An analysis of defibrillation and cardiac resynchronization therapy strategies in patients with failing systemic right ventricles.

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The candidate confirms that the work submitted is his own and that acknowledgement has been given where reference has been made to the work of others.

Abstract:

Background: The expanding application of cardiac resynchronization (CRT) and implantable cardioverter-defibrillator therapy (ICD) to include patients with congenital heart disease requires careful evaluation of selection criteria and unconventional adaptive strategies to ensure clinical efficacy

Methods: A single centre prospective analysis of adults post atrial redirection surgery (Mustard operation) for dextro-transposition of the great arteries (d-TGA) presenting with systemic right ventricular (sRV) dysfunction and at risk of sudden cardiac death (SCD).

Results: All patients (mean age 25 years, range 18-35) with varying functional disability {New York Heart Association (NYHA) II-III} receiving ICDs ± concomitant CRT were evaluated . Total follow-up period was 24 months. A patient individualized approach was used for device implantation. Endocardial, epicardial and transthoracic defibrillation strategies were examined in 5 consecutive cases. A hybridized form of CRT was employed in two patients. Only one patient demonstrated response to therapy while the other deteriorated during biventricular pacing (BVP). This prompted a novel approach to CRT using non-contact mapping (NCM) and acute intra-arterial blood pressure response to guide endocardial sRV lead placement in a single patient. The ejection fraction increased from 23 -33% within 1 week post procedure and clinical improvement was sustained after 6-months follow-up.

Conclusion: Application of CRT/ICD therapy to patients with sRV dysfunction requires individualized and adaptive strategies to overcome anatomical constraints. This study represents a chronological and evolutionary account of these measures.

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Publications and presentations arising from this dissertation

Defibrillator and cardiac resynchronisation therapy after Mustard surgery for transposition of the great arteries....Michael KA, Veldtman G, Paisey JR, Yue AM, Allen S, *Robinson S,* Sunni N, Roberts PR, Morgan JM. Europace 2006:8, supplement 1: 99PW/8 (Abstract at Cardiostim 2006).

Use of non-contact mapping and acute haemodynamic monitoring to guide cardiac resynchronisation (CRT) in systemic right ventricular dysfunction (sRV) dysfunction after Mustard surgery(MS).... KA Michael, S Robinson, GR Veldtman, JR Paisey, NS Sunni, S Allen , PR Roberts, JM Morgan. (Abstract at Heart Rhythm UK, Birmingham September 2006).

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Abbreviations

sRV	**-**	**systemic right ventricle**
pLV	**-**	**sub-pulmonary left ventricle**
RA	**-**	**right atrium**
CS	**-**	**coronary sinus**
NYHA	**-**	**New York Heart Asoociation**
ICD	**-**	**implantable cardiovert-defibrillator**
CRT/D	**-**	**cardiac resynchronization/defibrillator therapy**
BVP	**-**	**biventricular pacing**
J	**-**	**joules**
AVD	**-**	**atrioventricular delay**
NCM	**-**	**non-contact mapping**
DFT	**-**	**defibrillation threshold**
TTE	**-**	**transthoracic echocardiogram**
ECG	**-**	**electrocardiogram**
VT	**-**	**ventricular tachycardia**
VF	**-**	**ventricular fibrillation**
SCD	**-**	**sudden cardiac death**

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1. Introduction

1.1 History of atrial re-direction surgery

Atrial redirection surgery, brought into common use by Mustard's modification of the Senning procedure, transformed the natural history of dextro-transposition of the great arteries (d-TGA) from a 90% one year mortality to a 90% 1 year survival(1). Although rendering the infant acyanotic with excellent functional capacity, the morphological right ventricle(sRV) is required to support the systemic circulation. The sRV faces substantial pressure overload resulting in a high incidence of late ventricular failure(2). This prompted an evolution to a more physiologically acceptable correction in the form of the arterial switch or Jatene operation(3). The arrhythmias and heart failure that usually manifest by the second decade of life in patients after atrial redirection surgery pose a challenge to management.

1.2 Late complications of atrial redirection surgery.

Apart from the progressive sRV dysfunction and heart failure, sinus bradycardia commonly arises because of surgical disruption to the sino-atrial node blood supply warranting early pacemaker implantation (commonly encountered in our cohort) (4). The incidence of tachyarrythmias, most notably atrial flutter and fibrillation, may be related to ventricular dysfunction or as a consequence of atrial scarring following surgery. Ventricular tachycardia (VT) and fibrillation (VF) have been documented on holter monitoring in various long term studies and the incidence of sudden cardiac death (SCD) ranges between 2-11%(5). Mechanical complications include severe tricuspid regurgitation, valvar and sub-valvar pulmonary stenosis, intra-baffle leaks and obstruction to blood flow either at the level of the systemic cardiac veins or within the baffle because of stenosis or thrombosis. These cause haemodynamic compromise, potentially impede device implantation and may require preceding intervention to facilitate access of pacing/defibrillator leads into the cardiac chambers(1) .

1.3 Anatomy of the atrial switch operation.

Dextro-transposition is incompatible with life because of ventriculo-arterial discordance. The systemic venous blood from the superior and inferior vena cavae drain into the right atrium (RA), through the tricuspid valve and is ejected into the aorta. The pulmonary veins drain into the left atrium and then sub-pulmonary left ventricle (pLV) through the mitral valve and empty into the pulmonary artery. There is invariably mixing at atrial level enhanced by presence of a patent ductus arteriosus ($^1/_3$ of patients) or a ventricular septal defect ($^2/_3$ of patients). A *complex transposition* refers to the co-existence of either a ventricular-septal defect or sub-pulmonary stenosis in contrast to a *simple transposition* where there is no haemodynamically significant concomitant lesion(6).

In d-TGA, an atrial septostomy is often employed as a palliative procedure until definitive correction. The latter previously involved atrial redirection of blood flow utilising a either dacron or pericardial patch in the Mustard operation or just atrial tissue in the technically more difficult Senning operation(7). These procedures created a revolution in the management of d-TGA increasing patient survival to adulthood. The atrium is essentially divided into an anterior and posterior compartment separating the passage of systemic venous return to the pLV and oxygenated pulmonary flow to the sRV.

1.4 The coronary venous anatomy in relation to transposition.

The coronary sinus (CS) in d-TGA, as in the normal human heart, lies in the atrio-ventricular groove between the left atrium and left ventricle. In the case of surgically altered d-TGA, the resultant sRV, is therefore not encircled by the CS. This limits transvenous access to the lateral wall of the sRV, for lead placement. A large aberrant coronary vein arising from the sRV may drain into the CS or directly into the RA. This may present an option for lead placement. An anterolateral cardiac vein may be regarded as a poor pacing site for a failing systemic LV but may be entirely suitable for pacing the sRV. In an anatomical study by Uemura et al, in hearts with congenitally corrected transposition (atrio-ventricular and ventriculo-arterial discordance), the CS drained the sRV in the majority (87%) of specimens

