Study Title: SCar location and **A**cute haemodynamic **R**esponse to **M**ulti**P**oint **P**acing in patients with cardiomyopathy

Internal Reference Number / Short title: SCAR MPP study

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Chief Investigator:	**Dr Tim R Betts**, Consultant Cardiologist and Electrophysiologist
	Oxford University Hospitals NHS Foundation Trust
Investigators:	**Dr Milena Leo**, Clinical Research Fellow
	Oxford University Hospitals NHS Foundation Trust
	Dr Erica Dall'Armellina, BHF Intermediate Clinical Research Fellow and University Research Lecturer, AVIC Clinical CMR Lead, Honorary Consultant Cardiologist
	University of Oxford
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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Study Title	**SC**ar location and **A**cute haemodynamic **R**esponse to **M**ulti**P**oint **P**acing in patients with cardiomyopathy	
Internal ref. no. / short title	**Scar MPP study**	
Study Design	Pilot study	
Study Participants	Patients with left ventricular myocardial scar and clinical indication to implant of a Cardiac Resynchronization Therapy- Defibrillator (CRT-D) device	
Planned Sample Size	15 patients	
Planned Follow-up duration	1 day	
Recruitment end date	31st June 2020	
	Objectives	**Outcome Measures**
Primary	To assess whether the added benefit of multipoint pacing (MPP) over conventional single-site LV pacing is consistent in the peri-scar region compared to the remote myocardium	- Acute haemodynamic response to MPP (percentage increase of LV-dP/dTmax produced by MPP over spontaneous ventricular activation) in the peri-scar region and in the remote myocardium - Percentage increase of LV dP/dT max produced by MPP over conventional single-site LV pacing in the peri-scar region and in the remote myocardium

2. ABBREVIATIONS

AHR	Acute Haemodynamic Response
BiV	Biventricular
CRM	Cardiac Rhythm Management
CRT	Cardiac Resynchronization Therapy
CS	Coronary sinus
GP	General practitioner
LV	Left ventricle/ ventricular
MPP	MultiPoint Pacing
LV-dP/dT max	Maximal (max) rate of rise of left ventricular pressure (LV-dP) over time (dT)
MRI	Magnetic Resonance Imaging
NHS	National Health System
OUH	Oxford University Hospitals
QoL	Quality of Life
RV	Right ventricle/ventricular
SOP	Standard Operating Procedure

3. KEY CONTACTS SECTION

Chief Investigator	Dr Tim R Betts, Consultant Cardiologist and Electrophysiologist Department of Cardiology, Level 2, Blue Outpatient Area John Radcliffe Hospital Oxford University Hospitals NHS Foundation Trust Headley Way, Oxford OX3 9DU Tel: 01865 220256 Fax: 01865 221194 E-mail: tim.betts@ouh.nhs.uk
Leading fellow	Dr Milena Leo, Clinical Research Fellow Clinical Research Fellows Office, Level 2, Blue Outpatient Area John Radcliffe Hospital Oxford University Hospitals NHS Foundation Trust, Headley Way Oxford OX3 9DU Tel 01865 220255 e-mail: milena.leo@ouh.nhs.uk
Sponsor	Ms Heather House Research and Development Department, Joint Research Office Block 60, Churchill Hospital Oxford OX3 7LE Tel 01865 (5) 72970 E-mail: ouh.sponsorship@nhs.net

4. BACKGROUND AND RATIONALE

Many patients with cardiomyopathy and heart failure have an abnormality of the heart's electrical system resulting in an uncoordinated (asynchronous) contraction pattern of the bottom chambers of the heart (electrical dissynchrony). This further reduces the pumping ability of a weakened heart muscle.

Cardiac resynchronization therapy (CRT) is a widely accepted treatment option in these patients. It works by sending tiny electrical impulses to the bottom chambers (ventricles) of the heart to make them beat together again in a more synchronised pattern. The heart's ability to pump blood and oxygen to the body is so improved.

A CRT device consists of a unique type of cardiac pacemaker which has two or three electrodes (or leads), one in the right ventricle, one in one of the branches of a vein on the outer surface of the left ventricle (called coronary sinus or CS), and often one in the right atrium (right top chamber, in order to ensure also synchronism between top and bottom chambers) (fig 1).

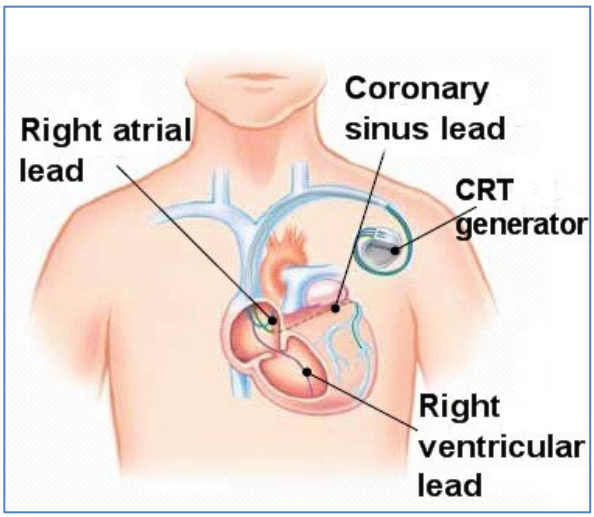

Fig 1. CRT device components.

