%	0.216/.167	Sig. (2 Tailed)/Correlation Coefficient

Table 9.9.2 Spearman rho correlation between percentage of RV pacing and atrial fibrillation. Table details the p value/correlation co-efficient for each correlation

This table shows that in all years except year 5, there is a correlation between the overall annual percentage of RV pacing and the overall annual percentage of AF, correlated at significance of $p<0.05$.

In terms of atrial fibrillation, there is a direct correlation between the degree of RV pacing and the burden of AF as detailed in Section 9.7. As algorithm category indices are in no particular order they cannot be correlated with AF and therefore correlation analysis could not be undertaken. However it could be concluded that any algorithm that reduces RV pacing is likely reduce the amount of AF.

It can therefore be concluded that there is a direct influence of the programmed algorithm on the overall percentage of RV pacing which in turn appears to affect the prevalence of AF.

As with other aspects of the research analysis, the overall sample size and range across the differing algorithms is small and poorly distributed, this skews the analysis and makes year 5 less reliable in terms of generating robust conclusions.

Chapter 10 – Discussion

10.1. Clinical Overview of Cardiac Pacing

Bradyarrhythmias are commonly as a result of degeneration of the cardiac electrical conduction system. The heart has its own intrinsic electrical conduction system which stimulates the mechanical events of systole and diastole, although there are sympathetic and parasympathetic influences on heart rate, the cardiac conduction system is largely independent of overall neurological control.

Cardiac muscle, like other muscles, has the ability to react to external artificial electrical stimulus thus producing an action potential resulting in contraction. These cardiac features have allowed for the development of small electrical generators to be implanted connected to electrical conductors (leads) sited in or on the heart muscle surface. These electrical pulse generators called pacemakers, support the intrinsic electrical conduction of the heart and hence maintain the mechanical events that will sustain life.

The use of artificial cardiac pacing as the treatment of choice for chronic symptomatic bradycardias has been well established worldwide. Although there has been considerable technological advancement in terms of the size, longevity and programming sophistication of these devices, it cannot be ignored that the artificial replication of the cardiac conduction by these devices is not without its haemodynamic and physiological compromise and consequences.

There are certainly cardiac conduction abnormalities for which ventricular pacing is unavoidable, such as atrioventricular block and chronic atrial fibrillation with bradycardia; there is however programming scope and device decisions that can be made to minimise the degree of RVP.

10.2. Review of Implanting Practice- CDDFT

There are clear guidelines on the use of devices for specific cardiac conduction abnormalities (Epstein, DiMarco et al. 2008), and reviewing CDDFT implanting data

against the local and national practice would suggest that there is compliance with appropriate device and mode prescription.

In the pacemaker implant population, the national incidence of SSS was 27.5% in 2010, with the incidence in the population of County Durham and Darlington at 29.3%.

The guidance recommends that patients with an indication of SSS should receive an atrial based pacing system for the treatment of this syndrome. In 2010 the UK rate of atrial based pacing systems for SSS was 84%. For the 2 implanting centres in CDDFT there was 91.9% atrial based pacing for SSS in UHND and 95.2% in DMH.

This would suggest that the local pacemaker implanting practice for patients in County Durham and Darlington with an aetiology of SSS is in keeping with international guidelines and at rates higher than the national average.(Cunningham 2010)

In 2010, CDDFT implanted 0.6% AAIR devices in total with the majority of patient receiving DDDR devices for all aetiologies. Again these data indicate that the implanting practice for CDDFT is largely in-line with national and regional practice for SSS with a strong compliance against the use of systems that are solely atrial based: the almost exclusive preference was for the use of DDDR systems.

10.2.1. Use of Device Modes in SSS (study population)

Out of the 349 patients reviewed in year 1 of the study with an aetiology of SSS, only 3 patients did not have a rate responsive pacemaker for rate regulation.

100 (28.7%) devices had a minimal ventricular pacing algorithm programmes AAI⇔DDD, 96 (27.5%) had a long AVD and AV search programmed, 83 (23.8%) had AV search only, 56 (16%) AVD long only and 14 (4%) patients had no algorithm programmed in an effort to reduce RV pacing.

This would indicate that there is a proactive effort in the pacemaker clinics in CDDFT to use devices and algorithms in an attempt to reduce the need for unnecessary RV pacing in patients with SSS.

10.3. Review of Efficacy of Pacing Strategies Utilised in CDDFT

Chapter 9 compared all strategies employed in CDDFT cardiac device services in an effort to reduce ventricular pacing. It must be noted that in only 4% of patients(14 in year 1) there had been no active programming to reduce RV pacing, although these

devices did have the capability for AVD modification/extension, it was not programmed *per se*. It may be appropriate to review these 14 patient files to understand the rationale in these cases.

What is unclear from the national and regional reported data is whether CDDFT is unusual in its proactive approach to reducing unnecessary RVP or whether this is common practice regionally or indeed nationally.