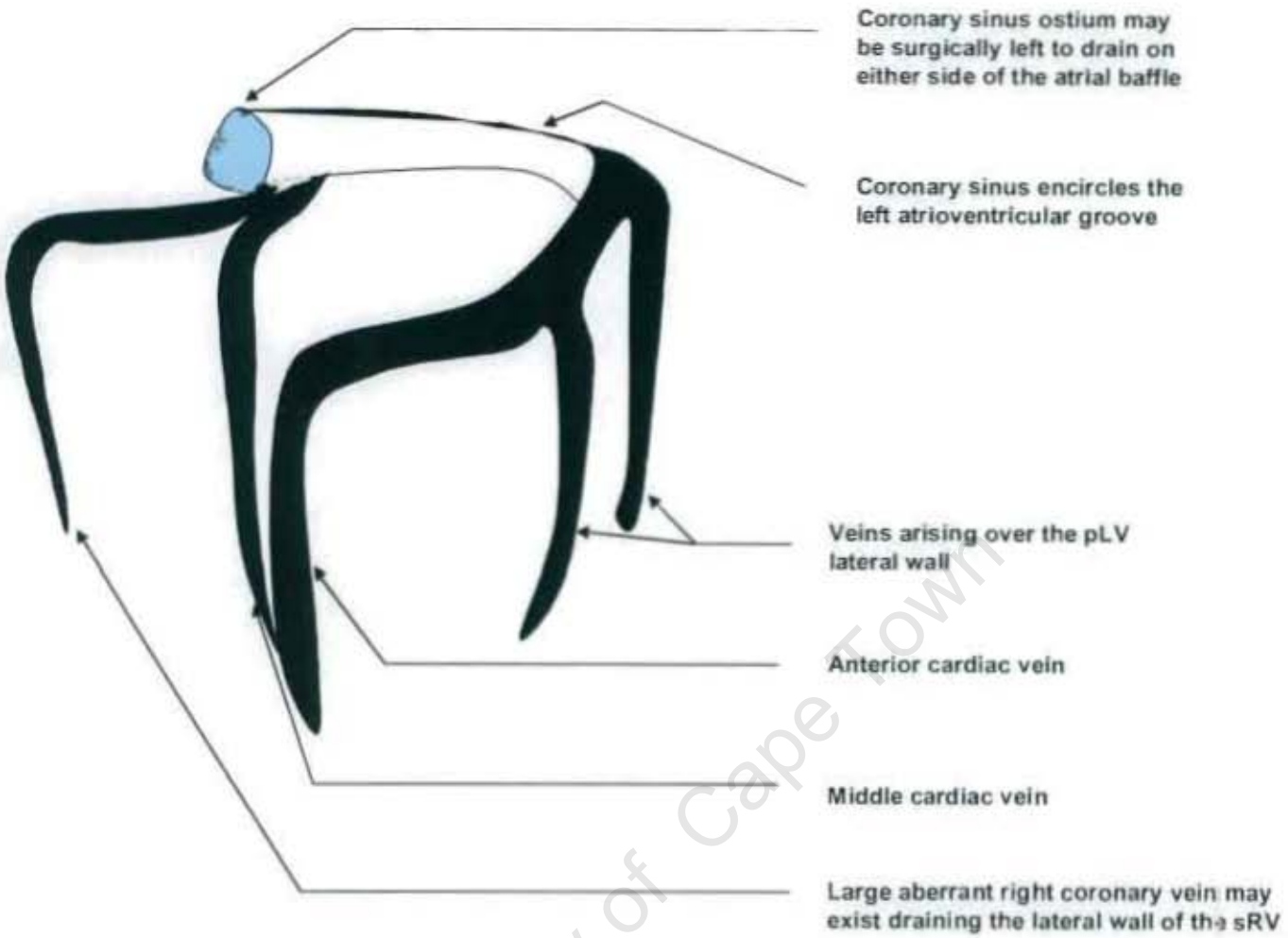


Figure 1.1 The coronary veinous structure.

with 5 having partial/ complete drainage directly into the atrium(8). Access to the coronary venous vasculature post Mustard surgery in d-TGA is also depend on whether the surgeon leaves the CS os open to the systemic-atrial side of the baffle or to the pulmonary-venous portion. The next challenge is being able to cannulate the CS percutaneously given the altered atrial structure. Direct imagining using cardiac magnetic resonance imaging, computerized tomography, intracardiac or transoesophageal echocardiograpy improves identification of coronary venous anatomy(9-11). These, however, depend on local expertise, availability and cost considerations. They were not employed in this cohort.

1.5 The implantable cardioverter-defibrillator

The concept of an implantable defibrillator, the size of a pacemaker, is attributed to Michel Mirowski in the 1960`s which later, in collaboration with Morton Mower, lead to animal experimentation in the 1970`s and the first human studies in 1980(8;12).

The ICD, in essence, consists of a capacitor which stores and then dissipates the charge, a battery and a processing unit. The size of the ICD is mainly dependent on the former two components and with current technology this has been reduced to 35 cm^3 allowing for pre-pectoral implantation performed under conscious sedation just like a pacemaker(13). Initial implants utilised epicardial patch electrodes with a surgical implantation of the ICD into an abdominal location, however development of a coil electrode mounted around the lead, allowed for transvenous implantation to the endocardial surface of the RV(14). Implantable cardioverter-defibrillators now also incorporate brady- and antitachycardia pacing in addition to defibrillation functions. Sophisticated algorithms have also evolved to limit the occurrence of inappropriate therapies, in the hope of achieving painless resolution of VT and to conserve battery life. The latter still remains limited to just 4-5 years relative to 7-10 years achieved by modern pacemakers and is largely due to the charging of the capacitor in addition to supporting complex circuitry and pacemaker functions(15;16).

1.6 Defibrillation concepts

Our understanding of the mechanisms of ventricular fibrillation(VF) have evolved from a simplistic view of random chaotic electrical activity to a more structured re-entry mechanism consisting of self replicating rotors(17). The origin of each rotor may depend on the underlying myocardial substrate(18). Initiation may be spontaneous (as in a clinical setting) or induced by high frequency burst pacing (typically 50 or 60Hz), direct current application across cardiac tissue, or by a low voltage shock delivered during the vulnerable repolarization phase.

Effective arrest of VF in a clinical setting, is the challenge to current medical technology. It relies on a discharge of electrical energy from the defibrillator applied across epicardial/endocardial/subcutaneous electrodes. These pulses of energy are delivered as two components with the highest voltage in the leading edge and typically decays to a pre-defined limit (usually 50 or 60%). The polarity of the pulse is then reversed and it continues to decay to completion(figure 1.1). The duration of each pulse, referred to as the pulse width, is a reflection of capacitance and influences efficacy(19). This dual component waveform is described as *biphasic*. It has been shown in studies to be superior to monophasic and even triphasic patterns and is the standard in current commercially available ICDs although variation exists between manufacturers for nominal settings(20).

The energy required to defibrillate is subject to characteristics of both the substrate and device components. A high body mass index and ventricular hypertrophy/ dilation has been shown to reduce defibrillation efficacy. Also, the longer the duration of VF, the more difficult it becomes to effect defibrillation, emphasising the need for shorter capacitor charge times and for initial device therapies to be effective(19;21;22).

The implanted defibrillator system can be adapted to overcome these limitations to some extent. Increased electrode width and surface area improves defibrillation thresholds (DFTs). So the addition of adjunctive subcutaneous, epicardial or transvenous leads may be used to

enhance efficacy in a clinical setting(23). The position of electrodes, particularly in an endocardial system, may alter the path of current or improve the contact with the ventricular surface. The ventricular septum represents the largest myocardial bulk and therefore it necessary to maintain this cardiac tissue juxtaposed within the path of the defibrillation current(24).

Reversal of the polarity of the first phase may, also improve defibrillation outcome, therefore the ICD is programmed to automatically reverse the polarity of the shock waveform after several failures (25).

The use of a high energy device (maximum 41J available commercially) may also be used to achieve successful defibrillation although this measure increases cost particularly if performed as a revision procedure.

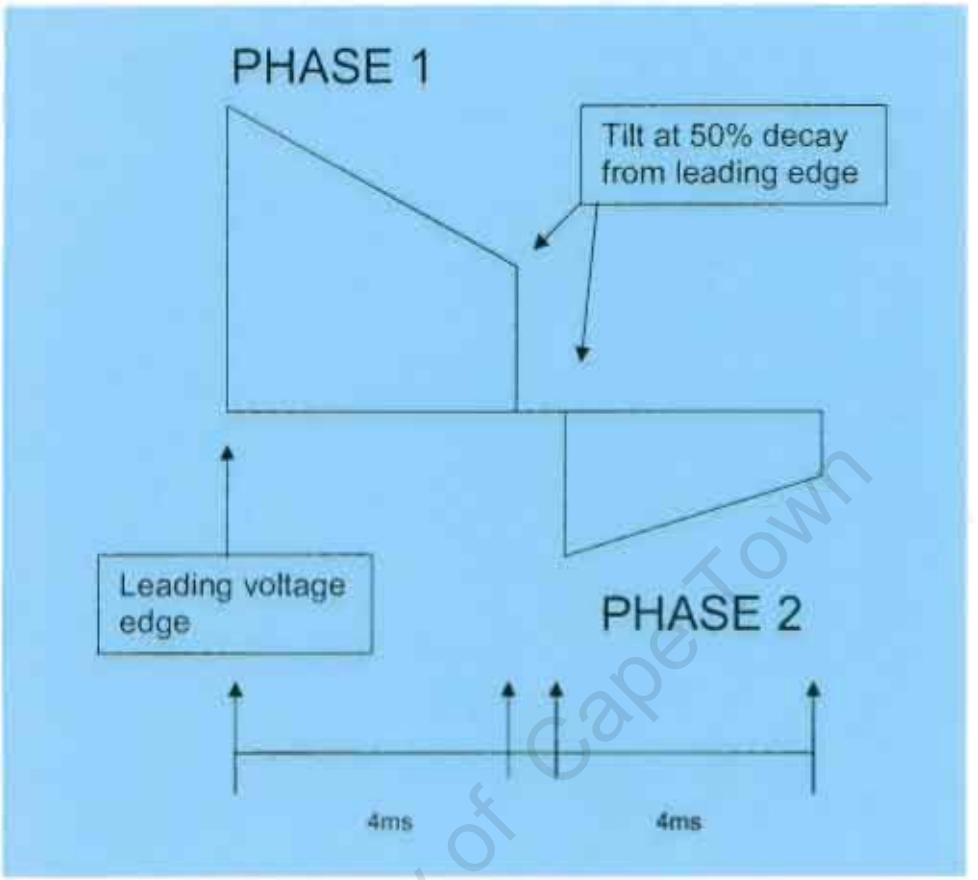


Figure 1.2 An example of a biphasic defibrillation waveform: Phase 1 discharged at normal polarity ie. distal electrode is anodal. The waveform "tilt" occurs after 50% decay from the leading voltage to deliver the remaining energy as phase 2 at reversed polarity.

1.7 Evolving concepts of cardiac resynchronization therapy

Cardiac resychronization therapy (CRT) has become an integral part of the management of patients with ischaemic and non-ischaemic cardiomyopathies presenting with advanced heart failure. It not only forms a bridge to transplantation and an effective measure to improve functional status but positively influences ventricular remodelling translated into decrease of cardiac dimensions, increased EF and reduced mortality(26). This device based strategy has also been successfully applied in patients with adult congenital heart disease and ventricular dysfunction(27). Experience is however limited in patients with morphological sRVs and selection criteria are being defined in the face of the expanding application of CRT(28;29).