The simultaneous activation of the left and right ventricle can restore a coordinated, or synchronous, pumping action (1). In most patients CRT improves symptoms of heart failure and quality of life, reduces the chance of being admitted to hospital with worsening heart failure, it makes people live longer (2,3).

The implant procedure usually takes a few hours and it is performed under X-ray guidance. Local anaesthetic is injected into the upper chest wall, most commonly on the left side. An incision is made and a pocket is created under the skin. A venous blood vessel is punctured under the clavicle and pacing leads are guided through it into the heart chambers. A contrast injection (venogram) is usually performed in the coronary sinus in order to identify its branches and guide the placement of the LV lead. The leads are attached to the generator box, or battery, and all device components are placed into the pocket. The site is then sutured either with dissolvable or not dissolvable sutures which if the later, need to be removed 7-10 days post procedure. A chest x-ray and a pacing check are carried out post procedure to ensure that the pacing leads are in the correct position, and that the pacemaker is functioning correctly.

Once implanted, the device needs to be worn permanently and stimulate the heart continuously in order to keep its positive effects on heart function. The battery needs to be replaced every few years (depending on

amount of pacing and battery characteristics); the leads do not need replacement unless in case of malfunction.

Although most patients have a significant improvement from CRT therapy, up to one third of patients do not benefit from it and to date there are no useful criteria to predict the response to CRT (4).

In an effort to improve CRT response, alternative methods of CRT delivery have been developed. One potential strategy to improve response is multisite left ventricular (LV) stimulation, i.e. simultaneous stimulation of more than one area of the left ventricle in addition to right ventricular (RV) pacing.

In this scenario, a new pacing feature has been recently become available that allows simultaneous LV stimulation from two different sites by means of a single lead with four electrodes (quadripolar lead). It is called MultiPoint Pacing (MPP; St. Jude Medical, Sylmar, CA) and it is available for some CRT devices in combination with a quadripolar LV lead. Both the devices with MPP and the quadripolar leads are already widely used as part of standard care and they are CE-marked. Of note, they are already used as standard care at Oxford University Hospitals (OUH) NHS Foundation Trust.

Simultaneous excitation of a larger mass or volume of cardiac tissue through MPP should theoretically result in faster depolarization velocity and early depolarization of sites of late intrinsic activation, with shorter LV trans-ventricular conduction times, better synchronization and increased cardiac output (5-7).

Although the MPP technology has a proven safety and efficacy profile comparable to the other CRT techonology, evidence regarding the long term additional benefits of this pacing modality over conventional single site LV pacing is lacking. To this aim, a randomized multicentre study (MORE CRT MPP study) is currently underway to show the superiority of MPP over conventional single site LV pacing.

Some data are available about acute effects of MPP, i.e. the acute change in cardiac haemodynamics as MPP is activated. LV-dP/dT_{max}, consisting in the maximal rate of rise of LV pressure during cardiac contraction, is often measured to this aim. Basically a pressure manometer wire is temporarily placed into the LV during the CRT procedure and it continuously measures the left ventricular pressure. Studies investigating the Acute Haemodynamic Response (AHR) of MPP over conventional single site LV pacing with this or other techniques have documented small, variable and often not clinically significant improvements from MPP compared to single site LV pacing.

Study sub-analyses seem to suggest that MPP pacing could be particularly beneficial in specific subgroups of patients (12) and when stimulating particular areas of the LV, with up to 35-40% improvement in LV dP/dt_{max} if compared to conventional single-site LV pacing in the same site (13). Studies using biophysical modelling suggest that MPP from a quadripolar lead may exert its benefit mainly in patients with ischaemic heart disease resulting in LV scar (14).

In order to optimize the response rate to CRT, it is extremely important to understand how MPP works, which subgroup of patients may benefit more from it and if a specific LV location should be chosen in order to have an added benefit from it. Of note, this pacing feature requires specific devices and higher energy, with increased battery drainage leading to more frequent battery changes and increased risk of infections so it is really important to understand when it is worth using it.

3.1 Research question and hypothesis

We plan to investigate if the added benefit of MultiPoint Pacing over conventional single-site LV pacing is related to the presence of scar in the left ventricle and the position of the pacing lead relative to it.

Our hypothesis is that MMP produces a better AHR compared to conventional single site LV pacing if there is scar in the left ventricle and when the lead is placed closed to the scar because this allows the recruitment of large areas of peri-scar viable tissue, characterized by slow conduction, with quicker electrical activation and more vigorous contraction (fig.2).