Given the volume of evidence supporting the potential for adverse effects of inappropriate RV pacing, there is no national guidance on post implant programming or benchmarking against this as a standard in cardiac device management. The nationally reported data only covers the immediate device prescription.

Data analysis of the study dataset indicates an overwhelming reduction in RV pacing using the more recent MVP algorithms AAI⇔DDD over any of the other strategies involving AVD programming.

Years 1-3 showed <4% RV pacing burden with both minimal ventricular pacing algorithms, compared to an RV pacing burden of between 17% and 27% for all other programmed algorithms. Of the AVD algorithms AVD long + search being the most effective in years 1-3. By comparison, patients with no algorithm had an RV pacing percentage of 46-78% over years 1-3.

The data in years 4 and 5 are less reliable as the sample size reduces to 116 and 59 respectively, with each algorithm disproportionately represented for reliable comparison.

Given that MVP and “no algorithm” showing respectively the lowest and highest percentage of RVP, further statistical analysis of the data was undertaken to assess if there was any statistically significant difference between the 3 AV extension algorithms - AVD long, AV search and AVD long +search in their effect on the amount of RV pacing.

It was concluded that there was no statistically significant difference between these 3 algorithms in the effect on the overall percentage of RVP at a p value of ≤ 0.05.

In terms of the effect of varying programming strategies on the burden of atrial fibrillation, testing was not able to reliably show any direct correlation between algorithm and the overall burden of atrial fibrillation. However, in keeping with the

research, there is a statistically significant correlation between the percentage of RV pacing and the burden of AF in years 1-4 ($p=<0.05$)

10.4. Study Limitations

This study was a non-randomised review of patients with existing devices, there are obvious opportunities for bias in terms of the original implant, the programming and the data selection. The conclusions should be considered against a background of these limitations.

This study reviewed patients with SSS only; there is scope for reviewing the use of algorithms, such as MVP, in patients with intermittent AV block given the same potential for deleterious effects due to long term RV pacing especially if the AV block is not a chronic condition in many patients.

The study sought to review RV pacing over a number of years from implant to see if efficacy of algorithms altered with time, this data became unreliable after year 3 due to small numbers and large variability between numbers in each of the algorithm groups.

Given the analysis of the data of AVB/AF development from implant, suggesting that development of AVB or AF occurred within the first year from implant (Section 9.1.3), the development of chronic AVB or AF does not seem to develop in greater proportions in the SSS population than the normal elderly population. The value of the data collected beyond the first or second year added little value to the research overall.

Chapter 11 – Recommendations and Conclusions

11.1. Recommendations for CDDFT

The research sought to identify "cardiac device algorithms for optimal outcomes in patients with sick sinus syndrome" by posing the following key questions:

I. What is the most effective programmable algorithm or programming strategy to avoid ventricular pacing in patients with pure sick sinus syndrome?

II. Is there a correlation between these strategies and the burden of atrial fibrillation?

The use of MVP algorithms that use the mode AAI⇔DDD was associated with superior effectiveness in reducing the amount of RV pacing in patients with sick sinus syndrome. The efficacy of the other programmable algorithms, although effective at below 30%, were all less effective that MVP. There is no statistically significant difference in the efficacy between AVD long, AV search and AV search+long.

In terms of atrial fibrillation, there is a direct correlation between the degree of RV pacing and the burden of AF. As algorithm category indices are in no particular order they cannot be correlated with AF and therefore correlation analysis could not be undertaken. However it could be concluded that any algorithm that reduces RV pacing is likely reduce the amount of AF.

This research did not include a cost-based analysis, and it must be recognised that MVP devices are more expensive than standard dual chamber devices and as such any recommendations will be based purely on the clinical evidence.

The recommendations from this research for CDDFT pacemaker implanting and follow-up service is to implant devices with available MVP algorithms in patients with sick sinus syndrome as this will reduce unnecessary ventricular pacing, with its potential deleterious effects on cardiac function, and reduce the burden of AF and its potential for thromboembolisms and stroke.

11.2. Conclusions

This research project has identified the historical inconsistencies of implanting and programming practice in CDDFT. The long term effects of pacing, as the treatment of choice for bradyarrhythmias, has only relatively recently been fully evaluated and widely published.

An integral part of this research project was evaluation of the literature and review of the clinical trials in relation to deleterious effects of RVP, this evidence must form an integral part of the decision making process when decisions are made on the implantation and programming practice.

The national guidelines have been the mainstay of benchmarking and performance review in terms of appropriate devices for the indication for pacing, however this research project would suggest that the wider context of available programming strategies to ensure that the level of pacing delivered is clinically effective in terms of maintaining adequate conduction support but ensuring as normal an intrinsic conduction as possible.

In the case of SSS, the evidence would support the use of MVP devices as being the most effective pacing strategy, with little evidence of adverse consequences.