Cardiac asynchrony has been traditionally defined in patients in terms of electrical (QRS width >120ms) and doppler echocardiography (conventional/ tissue doppler). The CRT non-responder population however remains between 20-30% warranting evaluation of additional or alternative measurements(30).

Electrical stimulation of the failing systemic ventricle is usually achieved transvenously via CS cannulation, utilising specially designed left venticular pacing leads. If this is unsuccessful (eg. lack of a suitable ventricular vein) a trans-sternal, surgical approach may be used. The latter ,however, may be preferable if conducted at the time of cardiac surgery or with surgically/ congenitally altered anatomy that makes transvenous CS access difficult or unachievable.

1.8 Three dimensional (non-contact) electrophysiological mapping

The non-contact multi-electrode array (MEA) system (Ensite3000. St. Jude Medical, USA) consists of 64 electrode wires woven in a basket conformation around a balloon (figure 1.2). It is deployed in a collapsed state into the chamber to be evaluated. In this study, the MEA was advanced over a 0.032in J-tipped wired trans-aortically and retrogradely over the aortic valve into the sRV. The balloon was then inflated with a contrast-saline solution to a volume where the electrodes lay in close proximity but not touching the endocardium.

Acquisition of far field electrograms are amplified by system, and generate up to 3360 virtual electrograms across the endocardium of the sampled cardiac chamber. This method then, uses inverse mathematical formulae, in order to generate dynamic voltage maps of the endocardium in sinus rhythm and arrhythmia. Static maps are also possible by generating a colour representation of the temporal sequence of activation of the endocardium as well as the location of scar tissue derived from measured voltage gradients. The sampling is instantaneous and intuitive in that it is presented in a three dimensional recreation of the cardiac chamber(31;32).

Apart from its validation in mapping of re-entry and focal/automatic arrhythmias, Lambiase et al, have demonstrated its use in defining areas of slow electrical conduction, thus guiding CRT to more optimal sites for "LV" lead placement(33).

Figure 1.3 The muliti-electrode array (Ensite™) catheter is able to acquire up to 3360 isopotentials instantaneously recreating a 3-dimensional virtual electrode map of the endocardial surface of the cardiac chamber.

* Reproduced by kind permission of St. Jude Medical, UK.

2 Study Design

2.1 Ethical considerations

All patients where jointly managed at a tertiary referral centre for clinical electrophysiology and adult congenital heart disease in the United Kingdom. Informed consent was obtained from each patient included in this study. Formal ethical approval for this descriptive, prospective investigational study was not required as all patients had severe debilitating heart failure symptoms and/ or risk of SCD. Conventional management would have entailed inevitable cardiac transplantation, its associated complications and limited longevity. The decision to resort to device therapy was therefore taken out of clinical and life-saving necessity and was conducted in terms of our current understanding of best clinical practice. Where innovative strategies were employed, this was used primarily to increase patient benefit from a more refined and patient-tailored technique.

2.2 Statistical analysis

The studies mentioned make use of standard descriptive biographical data captured using Excel (Microsoft™) and where necessary tests of significance were conducted using SPSS™.

3. Cardiac defibrillator therapy for at risk patients with failing systemic right ventricles.

3.1 Introduction

Patients post Mustard correction have been demonstrated to be at increased risk of SCD proportional to the degree of sRV dysfunction as well the presence of atrial arrhythmias (34). In other populations recognised to be at high risk of SCD, it is well recognised that ICD therapy is a highly effective, and arguably the only effective treatment modality(35;36). Given the particular anatomy after a Mustard procedure, problems with transvenous access to the pLV and altered vectors of defibrillation, it cannot be assumed that the general efficacy of ICDs will be reproduced in these individuals. In order to describe the technical considerations involved, a single centre experience of ICD therapy in 5 consecutive patients with a Mustard procedure for d-TGA considered to be at high risk of SCD was reviewed.

3.2 Methods:

A prospective evaluation was conducted of the technical considerations, implant details, and follow-up on 5 patients with d-TGA and a Mustard procedure receiving an ICD ± concomitant CRT. Functional status, arrhythmia history and echocardiographic data before implant were reviewed. Right ventricular function was assessed by a single experienced operator combining echocardiographic visual appraisal and planimetry as well as RV angiography. An individualized approach to implantation was undertaken, taking into consideration existing transvenous electrodes and post surgical cardiac anatomy. Following implantation, patients were followed-up at 4-6 weeks and then 6-monthly intervals. Data at follow-up including functional assessment, device interrogation, ECG and TTEs were reviewed.

3.3 Results:

The baseline characteristics of the 5 patients (4 male, age 18-35 years) studied are shown in figure 3.1. All had significantly impaired sRV function {mean sRV EF=30%} and impaired functional class (NYHA class II-III). Two patients had sustained VT, 3 non-sustained VT, and 4 had atrial arrhythmias. Four patients had previously implanted pacemakers. Pre-implant electrophysiological studies were not performed.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years) at implantation	24	22	35	18	25
Documented arrhythmias	Sinus bradycardia, atrial flutter, *NSVT	Sinus bradycardia, ‡VT, *NSVT	Sinus bradycardia, atrial flutter, *NSVT	†SVT, *NSVT	Sinus bradycarcia, †SVT, *NSVT, ‡VT
RVEF (%)	25	25	30	35	35
Pre-existing device	Yes	Yes	Yes	No	Yes
Weight (kg)	110.2	106.1	77	67.4	54
Implant	Surgical	Surgical	Transvenous	Transvenous	Transvet ous

*NSVT=non-sustained ventricular tachycardia, †SVT=supra-ventricular tachycardia,

‡VT=ventricular tachycardia

Figure 3.1 Salient baseline clinical characteristics of patients receiving defibrillators

3.3.1 Implant considerations:

Implanting a transvenous electrode into the pLV requires that lead navigate the surgical baffle. Baffle stenosis impeding flow from the superior caval vein (SVC) to the pLV is common post Mustard modification(1). Defibrillator electrode placement will potentially further impede venous drainage and pLV filling. A strategic decision was therefore made not to implant multiple leads via anatomically narrow baffles and to treat any baffle stenosis prior to the implant. An exclusively transthoracic defibrillation strategy was therefore employed in the first patient using a high energy defibrillator (maximum output of 41J) with subcutaneous, single finger arrays (Model 6996. 25cm coil, 500cm^2 surface. Medtronic, USA). Despite this defibrillation was not effective (figure 3.2). A revision procedure was deferred to consider alternative strategies. Surgical placement of epicardial electrodes is a consideration, but in view of our subsequent success with endocardial defibrillation from within the pLV a transvenous approach will be adopted.

Of the 4 patients with pre-existing pacemakers, 2 were demonstrated to have functional baffle stenosis and therefore underwent lead extraction and stent angioplasty at separate procedures at least 48 hours prior to transvenous insertion of a defibrillator lead. Those patients who had lead extractions and the patient with no pre-existing pacemaker underwent standard transvenous implantation with endocardial defibrillator coils placed via the subclavian vein into the pLV. Two patients with existing pacemakers and no evidence of baffle stenosis on cardiac catheterisation had their existing endocardial (pLV) pace/sense electrodes preserved; 1 then had epicardial patch electrodes and 1 had subcutaneous arrays implanted at the time of trans-sternal, epicardial CRT.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Defibrillation vector	Anterior and posterior chest subcutaneous arrays	Anterolateral and inferior sRV epicardial patches	pLV coil to Can (SVC excluded)	Can to pLV coil (SVC excluded)	Can to pLV coil (No SVC coil)
No. of shocks	6	2	4	3	2
Total energy delivered during defibrillation test	262J	50J	100J	75J	50J
Successful 25J shock	No	Yes	Yes	Yes	Yes
Avg. Impedance (ohm)	873.5	63.0	66.3	49.3	71.0

Figure 3.3. Characteristics of defibrillation testing in patients post device implantation

3.3.2 Defibrillation circuits and testing

The patient with subcutaneous arrays, had the electrodes placed in an antero-posterior configuration around the left chest wall with a left sub-pectoral can implantation (figure3.3). Ventricular fibrillation was induced via the chronic pLV endocardial pace/sense lead and therapies were delivered between the anterior and posterior subcutaneous arrays. A series of 6 inductions were performed with therapies of 25 to 41J but none were successful in terminating VF and external rescue shocks were required. Inclusion of the active can in the circuit did not improve defibrillation outcome.

One patient underwent epicardial patch electrode placement in the anterolateral and inferior positions over the systemic ventricle. This strategy was successful in defibrillating VF at 25J on the first induction (a 10J safety margin).

The remaining 3 patients underwent standard transvenous system implants. An active can was placed in the left sub-pectoral region and a defibrillation coil advanced under fluoroscopy to the pLV via the subclavian vein. The first 2 transvenous implants received dual coil leads (as is our standard practice when high DFTs are anticipated) but both had failed initial defibrillation, requiring exclusion of the SVC coil from the circuit. In 1 of these patients, a pLV to Can vector provided effective defibrillation at 25J, and in the other it was also necessary to reverse the polarity of the circuit to achieve this safety margin. This patient underwent 4 VF inductions and subsequently developed pulmonary oedema during the procedure.