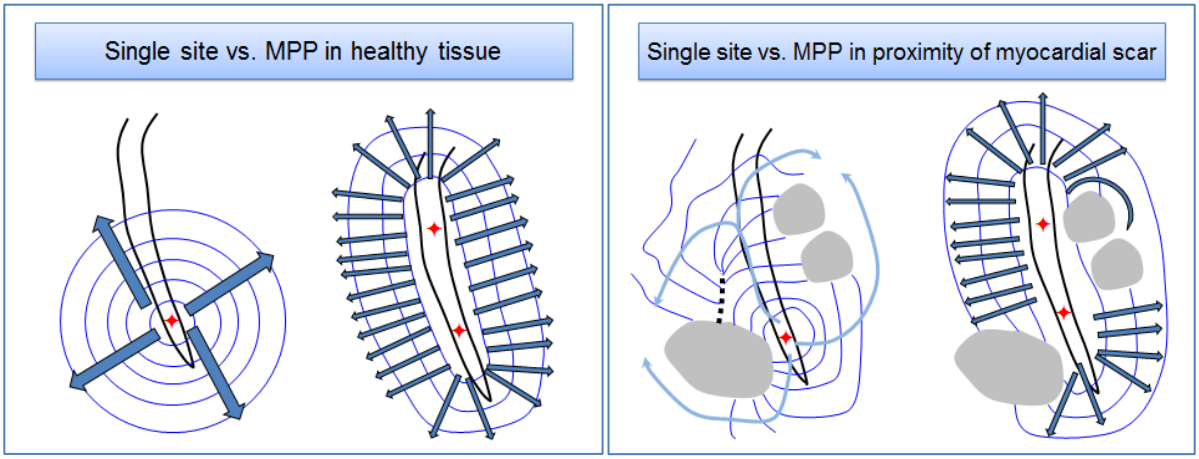

Fig.2. When positioned at sites of healthy myocardium, MPP gives no incremental benefit over conventional single site LV pacing because there are no areas of slow conduction and block (left panel). On the other hand, when the LV lead is positioned next to myocardial scar, where there are areas of slow ventricular conduction and block, MPP can improve the electrical activation by recruiting more tissue at the same time (right panel).

5. STUDY DESIGN

A prospective single-centre pilot study will be conducted to investigate this topic. Fifteen patients with both ischemic and non-ischemic cardiomyopathy resulting in left ventricular myocardial scar and elected to CRT implant at the OUH, will be enrolled in this study.

Compared to standard practice, additional research investigations will be a baseline visit for eligibility assessment, informed consent and pre-CRT implant cardiac MRI, a three-dimensional electroanatomical map reconstruction of the CS venous system during the standard CRT implant and the evaluation of the acute haemodynamic response (AHR, percentage increase of LV-dP/dT max) of MPP over conventional single-site LV pacing during the CRT implant.

1. The cardiac Magnetic Resonance Imaging (MRI) will be performed in each patient 1-2 weeks before the CRT implant during the baseline visit. It will provide information regarding left ventricular (LV) function and volumes, characterization of LV tissue, presence and location of myocardial scar, anatomy of the CS venous system. Moreover, the peri-scar region (viable tissue immediately close to the scar) and the remote

myocardium (viable tissue farther from it) will be identified according to a 17-segments LV segmentation model (see intervention section for more details).

2. A de-novo CRT implant will be performed under fluoroscopic guidance as per standard care. All subjects will be implanted with a regulatory approved St. Jude Medical CRT device compatible with MPP feature (models n° CD3271-40(Q), CD3371-40(Q), CD3371-40C(QC) or newer) and St. Jude Medical quadripolar left ventricular lead (Quartet 1458Q or newer). The choice of the right ventricular and right atrial leads will be left to the operator. After implant of the right ventricular and right atrial leads, a CS venogram will be then performed as per standard practice (see intervention section for more details).

3. A three-dimensional electroanatomical map of the CS venous system will be constructed with Precision mapping system and a Biotronik Vision wire (Biotronik Se & Co. KG, Berlin, Germany) by using the CS venogram as a guide. The map will be merged with the correspondent cardiac MRI images in order to locate the myocardial scar in respect to the CS branches. This will allow the identification of two target CS branches for the study measurements, one located in the peri-scar region and one located in the remote myocardium.

4. A Certus PressureWire will be then introduced into the LV. A PhysioMon software (Radi Medical Systems, Uppsala, Sweden) will be used for electronic calculation of the LV-dP/dTmax from every heartbeat for a period of at least thirty seconds to ensure steady-state conditions. The baseline LV-dP/dTmax will be measured during ventricular spontaneous rhythm.

A St. Jude Medical quadripolar left ventricular lead will be sequentially placed in the “peri-scar” CS branch and in the “remote myocardium” CS branch. In each site the percentage increase in LV-dP/dTmax (Acute Haemodynamic Response, AHR) produced by both conventional single-site and MPP LV pacing to will be measured. All 4 poles of the quadripolar lead will be used in turn for conventional single-site LV pacing, 3 different configurations will be used in turn for MPP. The LV-dP/dTmax will be recorded for each pacing configuration in order to identify the MPP and the single-site LV pacing configurations producing the best AHR (best percentage increase of LV-dP/dTmax).

The AHR produced by the best MPP configuration in peri-scar region will be compared with the AHR produced by the best MPP configuration in the remote myocardium. Moreover, the percentage increase of LV-dP/dTmax produced by the best MPP configuration over the best conventional single-site LV pacing in the peri-scar region will be compared with the same measurement obtained in the remote myocardium.

The decision about the final position of the LV lead and the activation of MPP feature after the CRT implant will be left to operator preference. This is usually decided on the basis of minimum pacing output required to achieve capture, lead stability and ECG changes suggestive of good resynchronization.

