EPORVA

Electrophysiological Phenotyping Of Patients At Risk Of Ventricular Arrhythmia

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STUDY COORDINATION CENTRE: Hammersmith Hospital

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Clinical Queries
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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 9459/ 0207 594 1862**
http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

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This protocol describes the EPORVA study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

KEYWORDS
Obesity, rheumatoid arthritis, dilated cardiomyopathy, ventricle, arrhythmia,

STUDY SUMMARY

TITLE	Electrophysiological phenotyping of patients at risk of ventricular arrhythmia
DESIGN	Prospective case-control/cohort
AIMS	To understand the electrical properties of the heart in patients at a higher risk of heart rhythm abnormalities To identify if medical or surgical treatment can cause changes in the heart's electrical circuit to reduce risk of heart rhythm abnormalities
OUTCOME MEASURES	Parameters quantifying electrical properties (conduction and relaxation) in the heart muscle
POPULATION	1. Obese patients awaiting weight-reduction surgery 2. Rheumatoid arthritis awaiting biologic therapy 3. Dilated cardiomyopathy patients with and without titin (gene) mutation 4. Healthy volunteers
ELIGIBILITY	**Inclusion criteria** Age 18-75 (inclusive) Patients awaiting weight-reduction surgery Patients awaiting biologic treatment for rheumatoid arthritis Patients with known dilated cardiomyopathy with or without titin (gene) mutation Healthy volunteers (no known/diagnosed medical problems) **Exclusion criteria** Pregnancy (or positive urine test for pregnancy) Breastfeeding Outside specific age range (under 18 or over 75 years) Known hepatitis B or C, HIV or CJD infection Unable to provide verbal or signed written informed consent
DURATION	2.5 years

1. INTRODUCTION

Some common medical problems, like obesity, arthritis and dilated cardiomyopathy can cause changes in the heart's electrical circuit. This can increase the risk of heart rhythm disturbance. Symptoms associated with rhythm disturbance of the heart can include palpitations ("skipped", "extra" or "fast" heart beats), breathlessness, and chest discomfort. In some cases, these heart rhythm abnormalities can be dangerous and life-threatening.

Although it is known that some patients with obesity, rheumatoid arthritis and dilated cardiomyopathy are at higher risk of heart rhythm problems, the mechanisms by which these disturbances are generated in the heart are not fully understood.

It is also not known if and how surgical treatment for obesity and medical treatment for rheumatoid arthritis can cause changes in the heart's electrical circuit, to reduce the risk of heart rhythm problems.

To answer these specific unanswered questions we will use a sophisticated and detailed method, called electrocardiographic imaging (ECGi), to record the heart's electrical activity in patient groups that have a higher risk of heart rhythm problems. This will give us more information about the heart's electrical properties that a standard electrical recording.

2. STUDY OBJECTIVES

AIMS

1) To compare the electrical activity of the heart in patients at higher risk of heart rhythm problems (obese, rheumatoid arthritis, and dilated cardiomyopathy) with healthy volunteers

2) To establish if weight reduction surgery for obesity, and specialist (biologic) medical treatment for rheumatoid arthritis, causes changes in the heart's electrical properties to reduce the risk of heart rhythm problems in these groups

3) To compare the electrical properties of the hearts in patients with genetic (titin) mutation dilated cardiomyopathy with those who do not have titin mutation

3. STUDY DESIGN

This will be a 2.5-year study in which participants will be recruited prospectively from Imperial College Healthcare NHS Trust, or recalled from existing registry databases where individuals have given their consent to be contacted for research purposes.

We will perform ECGi in four well-defined cohorts of interest to identify specific, and potentially reversible, electrical disturbances of the heart. ECGi will be performed:

i. Before and after weight reduction surgery in obese patients with a body mass index >40
ii. Before and after biologic treatment in patients with rheumatoid arthritis
iii. In titin (gene)-positive and titin-negative dilated cardiomyopathy
iv. Healthy volunteers

Participation in this study will be entirely voluntary and will not affect participants' current or future care. Participants will be free to withdraw from the study at any time without having to provide a reason. Participants will be recruited prospectively and consecutively from clinic or via recall from a registry database, on a first-come first-serve basis, to minimise bias. Recruitment will continue throughout the study until the required sample size is obtained.