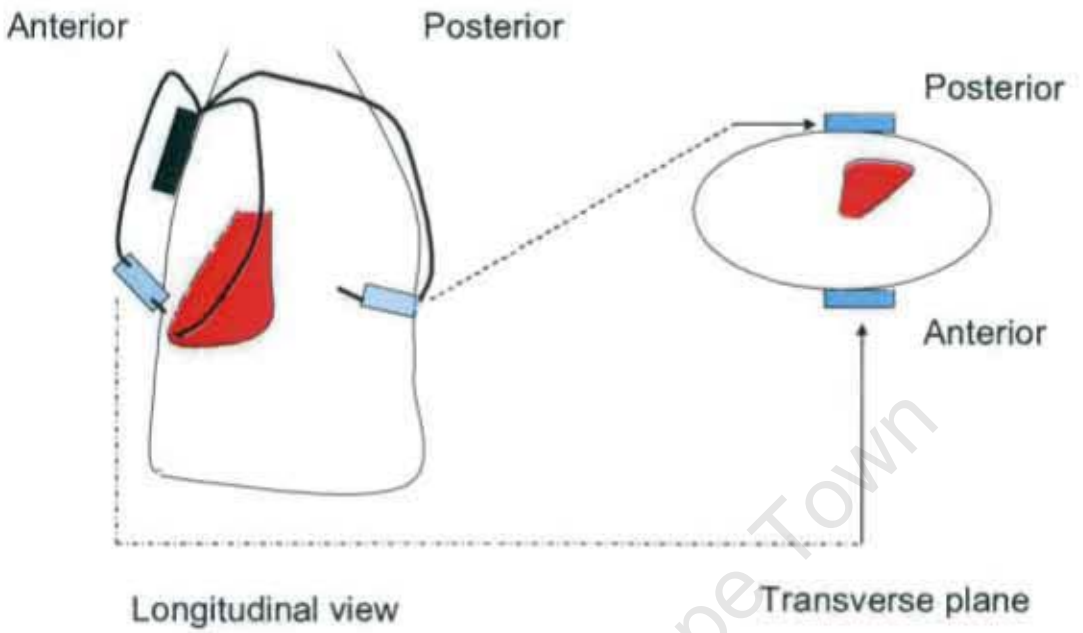


Figure 3.2 Diagrammatic view of the placement of the subcutaneous arrays (arrowed) around the chest wall in patient 1 with a sensing lead in the pLV.

3.3.3 Follow Up

The median follow-up in all 5 patients was 20 months (range 15-24). A total of 4083 non-sustained tachycardias have been documented in the cohort over this period. One patient has had VT with pre-syncope which was correctly diagnosed and treated by a discharge by the ICD.

3.4 Discussion

Mustard patients are at increased risk of SCD defined by sRV dysfunction, heart failure functional status, non-sustained VT and atrial arrhythmias (5). Only 1 patient in the cohort had a preceding out-of-hospital arrest but all patients had documented multiple ventricular ectopics on 24-hour holter analysis. None of the patients received formal electrophysiological studies as we felt that a negative study should not disqualify them. The patients are young (<40years of age) and lived productive lives up to the point of referral. The absence of therapies in the majority of the patients (4/5) over 2 years follow-up does not mean the decision to implant them was incorrect. The time to the first appropriate therapy in other patient groups with ICD often exceeds 2 years (37).

It has also not previously been demonstrated that the gold standard treatment for prevention of SCD, namely ICDs, are effective in this population, and given the variation from normal anatomy, efficacy should not be assumed. Appropriate vectors of defibrillation, as determined by electrode placement, are the key determinants of defibrillation success(38). The SVC cavity to pLV vector in particular appears to exclude much of the sRV and septum (figure3.4), whilst severe chamber dilatation, common in Mustard patients, is recognised from other populations to be associated with less effective defibrillation(39).

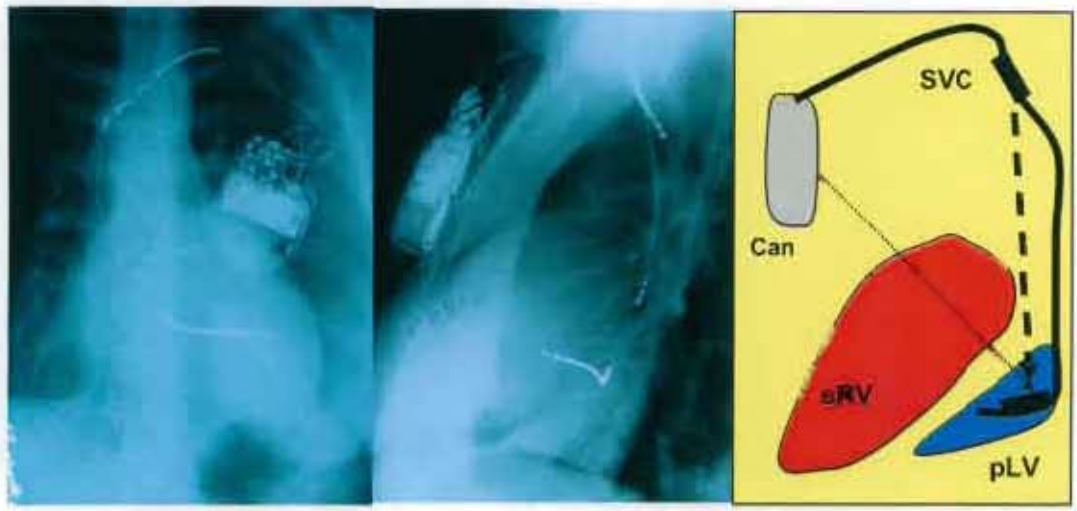


Figure 3.4 Electrode positions and defibrillation pathways of a dual coil lead system in a patient post Mustard correction. A dual coil defibrillator lead implanted into the pLV tends to be located more superiorly than when it is in an apical position in the right ventricle. The result is that the proximal electrode rests within the SVC/left subclavian vein. The defibrillation vector between the SVC and pLV thus excludes the major myocardial mass, reducing defibrillation efficacy.

The role of polarity reversal is less well established. Data from randomised trials provides some evidence but no rational explanation, that by inverting vectors, efficacy may be improved in patients(40). However, with a limited number of inductions in any given individual, apparent differences in efficacy may be no more than a reflection of the probabilistic nature of defibrillation success and we need to be cautious in making finite decisions as regards what will and will not work in individual patients.

The single patient experience with subcutaneous defibrillation was plainly suboptimal with no successful defibrillation achieved. This may be a reflection of the Mustard anatomy or other independent factors that potentially may affect defibrillation efficacy. This patient had a body mass index of 33 and gross cardiomegaly(21).

Cardiac resynchronisation in this group was performed as an adjunct to ICD implantation and presented its own challenges eventually requiring a hybrid approach in 2 patients with endocardial/epicardial systems and is covered in the next chapter.

The central issue explored in this report is how to manage this population at increased risk of SCD with particular challenges to effective defibrillator implantation. Our experience demonstrates that transvenous implantation is feasible but may require interventions such as lead extraction and angioplasty of the atrial baffle to avoid venous pathway obstruction. The optimal defibrillation vector with a transvenous implant appears to be pLV to active can and as such, single coil leads are preferred. Our experience with subcutaneous arrays alone was unsatisfactory. Efficacy may be improved by selecting patients with a smaller body habitus and by incorporating intra-thoracic electrodes. Epicardial patches require an open chest procedure and may be placed at the time of concomitant epicardial CRT if indicated in the individual patient.

Our findings mandate the use of high output devices, regardless of the configuration, in anticipation of compromised defibrillation efficacy in similar patients which ultimately may prove more cost effective than undertaking revision procedures.

The patient that underwent a prolonged procedure prior to DFT testing resulting in post-procedural pulmonary oedema, emphasised the inability of the compromised myocardium to sustain stresses. We therefore now undertake a staged approach to the ICD implantation, deferring defibrillation testing to another session if the implant procedure was prolonged or complicated. This practice however increases the probability of re-intervention if a suitable defibrillation safety margin is not attained.

3.5 Limitations:

This is a descriptive report on a small cohort and as such does not provide sufficient quantitative data. Given the low likelihood of a randomised trial, multi-centre, pooled, observational data is necessary to obtain a greater understanding of device therapy in this population.

3.6 Conclusion:

Defibrillator implantation in Mustard patients is feasible though challenging. Clinicians planning to implant such patients must be prepared to optimise the systemic venous access of the baffle prior to implantation and then to have strategies in place to tackle high defibrillation thresholds and the decompensation that may result from multiple VF inductions. Endocardial pLV to active can and epicardial patches are effective defibrillation strategies in this group.

4. A hybrid form of cardiac resynchronisation therapy in patients yielding contrasting results.

4.1 Introduction

Although the atrial switch was abandoned in the 1980s for the Jatene (arterial switch) procedure, a considerable number of patients have survived into their third decade of life(41). The right ventricle is not capable of supporting the systemic circulation for this extended period. Patients post Senning or Mustard operations, invariably experience right ventricular failure by the second and third decades of life(4;42). If cardiac transplantation is their only option, these patients face a post operative average life expectancy of just 10 years(43). Coupled with the limited availability of donors, this management plan is suboptimal for these, generally young patients. Cardiac resynchronisation therapy combined with defibrillation (CRT/D) has impacted on both quality and quantity of life in patients with severe ventricular dysfunction (44). The application of device therapy to patients with RV failure provides an attractive option. I present here 2 cases who had pre-existing dual chamber pacemakers upgraded to CRT/D, using epicardial leads implanted by surgical thoracotomy. Although the results varied for both cases, they demonstrate a plausible alternative to management.