As standard practice, the patient will be discharged the day after the procedure. A pre-discharge review will be performed by the patient’s standard care team. Any recorded peri-procedural complications will be communicated to the research team who will report them in the correspondent study CRF.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of outcome measure
Primary To assess whether the added benefit of multipoint pacing (MPP) over conventional single-site LV pacing is consistent in the peri-scar region compared to the remote myocardium	- Acute haemodynamic response to MPP (percentage increase of LV-dP/dTmax produced by MPP over spontaneous ventricular activation) in the peri-scar region and in the remote myocardium - Percentage increase of LV dP/dT max produced by MPP over conventional single-site LV pacing in the peri-scar region and in the remote myocardium	CRT-D implant procedure

7. STUDY RISKS AND BENEFITS

7.1. Study risks

7.1.1 Cardiac MRI

Cardiac MRI is a safe and non-invasive technique with no known risks when appropriately supervised. It does not involve ionising radiation. Potential participants with ferromagnetic objects in their bodies or with implanted devices will be excluded (see Exclusion Criteria) because the cardiac MRI magnet could cause heating issues, dislocation of leads , malfunction of the device. All participants entering the scanner room are currently screened for such objects.

Gadolinium contrast is widely used for clinical indications in cardiac MRI and it is safe. Occasionally it may cause a mild headache, nausea, itching and very rarely (< 1 in 1000) a more severe allergic reaction. It is cleared within hours by the body. Gadolinium has recently been associated with nephrogenic systemic fibrosis in patients with severe renal dysfunction; hence, according to Food and Drug Administration guidelines, all patients with glomerular filtration rate (GFR) < 30 ml/min (stage 3-5 renal disease) should not be given gadolinium. For this study, all potential participants with a GFR < 30 ml/min will be excluded (see Exclusion Criteria).

7.1.2. CRT-D implant

Standard risks associated to a CRT-D implant are:

- incision site complications: pain, bruising, bleeding or haematoma. In general pain from the incision is easily controlled with simple analgesia and resolves after a few days (significant bruising occurs in about 10-20% of patients).

- vascular access complications: venous bleeding, arterial damage (5% of patients).

- arrhythmia (approximately 5%). There is a risk of causing ventricular or atrial arrhythmias from the procedure. These can be treated at the time of occurrence as required.

- risk of lead displacement (approximately 3%).

- pneumothorax (approximately 1% of patients).

- additional lifetime risk of cancer due to radiation exposure for leads placement and CS venogram. The estimated radiation dose for a CRT implant is 13.5 mSv, equivalent to 5 years exposure to UK background radiation. It may theoretically be associated with an increased lifetime risk of developing a cancer of 0.03-0.06%. If compared with the lifetime risk of developing a cancer in the general population of around 30% to 40%, this overall represents a very small addition to the underlying cancer risk from all causes.

- infection of wound, device or leads (approximately 1%). It is known that infection of pacemaker devices or leads can lead to the need for extraction of the leads and device. In most cases this can be performed percutaneously, but very rarely open cardiac surgery can be required to remove the leads.

-Once implanted, the device needs to be worn permanently and stimulate the heart continuously in order to keep its positive effects on heart function. The battery needs to be replaced every few years (depending on amount of pacing and battery characteristics); the leads do not need replacement unless in case of malfunction. Every battery change or leads revision carries a 2-5% risk of device infection.

If compared with the standard procedure:

- the research CRT implant will take longer than a standard procedure (we estimate 20-30 additional minutes on average) due to movement of the left ventricular lead from one vein to another and due to AHR measurements;

- there will be a slightly increased risk of damage to the CS venous system from extra manipulation of leads within it.

Specific S Jude Medical devices and quadripolar leads allowing MPP algorithm will be chosen. They are already used as part of standard care at the OUH and they are CE-marked. The MPP feature will be used only for a few minutes during the implant procedure, therefore it will have a negligible effect on battery duration. The decision to use MPP after the implant will be left to the operator.

The potential risks and benefits of both procedures and implants will be explained to participants as part of their standard care.

7.1.3 Invasive acute haemodynamic measurements

- An arterial access will be required for the pressure wire. This will be performed via the femoral artery or radial artery on the contra-lateral side of the patient to the CRT procedure (so in most cases the right side.) The arterial access carries a small risk of vascular damage (approximately 1%) and rarely of coronary artery damage, arrhythmia or stroke (less than 0.1%). We will minimise the risk of vascular damage by performing the procedure from the radial artery where possible, which has been shown to reduce the vascular complications of these procedures.

- There is a small risk of thrombus (clot) forming on the pressure wire during the procedure, which could result in a stroke (less than 1%). This will be minimized by giving the patient a dose of intravenous heparin before the catheter is inserted. The use of heparin carries a small risk of increased bleeding during the CRT procedure, however trials have shown that performing CRT procedures on higher levels of anticoagulation is safe, and so we do not expect this to be problematic.

- There is a small risk of left ventricular perforation requiring a drain (less than 1%). This risk will be minimized by careful catheter manipulation.

- A small amount of extra radiographic screening will be needed to place the pressure wire in the LV. The additional dose required for insertion of RADI pressure wire under fluoroscopic guidance has been estimated as 3 mSv for a recent research study using RADI pressure wire measurements during CRT implant (RADI CRT study, randomized multicentre study currently ongoing also in our hospital). This dose is equivalent to 13 months exposure to UK background dose, 16 months exposure for domestic pilots, 150 hours of airline flights. It may theoretically be associated with an increased lifetime risk of developing a cancer of 0.005-0.001%. If compared with the lifetime risk of developing a cancer in the general population of around 30% to 40%, this overall this represents a very small addition to the underlying cancer risk from all causes.

7.1.4 Electroanatomical mapping of the CS venous system

- No additional venous access will be required for the electroanatomical mapping of the CS venous system because it will be performed via the same subclavian access used for the CRT-D implant procedure.
- The manipulation of the pacing lead or a wire into the CS venous system might be associated to a small risk of vascular damage. A careful technique will be used to prevent it.