The study will aim to achieve approximately equal numbers of females and males. Based on previous ECGi studies, loss to followup is expected to be low as participants will not require intensive followup with the research team, but all participants may be recalled for repeat tests while the study is ongoing. This is to ensure that sufficient data is acquired for analysis.

Data collected from participants prior to drop out or loss to follow-up will be included in the data analysis. We are not aware of any ongoing studies that are competing for the same group of participants or whose results may affect recruitment. Similarly, our study will not jeopardise other studies either. Currently, we are analysing ECGi signals from an unpublished, ongoing study in which 16 controls and 20 TTNtv hypertrophic cardiomyopathy patients have been recruited over 8 months at our institution, with an estimated consent rate of 70% and dropout rate of 10%.

3.1 STUDY OUTCOME MEASURES

Our primary endpoints will consist of parameters to calculate electrical (electrophysiological) parameters of the heart, that provide information about the heart's conduction and repolarisation properties. Specifically, these will include

i. Activation maps and epicardial electrograms at rest (baseline) and at peak exercise
ii. Mean activation-recovery intervals (ARI), corrected for heart rate, and spatial ARI dispersion at baseline and after exercise
iii. Conduction velocity (CV) at baseline and after exercise

Secondary analysis will be performed to gain further mechanistic insights into the arrhythmogenic mechanisms associated with common medical problems, such as obesity, RA and DCM. For example, this will include assessing the relative importance of depolarisation vs repolarisation abnormalities and the contribution of conduction slowing to fractionation of projected epicardial electrocardiograms.

In-keeping with our aims, our analysis will consist of the following comparisons:

1. before and after weight reduction surgery in obese patients
2. before and after medical treatment in patients with rheumatoid arthritis;
3. between titin-positive and titin-negative dilated cardiomyopathy patients
4. in all of the above cohorts with healthy, age- and sex- matched volunteers

This will facilitate investigation into the differences in the electrical properties of the hearts in our cohorts of interest. It will also provide information on whether or not medical or surgical treatment causes changes in the electrical properties of the heart to reduce risk of arrhythmia.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Female participants of child-bearing age will need to undergo a pregnancy (urine) test at the time of enrolment to the study and before the ECGi protocol.

Prospective participants need to fulfil at the inclusion criteria to enrol onto the study.

Participants with any one or more of the exclusion criteria will not be able to participate in the study or will be withdrawn from the study should any one of the exclusion criteria be met during the time that the study is ongoing.

4.2 INCLUSION CRITERIA

To take part in the study, participants must have **one** of the following:

a) obesity (BMI>40) and awaiting weight reduction surgery
b) rheumatoid arthritis awaiting specialist (biologic) treatment
c) titin-positive dilated cardiomyopathy
d) titn-negative dilated cardiomyopathy
e) be a healthy volunteer with no known medical condition

and both of the following:

f) aged 18 to 75 years, inclusive
g) able to provide verbal and signed written informed consent

4.3 EXCLUSION CRITERIA

Participants with any one of the following will not be able to take part in the study:

a) aged under 18 or over 75 years;
b) known HIV, hepatitis B & C or CJD infection;
c) unable to provide verbal or signed written informed consent;
d) pregnancy or positive urinary pregnancy test;
e) breastfeeding.

4.4 WITHDRAWAL CRITERIA

Participants will be withdrawn from the study if they fulfil at one of the following at any stage of the study:

a) Unable to proceed with tests listed on study protocol
b) Withdrawal of consent
c) Positive pregnancy test or new pregnancy during the course of the study
d) Fulfil any of the exclusion criteria during the time the study is ongoing

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject 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*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All serious & non serious adverse effects, whether expected or not, will be recorded. Depending on the nature of the event the reporting procedures below will be followed. Any questions concerning adverse event reporting will be directed to the Chief Investigator in the first instance.

Non serious AEs

All such events, whether expected or not, will be recorded.

Serious AEs

An SAE form will be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to any pre-existing medical or surgical conditions and hospitalisations for elective treatment of a pre-existing conditions will not be reported as SAEs.

All SAEs will be reported to the London Surrey REC where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

The Chief Investigator will inform the sponsor of the study of all SAEs. Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event.