4.2 Case presentations

4.2.1 *Case 1*

Patient 1 was 110 kg and 22 years old at time of implantation of his CRT/D system (figure 4.1). The underlying congenital anomaly of simple transposition was initially temporised by an atrial septostomy soon after birth and then with a Mustard operation at 7 months of age. At 18 years of age he presented with sino-atrial node dysfunction (a common complication following Mustard surgery) and therefore received a dual chamber pacemaker (Medtronic THERA DR 7968i. Medtronic. Inc., MA). Transthoracic echocardiogram revealed a dilated and myopathic sRV with an EF of 25% and a dp/dt ratio = 438.3 with evidence of asychronous ventricular contraction. The systemic ventricle (sRV) myocardial performance

index was 0.53. An exercise treadmill test showed a suboptimal response in the cardiac output of 3.9 l/min pre-exercise to 9.0 l/min at maximal exercise. He had underlying right bundle branch block QRS morphology. Recent evidence from other series also suggest an increase risk of VT/VF and SCD in patients following Mustard procedures presenting with sRV dysfunction and atrial tachyarrhythmias(1). Cardiac resynchronization and defibrillator therapy offered a plausible alternative to delaying cardiac transplantation. The implant was performed via a mini-thoracotomy through the lower part of the previous sternal incision. The chronic atrial and pLV leads were conserved and a steroid eluting pace/sense electrode was sutured to the inferior epicardial surface of the right ventricle (Medtronic 4968). Two single-finger subcutaneous defibrillator arrays (Medtronic 6996) were implanted in an antero-posterior configuration and connected to the defibrillator ports of a Contak RENEWAL 4HE defibrillator (Guidant Inc.). Attempts at biventricular pacing (BVP) were also of limited benefit. A TTE guided optimization of CRT resulted in the sRV being paced 40ms before the pLV. The paced QRS remained predominantly right bundle branch block in morphology but had increased to 200ms from a baseline width of 120ms. Apart from not experiencing a subjective improvement in symptoms, the patient presented with episodes of recurrent paroxysmal atrial flutter documented on holter analysis.

A successful flutter ablation was performed using non-contact mapping (Ensite™. St. Jude Medical). Two lines of block were created extending from the inferior vena cava to the inferior limb of the baffle and also from the tricuspid valve to the pulmonary venous side of the baffle. Despite further adjustment to the paced atrioventricular (AVD) and ventricular off-set, there was no improvement in symptoms. At his most recent follow-up doppler parameters suggested atrial pacing provided the optimal configuration (AAIR).

His effort tolerance was quantified objectively on the treadmill using the Bruce protocol and he exercised for 6.58 minutes. He is currently being managed medically.

	Patient 1	Patient 2
Age (years) at implantation	22	24
Wight (kg)	110	106
Onset of symptoms	15	16
Initial symptoms	Effort intolerance	Breathlessness & chest pain
Gender	M	M
NYHA	III	III
Drug therapy		
ACE inhibitor	Lisinopril	Lisinopril
Beta Blocker	Bisoprolol	Bisoprolol
Cardiac glycoside	Y	Y
Frusemide	Y	Y
Spironolactone	N	Y
Amiodarone	Y	N
Echo features		
sRV	Dilated. Severely impaired	Dilated, severely impaired
pLV	Moderately impaired	"Normal"
TR	Mild	Mild
MR	Trivial	-
ECG features		
BBB	RBBB	RBBB
AVB	First degree	First degree
QRS duration	120ms	160 ms
CXR Cardiothoracic ratio	0.6	0.7
SAN dysfunction	Sinus bradycardia	Sinus bradycardia
NSVT	Y	Y
VT	N	Y
VF	N	N
SVT	Atrial Flutter (ablated)	N

Figure 4.1 Baseline clinical characteristics of 2 patients with Mustard corrections receiving CRT.

*N-No Y-Yes mRV- morphological right ventricle mLV- morphological left ventricle TR-tricuspid regurgitation MR-mitral regurgitation BBB-Bundle branch block AVB-atrioventricular block SAN-sino-atrial node NSVT-non sustained VT VT-ventricular tachycardia VF-ventricular fibrillation SVT-supraventricular

4.2.2 *Case 2*

The second patient (24 years) weighed 106kg, was born with simple d-TGA and a large patent ductus arteriosus which had spontaneously closed by the time of atrial baffle construction at 6 months of age. Thereafter periodic surveillance with TTE revealed a mild stenosis of the inferior limb of the atrial baffle. Onset of dyspnoea and effort related chest pain with diaphoresis occurred at 17 years and was assumed to be due to sRV dysfunction and ischaemia on a functional basis after demonstration of unobstructed coronary arteries. Like the previous patient, profound sinus bradycardia was documented on holter monitoring which resulted in pacemaker implantation at the age of 22. Two years later, his effort tolerance deteriorated from NYHA grade II to III/IV with an episode of VT and accompanying syncope. The decision was made to upgrade to a CRT/D. Preceding angiography demonstrated a stenosis in the inferior limb of the atrial baffle for which balloon angioplasty was successfully performed.

The upgrade was performed by surgical thoracotomy, conserving the chronic atrial and ventricular pacing leads (Medtronic 5076). An epicardial steroid eluting electrode (Medtronic 4968) was attached to the inferior epicardial surface of the sRV. The pacing threshold of the sRV epicardial lead at implantation was 5.5v @ 0.5ms, with an R wave measuring 4.6mV and an impedance of 1100 ohms. The epicardial system showed a great variability in pacing parameters over a 9 month follow-up period post procedure (figure 4.2).
Once again, the atrioventricular delay (AVD) and ventricular pacing off-set was guided by echocardiography and the sRV was paced 40ms ahead of the pLV in the final programming. The patient has symptomatically improved to NYHA grade II.

	sRV epicardial lead		pLV endocardial lead		RA endocardial lead	
	Threshold	Resistance (ohms)	Threshold	Resistance (ohms)	Threshold	Resistance (ohms)
Implant	0.5ms@5.5v	1100	0.2ms@1.5v	448	0.3ms@1.5v	480
1month*	0.5ms@6.0v	576	0.2ms@1.0v	432	0.4ms@1.0v	496
6month	0.3ms@5.0v	624	0.4ms@1.2v	464	0.4ms@1.0v	624
9month	0.3ms@5.0v	648	0.2ms@1.5v	448	0.3ms@1.5v	480

*follow-up

Figure 4.2 Comparison of pacing parameters of epicardial and endocardial leads at sequential follow-up in patient 2 implanted post Mustard surgery with a hybrid CRT system.

4.3 Discussion

Cardiac resynchronization therapy has dramatically improved the quality of life in patients presenting with grade III and IV NYHA symptoms of heart failure(44). I have demonstrated its application in two patients with sRV dysfunction using surgically positioned epicardial leads.

It may be argued that preceding angioplasty of significant baffle related stenoses in both patients may have contributed to functional improvement in at least 1 of the patients. The baffle angioplasties were performed in both patients as a separate procedure at least 48 hours before device implantation. This was done primarily to reduce the duration of the device implantation procedure but neither patient demonstrated appreciable clinical or echocardiographic benefit from relief of the stenoses on myocardial function in the period leading up to the actual implant.

The RV in a normal heart is a thinner walled and crescent shaped structure, that is not a suitable long term substitute for the left ventricle. The concave intrusion of the septum into the cavity of the RV also provides the optimal geometry for overall RV function(45). If left to chronically support the systemic circulation, the RV hypertrophies and dilates with subsequent flattening of the interventricular septum. The resultant dyskinetic septal motion further worsens the functional impairment of the dysfunctional RV. Resynchronization therapy should therefore serve not only to pace the RV free wall but co-ordinate this with septal motion. This complex anatomical and functional interaction suggests that we need to take greater care in positioning pacing leads over the sRV, to ensure adequate septal and free wall recruitment during biventricular pacing.

From this discussion we can infer why CRT failed in the first patient. The epicardial lead was placed on the sRV at the discretion of the surgeon over its inferior border with no formal guidance. It was only limited by the pacing threshold at the respective site. This arbitrary

placement may have been responsible for the non-response. Perhaps a more guided approach such as that suggested by Dekker et al using intra-procedural pressure-volume loop monitoring may have altered the outcome(46).

Epicardial pacing systems have been more frequently associated, than transvenous systems, with higher pacing thresholds, diaphragmatic stimulation, lead fracture and insulation breaks(47).The use of steroid eluting leads, does alleviate some of the deterioration in pacing parameters but this unfortunately did not offer an advantage in the second patient(48). Due to previous surgery, the location of viable myocardium for pacing is difficult and placement of electrodes on the inferior aspect of both the sRVs was partially because of the ease of access to this area. This, however is more likely to increase the incidence of diaphragmatic pacing given its proximity and also does not truly pace the area of maximum mechanical delay

The role of an epicardial pacing strategy in CRT should however should not be underestimated. Transvenous attempts at coronary sinus cannulation have often resulted in failures and surgical epicardial lead placement is resorted to or this approach can be a primary strategy especially in patients like ours because of the complex anatomy. Mair et al in a comparative study, also demonstrated a higher complication rate with transvenous CS lead placement than with epicardial implantation via a mini-thoracotomy procedure(47). I am not advocating that epicardial pacing is the favoured approach in these patients, but rather wish to emphasise it as a potentially advantageous strategy particularly if combined with video-assisted thorascopy creating a minimally invasive percutaneous approach(49).