7.2. Study benefits

No direct benefit is anticipated for the study patients. However, a better understanding of the rationale behind MPP could translate into an increased response rate to CRT, with massive benefits for the future patients in terms of both quality (improved symptoms, reduced risk of hospital admissions) and quantity of life (reduced risk of death) and reduced costs for the health system. Moreover, the focused use of MPP would mean battery saving in the patients who would not benefit from it, with reduced number of battery

replacements and reduced risk of device infections. All these improvements would also translate into reduced health costs.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Patients with history of ischemic or non-ischemic cardiomyopathy and elected to a CRT-D implant procedure.

8.2. Inclusion Criteria

- Age of 18 years or over
- Left ventricular myocardial scar;
- Standard indication to CRT-D (NYHA functional class III-IV despite optimal medical therapy, LV ejection fraction (LVEF) ≤35 %, QRS duration ≥120 msec, LBBB);
- Will and ability to give informed consent for participation in the study.

8.3. Exclusion Criteria

- Pregnancy, trying for a baby or breast feeding;
- Any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study;
- Inability to tolerate MRI scanning (e.g. claustrophobia, unable to lie flat)
- Contraindications to MRI scanning (e.g. implantable devices, cranial aneurysm clips, metallic ocular foreign bodies, hypersensitivity to gadolinium);
- Significantly impaired renal function (eGFR < 30ml/min);
- History of allergy to cardiac MRI contrast media;
- Severe claustrophobia.

9. STUDY PROCEDURES

9.1. Recruitment

Potential participants will first be approached some weeks before the CRT-D procedure. They will be identified from CRT Device implantation clinic lists. Their outpatient clinic letters will be screened by a member of the research team to assess suitability for inclusion in the study. A letter of invitation, a patient information leaflet and a consent form will be given to potential participants by the researchers who are also members of the participant's care team at their routine clinic visits or sent by post at the time their procedure date is determined (usually 6 weeks in advance). The participant will be allowed time to consider the information, and the opportunity to ask questions to the Investigator, their GP or other independent parties to decide whether they will participate in the study. He/she will be invited to contact the investigator if wishes to discuss the study further. In case of will to take part, the participant will be approached at his/her pre-admission visit before the procedure (1-2 weeks before the implant) by a member of his/her care team, followed by a member of the research team for a baseline visit including informed consent, screening, eligibility assessment and cardiac MRI.

9.2. Baseline visit

9.2.1. Informed Consent

Informed consent will be obtained by a qualified and experienced investigator who is familiar with the study protocol and procedures. This may be the chief investigator, a principal investigator, the research fellow or a research nurse. The list of eligible individuals will be specified in the delegation log.

Written versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the study and the benefits and risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time without giving a reason or any prejudice to future care and rights.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. One original signed informed consent form will be retained by the participant, the other original will be kept in the participant's casenotes and a copy will be kept in the trial master file. A copy of the signed consent form will be given to the participants. The original signed form will be retained at the study site. The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

9.2.2. Screening and Eligibility Assessment

It will include:

a. demographics;
b. exclusion of pregnancy or breast feeding in case of child-bearing age female;
c. detailed collection of any relevant medical history;
d. list of current medications.

This information will be obtained from both participant and medical records. It will be recorded in a not identifiable paper CRF by a study investigator or a member of the research team.

9.2.3. Cardiac MRI

Cardiac MRI will be performed as additional research procedure during the baseline visit. It will comprehensively characterize myocardial tissue and assess myocardial function and metabolism.

In this research study, patients may undergo the following CMR imaging techniques:

a. Functional imaging/cine CMR to image the heart pumping the blood in circulation of the body and to assess ventricular and atrial volumes and function and define the anatomy of the CS venous system;
b. First pass perfusion and contrast based techniques (gadolinium enhancement techniques or tissue characterization techniques) which include the use of 'dye' to directly detect impaired blood supply patency of microvessels, capillary leak and myocardial fibrosis/irreversible damage;

These techniques will allow a clear location of myocardial scar, the peri-scar region and the remote myocardium and the definition of the anatomy of the CS venous system as detailed below.

As per standard practice, the LV walls will be artificially divided into 17 segments (fig. 3) and the positions of the scar, the viable tissue immediately around it (peri-scar region, 1 segment from scar) and of the viable tissue farther from it (remote myocardium, 2 or more segments from scar) will be identified according to this 17-segments model (fig.3).