Local investigators will report any SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

Contact details for reporting SAEs
jrco@imperial.ac.uk
CI email (Dr Fu Siong Ng; f.ng@imperial.ac.uk, 07740457874)

6. ASSESSMENT AND FOLLOW-UP

Participants' care will continue under their normal clinical or healthcare teams. Therefore, their followup will be arranged by and conducted by these team(s).

A baseline study assessment for all participants will comprise of a medical and physical assessment (including blood pressure, heart rate, weight, height), blood tests (where applicable, and where no results in the 3 months prior to enrolment to the study are available), 12-lead ECG recording and urine test (for females of childbearing age). ECGi protocol will comprise of 252-lead ECG with physical activity and thoracic MRI or CT scan.

Participants due to undergo weight reduction surgery for obesity or medical (biologic) treatment for rheumatoid arthritis will have ECGi before and after treatment.

Participants not due to undergo any specific, planned treatment ie dilated cardiomyopathy patients and heathy volunteers, will have ECGi once at baseline.

However, all participants may be recalled more than once during the course of the study duration for repeat tests or assessments either for more data or to improve the quality of data to facilitate analysis.

Wherever possible, MRI scan will be preferred over CT. Participants who cannot safely have thoracic MRI will instead have thoracic CT as part of the ECGi protocol. In this instance, radiation exposure will be limited by ensuring that each participant who cannot have MRI only has a maximum of two thoracic CT scans as part of the study protocol.

The end of the study will be defined as last followup required for the purposes of the study.

7. STATISTICS AND DATA ANALYSIS

No published studies have implemented ECGi before and after clinical intervention. We have used the results from other studies in which patients had QTc intervals measured before and after bariatric surgery using 12-lead ECG, to estimate our power calculations. Assuming a conservative effect size (change in QTc interval following bariatric surgery) of 12ms (standard deviation 10ms), and a delta of zero in the control arm (standard deviation 10ms), and a 1:1 randomisation ratio, 16 patients will be needed in each arm to provide 90% power to detect an effect at the two-tailed 5% significance level. Allowing for dropouts, we will therefore aim to recruit 20 participants to each study group (obesity, rheumatoid arthritis, titin-positive dilated cardiomyopathy, titin-negative dilated cardiomyopathy and healthy volunteers, respectively) to be confident that we have a sufficiently powered study to detect the significant differences we intend to demonstrate between our groups.

Data analysis will be performed within Imperial College London and National Heart and Lung Institute.

Primary endpoints will be assessing differences and magnitudes, or patterns, of change in activation and repolarisation. This will include, but may not be limited to:

- an assessment of differences and changes in mean global activation-recovery intervals (ARI);

- spatial ARI;
- conduction velocities (CV);
- CV dispersion;
- ARI and CV restitution slopes and curves

Secondary analysis will be performed to gain further mechanistic insights into the arrhythmogenic mechanisms associated with obesity, RA and DCM. For example, this will include:

- Assessment of the relative importance of depolarisation vs repolarisation abnormalities
- Contribution of conduction slowing to fractionation of projected epicardial electrocardiograms.

Corresponding to the study aims, we will compare electrophysiological parameters

- before and after bariatric surgery in obese patients
- before and after medical treatment rheumatoid arthritis patients
- between titin-positive and titin-negative DCM patients
- with healthy, age- and sex- matched volunteers for each of the above groups

Mean values for continuous variables in patients before and after an intervention (where applicable) will be compared using Student's t test for unpaired data and analysis of (co)variance for paired data. Non-normally distributed data will be compared using Mann-Whitney U test or Kruskall-Wallis test. The proportions of categorical variables before and after surgery will be compared using chi-square test or Fisher's exact test. Pearson's correlation analysis will be used to estimate the relationships between ECG and/or clinical parameters and echocardiographic variables. Demographic parameters will be entered into multiple linear regression analyses for adjustment of possible relationship with the examined dependent variables. A two tailed P value of 0.05 will be considered statistically significant.

Study data will be stored for a minimum of 10 years after the completion of the study, including the follow-up period. All other data, including personal data, will be irretrievably deleted and securely disposed at the end of the study.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from London Surrey Research Ethics Committee (REC) and Health Research Authority (HRA).

The study has obtained confirmation of capacity and capability from Imperial College Healthcare NHS Trust to accept participants into the study for the purposes of research.