Another explanation for the poor clinical response in the first patient, could be due to inappropriate device programming. Despite a TTE guided programming of the AVD and ventricular offset, the QRS width increased by 80ms during BVP. The use of standard spectral doppler to optimise pacing seems incongruous as there is as yet, no defined parameters of asynchrony evaluated for patients with sRV dysfunction nor for that matter,

generally in patients with underlying congenital cardiac disease. So the criteria to re-establish synchrony are thus dubious. It could mean that tissue doppler segmental analysis and three dimensional reconstruction are more sensitive models to use in this context(50).

Nevertheless, failure of epicardial pacing in both these patients did warrant evaluating a transvenous implantation strategy in patients with d-TGA after atrial switch.surgery. In their attempt at transvenous atrial pacing in patients presenting with sino-atrial node dysfunction following a Fontan procedure, Hansky et al, chose to detail the anatomy preoperatively with cardiac magnetic resonance imaging as well as angiographically(51). A similar strategy should be undertaken in patients following a Mustard or Senning procedure preceding transvenous device implantation. Stenosis of the superior limb of the baffle and superior vena cava has been mentioned in the literature and the incidence is higher following a Mustard operation than with the Senning procedure(7;49). None of our patients had magnetic resonance imaging because of cost as well as because of pre-existing pacemakers but detailed TTE and pre-operative angiography was performed to assess ventricular function and the patency of the atrial baffles. The presence of a dual chamber pacemaker leads would have made venous cannulation difficult because of limited space within the baffle, so epicardial lead implantation and conservation of the existing endocardial leads seemed sensible.
The feasibility and safety of endocardial pacing of the systemic ventricle using a transseptal route to the left ventricle in normally "transposed" hearts was shown by Jais et al in a small series of 11 patients(52). In patients post Mustard correction, this would mean perforation through the atrial baffle or passage through a baffle leak to implant the lead onto the endocardial surface of the sRV followed by life long anticoagulation because of the potential for paradoxical and systemic embolization. Disruption to the atrial structures and interference with the atrioventricular valve may become issues in the long term follow-up of these patients but this remains an option with the benefit of more stable endocardial pacing thresholds. I will explore this concept in the next chapter.

4.4 Conclusion

The application of CRT to patients following an atrial switch procedure with failing sRVs is a feasible alternative to delaying cardiac transplantation. I have presented 2 cases in whom an upgrade from dual chamber pacing to BVP was attempted using epicardial leads and by conserving the chronic endocardial electrodes. The limited success rate is not a deterrent for further evaluation but shows the need for refinement of this hybrid strategy.

5. A novel approach to cardiac resynchronisation therapy for a failing systemic right ventricle.

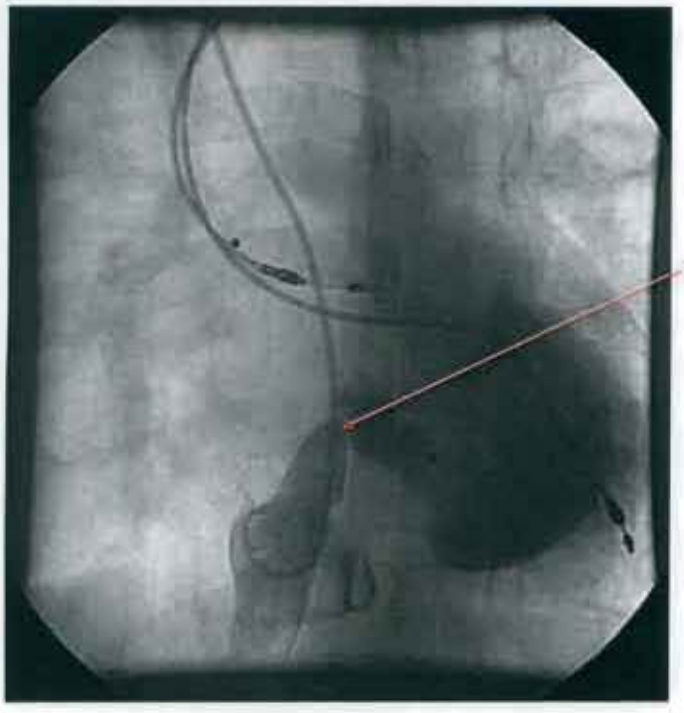
5.1 Introduction

Progressive sRV dysfunction, atrial and ventricular arrhythmias and SCD are well-recognized late sequelae of atrial redirection surgery(2). Although cardiac resynchronisation therapy poses an attractive therapeutic option, little is known about indications, patient selection, and technical aspects of best lead placement. I discussed in the previous chapter an attempt at CRT/D therapy in 2 patients who bear resemblance to the following case. Only 1 of these patients demonstrated clinical improvement. These mixed results prompted a more refined strategy to assess mechanical and electrical ventricular asynchrony and to attempt a fully percutaneous means of achieving CRT as is illustrated in the following case study.

5.2 Methods

A 27 year old female with a Mustard procedure for d-TGA, and subsequent DDDR pacemaker implantation for sinus node dysfunction at age 17years, presented with progressive effort intolerance. Transthoracic echocardiogram and angiography revealed a dilated sRV with systolic dysfunction (EF=23%) and predominant lateral free wall hypokinesia.
Holter monitoring revealed episodes of non-sustained ventricular tachycardia. The 12-lead electrocardiogram (ECG) revealed atrial and ventricular sequential pacing with fused sinus/paced QRS complexes measuring 130ms. She achieved just 4.8 minutes on treadmill testing (Bruce protocol) compared to just 8.4 minutes documented 10 years earlier.
Preceding diagnostic cardiac catheterization revealed severe stenosis of the inferior baffle and a minor leak in the superior baffle communicating with the pulmonary venous atrium. Stent angioplasty of the inferior baffle was performed to relieve the obstruction (figure 5.1).

A



B

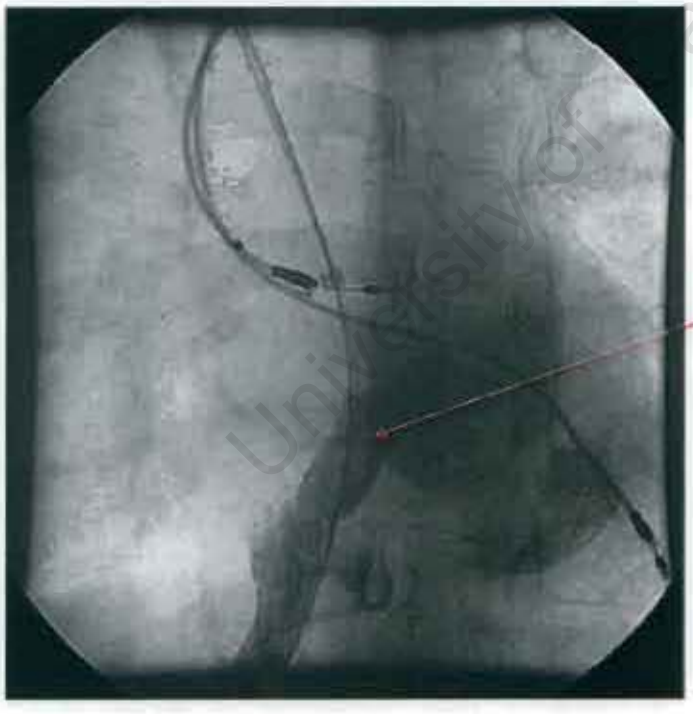


Figure 5.1 A. Shows the RA and pLV leads of the existing DDD pacemaker. Contrast injection into the IVC demonstrates a stenosis within the inferior baffle limb but was adequate to allow passage of the pigtail catheter. B. Shows the satisfactory post stent result.

A MEA catheter (Ensite 3000. St. Jude Medical. USA) was then inserted retrogradely across the aortic valve into the sRV and three dimensional isopotential (voltage) maps were created of the sRV during AAI, DDD pacing (RA+pLV then RA+sRV). Biventricular pacing (BVP) was simulated by pacing from a roving ablation catheter (7F Stinger. Bard. Minneapolis.USA) within the sRV and by triggering sRV pacing after the sensed pLV impulse (figure 5.2). Because of this there was an inherent delay of 20ms after pLV chamber pacing. Atrial pacing (AAI) achieved diffuse and rapid activation of the sRV however Wenckebach's phenomenon of the atrioventricular node was noted at just 70 beats per minute making constant ventricular pacing necessary. Voltage mapping during pLV apical pacing showed inhomogenous activation of the sRV in that the peak voltage activation waveform failed to involve considerable areas of the sRV free wall. Direct pacing of the endocardial surface of the sRV resulted in its diffuse and rapid activation (figure 5.3). This was achieved from multiple sites on the sRV free-wall endocardium extending from the apex to the base. Device implantation was performed at a separate procedure after echocardiographic confirmation of sRV dysfunction after baffle angioplasty and was done under general anaesthetic. A 4F lumenless pace/sense active fixation lead (SelectSecure™. Medtronic Inc.) was deployed using a steerable delivery sheath via a standard left subclavian vein approach with anticoagulation (heparin 1000units/kg maintaining an activated clotting time of ± 300seconds). The superior limb of the systemic baffle was crossed through the baffle leak and positioned in the antero-basal segment of the sRV (figure 5.4). Instantaneous intra-arterial blood pressure response was assessed during AAI, DDD (RA+pLV and RA+sRV) and simulated BVP (pLV+ sRV)(2). An arbitrary paced AVD of 110 ms was selected for DDD configurations. Defibrillation incorporated the pLV and active can electrodes, with the addition of a posterior single finger subcutaneous array (model 6996-58cm. Medtronic Inc.) implanted horizontally around the left chest wall (figure 5.5). Sequential TTEs were used to monitor ventricular function over the 6-month follow-up period.