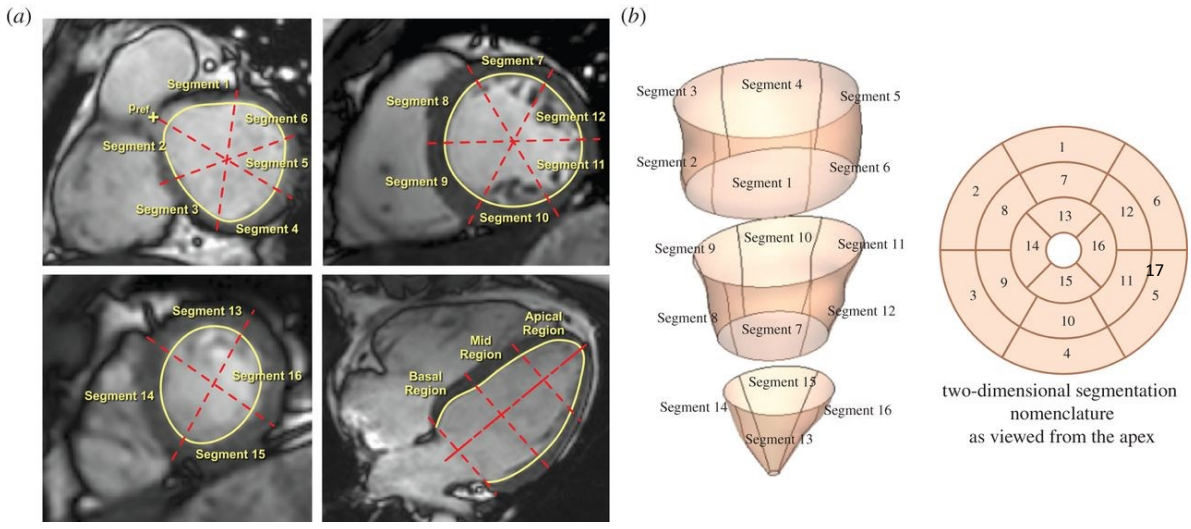

Fig.3. 17-segment model segmentation for LV.

The location of the myocardial scar, the peri-scar region and the remote myocardium in relation to the CS anatomy will allow the identification of a "peri-scar" CS branch and a "remote myocardium" CS branch (fig.4).

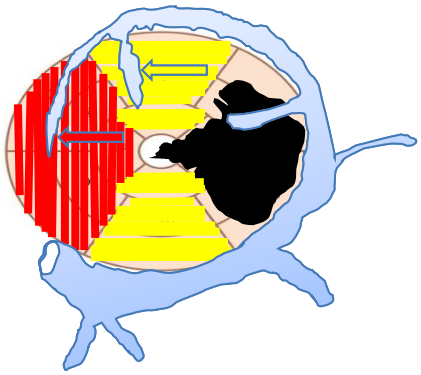

Fig.4. Schematic representation of LV Bull's eye view (LV seen from the apex), with myocardial scar (black area), peri-infact region (yellow-lined area) and correspondent CS branch (yellow arrow), remote myocardium (red-lined area) and correspondent CS branch (red arrow).

During the acquisition of the images, participants will be in constant communication with the staff running the scan and they will be able to decide to stop the scan at any time.

No scan report will be generated. In case of incidental findings the CMR consultant will oversee arrangements to contact the participant and to ensure that the participant's GP is notified as per internal SOP. Data will be recorded on a not identifiable paper CRF. No additional research analyses will be performed.

9.2.4. CRT-D implant procedure (including three dimensional mapping of the CS venous anatomy and invasive acute haemodynamic measurements)

The patient will be admitted, as routine for the procedure, generally 1-2 weeks after the baseline visit.

At first, arterial access will be obtained. A small 5 French sheath will be used to pass a 5F catheter into the left ventricle. A 2500 units bolus of heparin will be given intravenously to minimise the risk of thrombosis.

Venous subclavian access will be then obtained. A right ventricular lead and a right atrial lead will be placed as normal at the start of the procedure. The choice of the right ventricular and right atrial leads will be left to the operator.

ACS venogram will be then performed as per standard practice. Briefly, contrast dye will be injected in the CS under fluoroscopic guidance by using a dedicated occlusive catheter in order to delineate its anatomy and identify its branches.

A three-dimensional electroanatomical map of the CS venous system will also be constructed with Precision mapping system and a Biotronik Vision wire (Biotronik Se & Co. KG, Berlin, Germany) by using the CS venogram as a guide. The map will be merged with the correspondent cardiac MRI images in order to locate

the myocardial scar and the target CS branches for the study measurements, one located in the peri-scar region and one located in the remote myocardium.

A 0.014-inch diameter high fidelity Certus PressureWire will be then introduced into the LV from femoral or radial arterial access site. A PhysioMon software (Radi Medical Systems, Uppsala, Sweden) will be used to calculate electronically LV-dP/dT_{max} from every heartbeat for a period of at least thirty seconds to ensure steady-state conditions.

The LV-dP/dT_{max} will be measured during spontaneous ventricular rhythm. A St. Jude Medical quadripolar left ventricular lead (Quartet 1458Q or newer) will be then sequentially placed in the "peri-scar" CS branch and in the "remote myocardium" CS branch and the LV-dP/dT_{max} will be measured during conventional single-site and MPP LV pacing in each site. In each site the AHR to both conventional single-site and MPP LV pacing will be performed by measuring the percentage change in LV-dP/dT_{max} compared to spontaneous ventricular rhythm. Different single-site (all 4 poles in turn) and MPP (3 configurations) LV pacing settings will be tested to this aim in order to identify the best MPP and single-site LV pacing configurations.

The AHR produced by the best MPP configuration in peri-scar region will be compared with the AHR produced by the best MPP configuration in the remote myocardium. Moreover, the percentage increase of LV-dP/dT_{max} produced by the best MPP configuration over the best conventional single-site LV pacing in the peri-scar region will be compared will the same measurement obtained in the remote myocardium.

All measurements will be repeated at least twice in order to make sure they are reliable and reproducible. The pressure wire and the sheath will be removed after all measurements are complete.

Data will be electronically captured from the pressure wire and automatically extracted on an excel database.