This study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

A member of the clinical care team will approach prospective participants to offer participation in the study in the first instance.

Members of the research team will only make contact with prospective participants after a member of the clinical care team has introduced the option of partaking in this study to them.

In the case of healthy volunteers, members of the research team may make first contact with prospective participants, as it is envisaged that they will not have ongoing access to a clinical care team.

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet (patient information sheet) offered and time allowed for consideration. Signed written and verbal informed consent will be obtained from every participant at the beginning of the study at the point of enrolment. Participants' suitability to partake will be checked prior to tests occurring after enrolment, according to inclusion and exclusion criteria. The right of the participant to refuse to participate or withdraw from the study at any point without giving reasons will be respected at all times.

After the participant has entered the study, their medical or surgical team(s)/clinician(s) remain free to give an alternative treatment to that specified at the start of the research study, at any stage if they feel it is in the participant's best interest. The reasons for doing so will be recorded. In these cases, the participants can remain within the study for the purposes of data collection, follow-up and data analysis if they wish.

All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing current, further or future treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

All participants will have an anonymous identifier that will be generated by the research team during the recruitment process. Participants will be entered into a study database which will contain all research records. This database can be accessed at the National Heart and Lung Institute (NHLI) at the Hammersmith Hospital and specific PCs that are used by the research team within the Robert Steiner MRI Unit, Imperial College, MRC Clinical Sciences Centre, Hammersmith Hospital. It will be password protected and will have restricted access to specific members of the research team only. Anonymised data will be available to researchers. Similarly, during the course of the study, all medical history, physical assessment, ECG, imaging and any other clinical data for the study will be stored in an anonymised format and securely on a password protected study database at the NHLI at Hammersmith Hospital. This will also only be accessible by the research team.

The blood samples will be taken under the remit of NHS phlebotomy and blood services at Imperial College Healthcare NHS Trust and processed under that jurisdiction. It is envisaged that many of the participants will already undergo blood tests as part of their normal planned clinical care by their clinical teams. Where this is not the case and if

required, however, participants will have blood tests taken by appropriately trained, qualified and experienced members of the research team. In this instance, participants blood tests will be labelled with their usual NHS patient identification information for the purposes of having the tests processed under the remit of Imperial College Healthcare NHS Trust. The results of these will be available to their usual clinical teams. The research team will not hold, process, store or retain any biological samples at any stage of the research project or thereafter. Members of the research team with appropriate authorisation will have access to the results of blood tests via Imperial College Healthcare NHS Trust. These results will be entered and stored in an anonymised format on the password protected, and restricted-access study database. At no point during or after the study will members of the research team have access to the actual blood samples.

Urine samples provided by a participant will be tested (pregnancy test) contemporaneously by a qualified member of the research team, and then immediately discarded without being labelled with patient identifiable information. Therefore, urine samples will not be processed, used or retained for any other purpose.

Only authorised members of the research team will have access to participants' imaging records. MRI scans will be conducted and stored in an anonymised format the MRC Robert Steiner MRI unit at the Hammersmith Hospital. CT scans, where required, will be conducted and stored under Imperial College Healthcare NHS Trust jurisdiction. All imaging data will be transferred in an anonymised format to a password-protected and access-restricted study database for use by the research team.

Imperial College London retention schedule states that all study data should be retained for 10 years after completion of the study. This will include some identifiable data such as consent forms and will be stored in a secure Imperial College London archiving facility, in-line with institutional policy. All other personal data, such as contact details that will be kept securely during the study, will be irretrievably deleted and disposed at the end of the study.

Fully anonymised data from the database may be shared with approved research collaborators, if required during the course of the study.

In the event that the research participant loses capacity to consent during the study, their identifiable samples and data will be withdrawn from the study. Any samples or data that is not identifiable may be retained and used for the purpose of which they consented to.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

National Institute of Health Research Imperial College Biomedical Research Council (NIHR Imperial College BRC) are funding this study (code WHCF P74381).

No provision for payment to participants or investigators are intended as part of the study protocol.

8.7 AUDITS AND INSPECTIONS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the research team and clinical research fellow (Dr Kiran Patel) with overview from the principle investigator (Dr Fu Siong Ng).

10. PUBLICATION POLICY

All publications and data-sharing will be in accordance with the current guidance provided by the NHLI and Imperial College London.