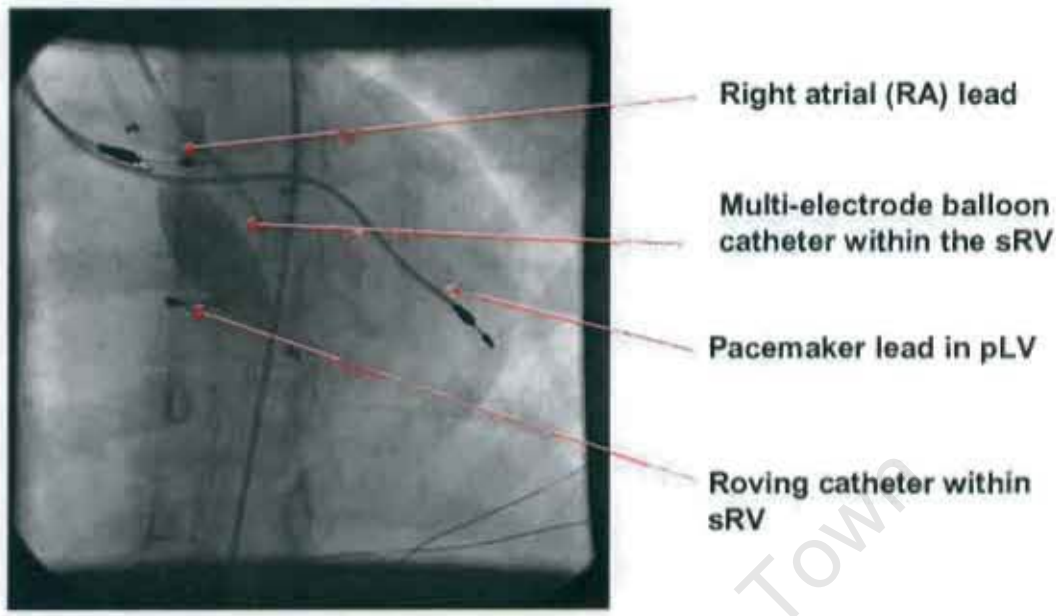


Figure 5.2 The MEA catheter is deployed in the sRV. Isopotential maps of the sRV are created from pacing off the RA & pLV leads and from a roving ablation catheter within the sRV.

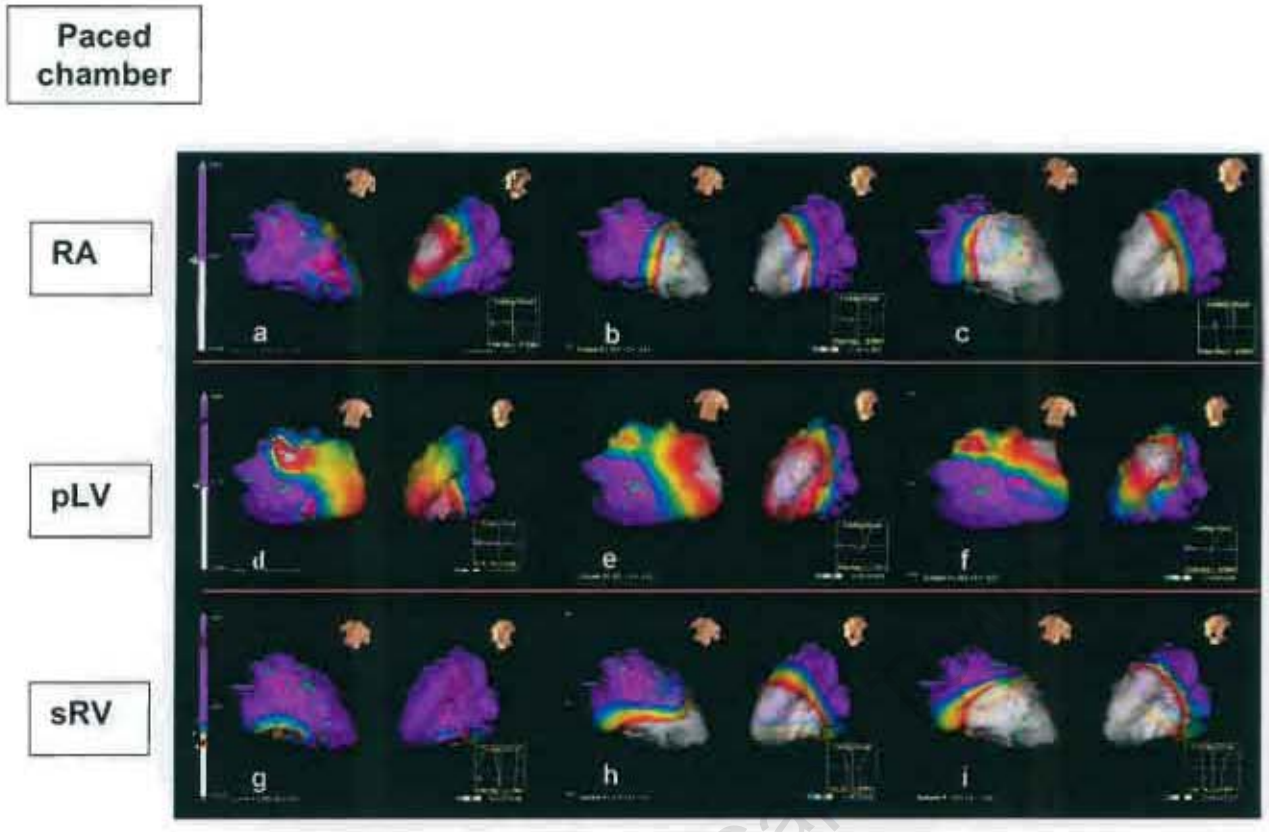


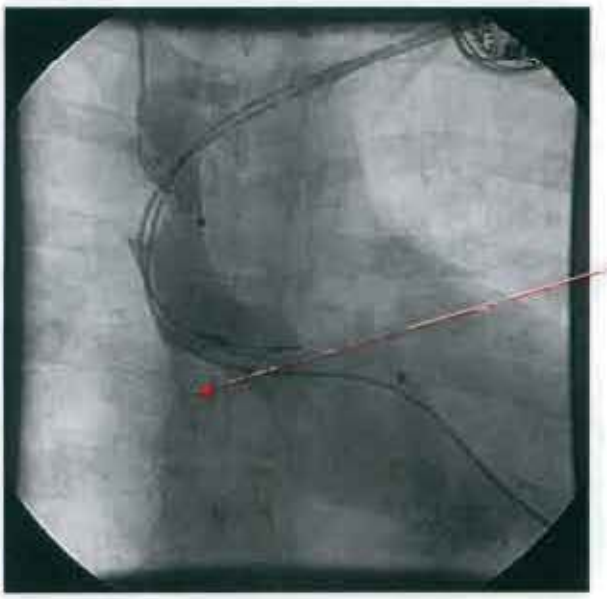
Figure 5.3. Sequence of voltage maps of the sRV depicting the motion of the peak endocardial depolarization (white=maximum voltage, purple=minimum voltage) in progression from left to right. The sRV is shown in right and left oblique views.

Top row of images during AAI pacing shows activation of the entire sRV starting at the interventricular septum (a) then apex (b) towards the basal segments (c).

Middle row during pLV stimulation shows an inhomogenous activation pattern: the peak depolarization wavefront remains over the superior septal and apical regions (d-f) and fails to involve the freewall and basal region before dissipating.

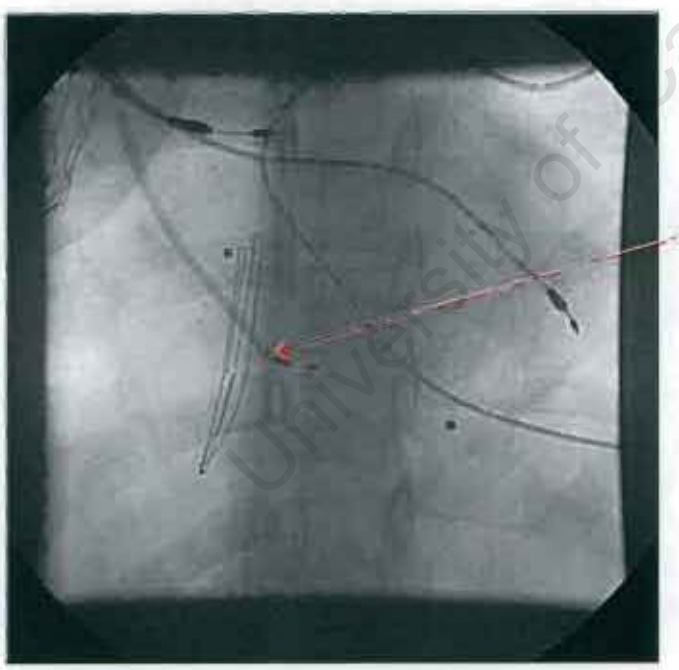
Pacing at a sRV lateral wall site (bottom row) shows peak endocardial voltages originating on the inferior aspect (g) spreading towards the apex (h) then involving the entire endocardial surface towards the base (i).