If we are to provide the best outcomes for pacemaker patients, then there needs to be a proactive attempt to reduce un-necessary RVP wherever possible, the evidence would also suggest that reducing the unnecessary pacing may also have an effect on reducing the incidence of atrial fibrillation.

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Appendices

Appendix 1 – Ethics Approval CDDFT

County Durham and Darlington NHS
NHS Foundation Trust

Research and Development Department
Darlington Memorial Hospital
Pierremont Unit
Hollyhurst Road
Darlington
DL3 6HX

Tel: 01325 743458

All studies are subject to the requirements of the DoH's Research Governance Framework 2005 Second Edition and subsequent amendments. If you have not read this document, or are unfamiliar with its contents you are strongly advised to refer to it before commencing with any research or data collection. You may not commence data collection until you have written formal authorisation from the Chair of the Research Review Board and an appropriate ethics committee.

Private and Confidential

18th October 2011

Jane Curry
Principle Cardiac Physiologist
Cardio Respiratory
Ground Floor
Darlington Memorial Hospital

Dear Jane

Project Title: Optimal Cardiac Device Algorithms in Patients with Sick Sinus Syndrome

R&D Ref: MED-153-2011

I am writing to inform you that you have trust approval to proceed with the above-titled study. This notification allows you to begin recruitment and data collection and acknowledges that trust approval procedures have been successfully completed.

Ethical approval is not required under the new Research Ethics Committees Regulations (Sept 2011 - Section 6) as you are not using identifiable data and it is data which has been collected during the course of care of the patients.

Approved documents

Document Type	**Version**	**Dated**
R&D Form	89071/245838/14/852	08/09/2011
SSIF	Not stated	07/09/2011
Protocol	Not stated	Not stated
CV - Jane Curry	-	21/09/2011
GCP Certificate – Jane curry	-	31/08/2011

Research Conduct, Management and Governance

It is the responsibility of the Chief Investigator/Principal Investigator to maintain robust management of the clinical trial and ensure that the study is conducted in compliance with the Organisational Research Review Board and Independent Ethics Committee approved Protocol. You are reminded to refer to your SOPs File to ensure good Conduct, Management and Governance of this Study.

The R&D Department will monitor the progress of the study (SOPs 11&14)

You will receive:

- A Start-up Form 6 weeks from the date of this Approval Letter.
  (Upon indication on the study start up form that accrual has commenced you will be required to complete an Accrual Pro-forma on a monthly basis).

- A Monitoring From 6 monthly/yearly

You are required to complete and return the above documents within two weeks of receipt. (SOP 14)

The R&D Department must be notified within 90 days of the close down of the study and within 15 days if terminated early. On receipt of notification of study closure the R&D Department will send a study closed down form for completion . A member of the R&D Department will arrange to meet with a member of the Research Team to finalise the closure of the Study (SOP 11).

The NHS Retention and Disposal schedule (HSC 1999/053) states that clinical notes of patients entered into clinical trials of medicinal projects should be retained for 15 years after conclusion of treatment. Please find enclosed the procedure for the identification of patients in clinical trials of medicinal products and study labels to identify notes

On completion of your study I would be grateful if you could forward a copy of your final report and any publications as a result of the study to the R&D Office at the above address.

The R&D committee wishes you every success with the completion of your study.

Yours sincerely

Dr Y Yiannakou

Research Review Board Chair

Copy to:

CI

Dr D Wilson

Durham University

School of Medicine and Health

Queens Campus

Stockton-on-Tees

TS17 6BH

Sponsor

Lynne Williams

R&D Manager

County Durham and Darlington Foundation NHS Trust

Appendix 2 – Good Clinical Practice Certificate

NHS
National Institute for Health Research
Clinical Research Network

Certificate of Attendance

Jane Curry

attended

Introduction to Good Clinical Practice (GCP): A practical guide to ethical and scientific quality standards in clinical research

on 31/08/2011

Sessions include:
1. The Value of Clinical Research and the role of the NIHR CRN
2. GCP: the standards and why we have them
3. Study set up: responsibilities, approvals and essential documents
4. The process of informed consent
5. Case report form, source data and data entry completion
6. Safety reporting in clinical trials

Paul Maher

Paul Maher
NIHR CRN GCP Training Manager

Appendix 3 – Ethics Approval Durham University

Dear Jane,

Thank you for sending me your proposal for an audit of all pacemakers implanted at CDDFT over the past 5 years. This will not require you to recruit participants and I am satisfied that this therefore does not require full committee review by the School of Medicine and Health Ethics Sub-Committee.

I am pleased to confirm ethical approval by Chair's action for your proposal.

Good luck with the audit, I hope that it goes well.

Kind regards
Rebecca

Rebecca Perrett
Research and Development Manager
Wolfson Research Institute
Durham University
Queen's Campus
Stockton-on-Tees
TS17 6BH

Tel: 0191 334 0425