The LV-dP/dT_{max} measurements will not influence the operator's decision about the final position of the LV lead. This will be dictated, as standard practice, by minimum pacing output required to achieve capture, lead stability and ECG changes suggestive of good resynchronization.

All subjects will be implanted with a regulatory approved St. Jude Medical CRT device compatible with MPP feature (models n° CD3271-40(Q), CD3371-40(Q), CD3371-40C(QC) or newer).

9.3. Pre-discharge review

As part of standard care, each patient will be reviewed the day after the procedure, before discharge. The occurrence of any procedural complications will be investigated and recorded by a study investigator or a member of the research team in a not identifiable paper CRF.

9.4. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements
- Withdrawal of Consent
- Loss to follow up

No specific procedures or observations will be required in case of discontinuation/withdrawal of participants from study rather than standard medical care.

The reason for withdrawal will be recorded in the CRF.

In case of withdrawal from the study in an early stage (before the study interventions), the patient data will be excluded from the analysis and a new participant will be enrolled.

9.5. Definition of End of Study

The end of study will be the date of CRT-D implant procedure of the last patient.

10. INTERVENTIONS

These are described in the Study Procedures section above.

11. SAFETY REPORTING

11.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- congenital anomaly/birth defect
- results in persistent or significant disability/incapacity

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

11.2. Reporting Procedures for Serious Adverse Events

12. 'A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website)'STATISTICS AND ANALYSIS

12.1. The Number of Participants

This is a pilot study that aims at investigating a possible relation between scar location and AHR to MPP more than proving a statistical significant different between AHR to MPP in the peri-scar region compared to the remote myocardium. Therefore, a small sample size of 15 patients has been chosen just in order to confirm the validity of the study hypothesis to be further investigated in a bigger study.

Of note, a recent study (13) has documented a variable AHR to MPP over single-site LV pacing with a percentage increase in LV-dP/dT between 0% and 40% according to LV site. If our hypothesis is confirmed and the best and worst MPP sites correspond to peri-scar and remote-myocardium respectively, 15 patients could be also enough in order to show a statistically significant difference between the two sites with a 95% confidence level and a 80% power.

12.2. Description of Statistical Methods

Comparison of response to the two different pacing sites will be made using appropriate statistical testing. We would expect the data to be normally distributed, in which case T-tests will be used.

12.3. Analysis of Outcome Measures

The following measurements will be collected and analysed:

- LV-dP/dT_{max} during spontaneous ventricular rhythm;

- LV-dP/dT_{max} during single site LV pacing in 4 different pacing configurations (4 different poles used in turn), with the LV lead either in the peri-scar CS branch or in the remote myocardium CS branch. The pacing configuration producing the biggest LV-dP/dT_{max} over spontaneous ventricular rhythm will be considered the best pacing configuration in each CS branch and used for further comparisons and analyses;

- LV-dP/dT_{max} during single MPP LV pacing in 3 different configurations, with the LV lead either in the peri-scar CS branch or in the remote myocardium CS branch. The pacing configuration producing the biggest LV-dP/dT_{max} will be considered the best pacing configuration in each CS branch and used for further comparisons and analyses.

The percentage change in LV-dP/dT_{max} produced by the best single site LV pacing configuration over spontaneous ventricular rhythm will represent the best Acute Haemodynamic Response (AHR) of single site LV pacing in each CS branch. The percentage change in LV-dP/dT_{max} produced by the best MPP LV pacing configuration over spontaneous ventricular rhythm will represent the best Acute Haemodynamic Response (AHR) of MPP LV pacing in each CS branch.

The following comparisons will be made as outcome measures:

- AHR produced by the best MPP configuration in the peri-scar region versus AHR produced by best MPP configuration in the remote myocardium;

- percentage increase of LV-dp/dT_{max} produced by the best MPP configuration over single site LV pacing in the peri-scar region versus percentage increase of LV-dp/dT_{max} produced by the best MPP configuration over the best conventional single-site LV pacing in the remote myocardium.

Our hypotheses are that:

- the AHR produced by the best MPP configuration will be consistently and statistically significantly higher in the peri-scar region compared to the remote myocardium;

- the percentage increase of LV-dp/dT_{max} produced by the best MPP configuration over single-site LV pacing will be consistently and statistically significantly higher in the peri-scar region compared to the remote myocardium.

13. DATA MANAGEMENT

13.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

13.2. Data Recording and Record Keeping

- The study staff will ensure that the participants' anonymity is maintained.
- NHS code of confidentiality will be followed.
- Personal data will be anonymised with the use of a study participant number. The study number will be correlated with personal data about the patient in one electronic file, which will be individually password protected and secured as above.
- All electronic records (excel databases) will be stored on a NHS server within password-protected user accounts and they will be anonymized.
- The MRI scans will be stored in the usual manner on the OCMR server.
- The file linking personal data to the study ID will be stored separately to the study data.
- Paper records will be stored in a locked filing cabinet to which only the research team have access. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

- EP data analysis will be performed by Dr Leo and Dr Betts in the JR hospital. No further data transfer will be performed.
- As per Trust Policy, after the end of the trial period, all study data will be kept for a further period of 5 years before being deleted, to allow for full analysis and results publication. Personal data will be only kept for a few months after the study has finished, before being destroyed.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

14.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.4. Reporting

The CI shall submit once a year throughout the study or, on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

14.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Participants anonymity will be maintained and no patient identifiable information will be published.