A



Leak within the superior baffle limb providing access to the sRV

B



4F pacing lead being positioned in the baso-lateral segment of the sRV

Figure 5.4 A Illustrates a small baffle leak in the superior limb allowing access for a sheath to deliver the 4F pacing lead into the sRV pictured in B.

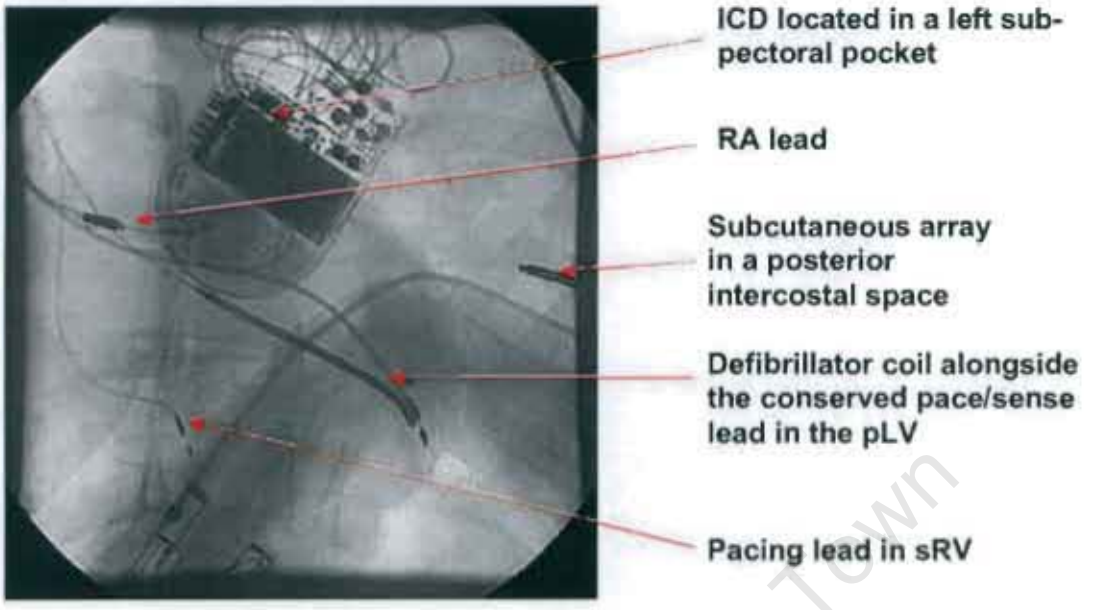


Figure 5.5 The final implanted system with conservation of the RA and pLV pacing leads. The 4F pacing lead is implanted at the base of the sRV through the baffle leak. An endocardial defibrillator lead has also been transvenously placed in the pLV. The can electrode is situated in a left sided sub-pectoral pocket and an additional single finger, subcutaneous array is implanted around the left chest wall, posteriorly.

5.3 Results

Despite the shortest activation time of 90ms occurring with AAI pacing, the maximal acute, blood pressure response of 73mmHg(average 60±9 mmHg) occurred during BVP (figure 5.6). An early (1week TTE) and sustained (after 6 months) 43% improvement in EF was also noted (23% to 33%). Effort tolerance improved from NYHA III to II accompanied by a decrease in QRS width from 130 to 120ms during consistent synchronous BVP in DDDR mode .No antitachycardia therapies have thus far been documented.

5.4 Discussion

We have presented here a novel strategy using ventricular activation maps to direct endocardial lead placement in an effort to achieve successful BVP in patients with a Mustard procedure and a failing sRV. The application of CRT has been extrapolated to the adult congenital heart disease population following success in treating patients with cardiomyopathies. Although no randomised controlled data exists for these patients, there has been documentation in the form of small case series(53;27). What is apparent is that conventional selection criteria may not apply and that there is variation in technical approaches sometimes requiring a combined endocardial and epicardial system. Conventional CRT has a non-responder rate of between 20-30%(50). This could potentially be higher in this exclusive group and hence the need for a more rigorous selection process. Non-contact mapping has been used to define areas of slow conduction guiding left ventricular pacing in cardiomyopathies (33). The MEA catheter (Ensite™. St. Jude Medical) was easily deployed into the sRV in our patient under anticoagulation. The late and possible non-activation of the sRV lateral wall during pLV pacing was made apparent by this three dimensional electrical mapping technique.

This correlated with mechanical evidence of severe hypokinesia in these segments on TTE. This observation suggests that pacing from the apex of the pLV not only results in delayed and asynchronous sRV activation, but may worsen sRV dysfunction - a phenomenon previously described in the non-paced ventricle(54).

Blood pressure response during pacing		
	Blood pressure (mmHg)	Mean Blood pressure
AAI	75/43	53
DDD (RA/pLV)*	76/41	55
DDD (RA/sRV)*	78/48	58
BVP (sRV+pLV)	100/58	73
		60±9 mmHg
**AVD=110 ms.*		

Figure 5.6 Tabulation of the maximal, acute, intra-procedural arterial blood pressure response obtained with each pacing modality. The AVD was arbitrarily set at 110ms.

The acute haemodynamic response during pacing is well documented and correlates with optimal pacing selection(55;56). The blood pressure response was used as a surrogate marker for the cardiac output during the implant procedure. This proved effective, fast and clinically relevant evidenced by a significant mean blood pressure rise of 18mmHg during BVP as opposed to DDD pacing (p=0.001). The baffle leak provided a portal of access to the sRV without causing disruption to baffle integrity. An epicardial position may have provided similar benefit but the equipment and expertise is currently not available to do this as a minimally invasive procedure at this unit. However, the sheathed delivery system used allowed the operator manoeuvrability within the sRV. The narrow diameter of the lead also helped minimise obstruction to the conduit and systemic atrioventricular valve function. However, the favourable lead profile does not reduce the risk of thrombo-embolism and the patient has therefore been anti-coagulated with warfarin.

5.5 Conclusion

Given the relative ease of accomplishing CRT guided by NCM and intra-procedural hemodynamic monitoring, we propose that a prospective evaluation of this approach is warranted. Long term follow-up is also needed to evaluate if the above strategy affords any advantage over current practice and an improvement in the non-responder rate. A minimally invasive epicardial lead implantation system, especially if possible under conscious sedation, has the advantage of access to the sRV without the need for anticoagulation and avoids intracardiac lead clutter. Further development is needed.

6. Conclusions

The advent of atrial redirection surgery heralded potential survival to adulthood for patients with d-TGA who would have otherwise faced inevitable childhood death. However, the late complications arising from this surgery, particularly progressive heart failure and the increase risk of SCD remain challenges for management. Technological advancement in terms of device therapy (CRT/D) have presented an alternative or bridge to cardiac transplantation in these patients.

The indications and best methods to effect successful CRT/D therapy however remain unknown apart from combined anecdotal evidence. In this patient cohort, the pLV to can defibrillation vector remained the most successful as was the use of epicardial patches. An exclusively transthoracic system utilizing subcutaneous electrodes proved unreliable because of the influence of weight in adult patients. A combination of intracardiac, intra-thoracic and subcutaneous electrodes is however sometimes necessary to enhance defibrillation efficacy.

The initial experience with CRT using a combined endocardial/epicardial lead system proved inconsistent and may have been because of poor patient selection but also because of suboptimal epicardial lead placement. The use of NCM in addition to echocardiographic criteria was used to define asynchrony and guide endocardial placement of a pacing lead within the sRV. This warranted anticoagulation, but was performed with relative ease as a transvenous procedure under conscious sedation demonstrating its potential sustainability.

7. Future directions

The ideas proposed by this dissertation may help clinicians faced with the management of similar, challenging patients. It is a chronological and evolutionary account of management strategies undertaken at a single tertiary level institution. It is unlikely that there will ever be a randomized controlled trial because of limited patient numbers and the highly varied patient characteristics requiring an individualized approach. This study does however emphasize the need for more data and technological advancement in order to assist management.

The limitations of current lead development and energy capabilities of modern ICDs are evident from failed endocardial and transthoracic defibrillation attempts. A more efficient minimally invasive mechanism is also needed for epicardial lead placement , in order to achieve CRT using this approach. Recent advances have expanded the use of tissue Doppler and three dimensional echocardiography ventricular asynchrony(57). Other imaging technologies that are being investigated or show potential for application in this sphere include intracardiac and transoesophageal echocardiography, multi-slice computerized tomography, magnetic resonance imaging and nuclear scintigraphy (9;10;21;58-59). The use of NCM to aid CRT is innovative and reveals the need for a more defined understanding of asynchrony in patients with congenital heart disease. These topics warrant further research.

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