14.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

We intend that the majority of study visits will be performed at the time of routine clinical visits to hospital so would not expect that patients will have to make many extra visits to hospital.

Light refreshments will also be available.

14.7. Other ethical considerations

No other ethical considerations are involved in this study.

15. FINANCE AND INSURANCE

15.1. Funding

This research study was selected for the NIHR Oxford Biomedical Research Centre (BRC) Young investigator Award in 2015 and will be supported by the corresponding research grant awarded. Any shortfalls will be covered by the CRM Hub.

15.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

16. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. For participants who have stated they wish to receive a copy of the research results, a copy of these results will be sent by post.

17. REFERENCES

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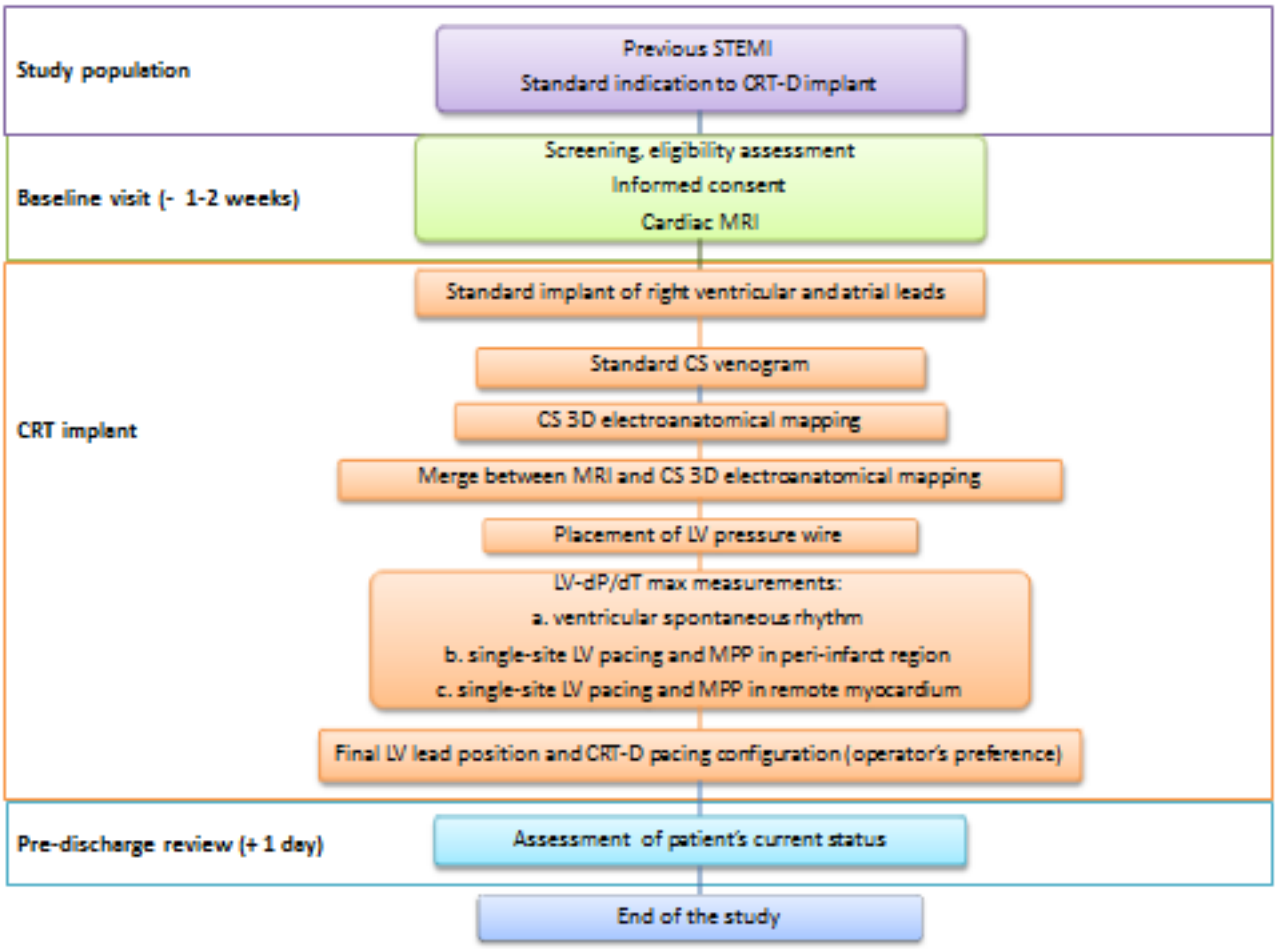
18. APPENDIX A: STUDY FLOW CHART



19. APPENDIX B: SCHEDULE OF TIMING OF STUDY APPOINTMENTS AND STUDY PROCEDURES

	Recruitment	Baseline visit	Study intervention	Pre-discharge review
Time since CRT-D implant procedure	≥ 6 wks	- 1-2 wks	0	+ 1 d
Study procedures				
Eligibility assessment	X	X		
Patient's information	X			
Informed consent		X		
Demographics		X		
Medical history		X		X
Cardiac MRI		X		
CRT-D implant			X	
3D map of CS venous system			X	
Acute haemodynamic response measurements			X	

d = day; f-up = follow-up; wks = weeks.

20. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1		M Leo, T Betts	- All Patients with myocardial scar (regardless of ischemic and non-ischemic aetiology) included in the study - Study end date extended of 12 months.