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How does sinus node disease maintain atrial fibrillation?

Submission date 08/04/2019	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 19/07/2019	**Overall study status** Completed	
Last Edited 21/08/2020	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims

The research study is intended to look at the specific role of sinus node disease (SND) in atrial fibrillation (AF), which to date has not been investigated. The mechanisms that maintain persistent AF are not well understood and the researchers want to investigate if SND can cause AF by altering the electrical properties of the right atrium and act as a driver to maintain AF. It is known that SND frequently co-exists with AF, and the presence of SND is a predictor of poor success rates of catheter ablation treatment for AF. To better understand the interplay between these two disease states, the researchers plan to use electrical mapping of the heart to define the difference in atrial activity when SND is present or not, and to identify markers of electrical abnormality. With this information they may be better placed to develop targeted and personalised treatments or investigate new avenues of treatment to those who suffer from persistent AF.

Who can participate?

Patients with (1) AF alone; (2) AF and SND; (3) No AF or SND; (4) SND alone, requiring pacemaker implantation. Participants in all categories will be due to undergo clinically indicated cardiac procedures; those in groups 1 and 2 will be due to undergo AF ablation, those in group 3 an SVT ablation and group 4 implantation of a permanent pacemaker.

What does the study involve?

Following or during the clinical procedure additional electrograms are carried out to map the atrial activity. For participants undergoing pacemaker implantation alone this requires carrying out an additional electrophysiology study.

What are the possible benefits and risks of participating?

No benefits are expected apart from increasing what is known about AF and SND. No major risks are expected, as the doctor performing the clinical procedure will not proceed to the mapping if he/she feels it is not safe to do so. The only risk is the increased exposure to ionising radiation (equivalent to 2 months' exposure to background radiation).

Where is the study run from?

1. Manchester University NHS Foundation Trust

2. Liverpool Heart and Chest Hospital NHS Foundation Trust
3. University Hospitals of Leicester NHS Trust
4. Barts Health NHS Trust
5. Manchester University NHS Foundation Trust
6. Royal Papworth Hospital NHS Foundation Trust

When is the study starting and how long is it expected to run for?
November 2018 to April 2024

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
249680

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
40926, IRAS 249680

Study information

Scientific Title
Endocardial mapping of atrial fibrillation in patients with sinus node disease

Study objectives
The research study is intended to look at the specific role of sinus node disease (SND) in atrial fibrillation (AF), which to date has not been investigated. The mechanisms that maintain persistent AF are not well understood and the researchers want to investigate if SND can cause AF by altering the electrical properties of the right atrium and act as a driver to maintain AF. It is known that SND frequently co-exists with AF, and the presence of SND is a predictor of poor success rates of catheter ablation treatment for AF. To better understand the interplay between these two disease states the researchers plan to use electrical mapping of the heart to define the difference in atrial activity when SND is present or not, and to identify markers of electrical abnormality. With this information researchers may be better placed to develop targeted and personalised treatments or investigate new avenues of treatment to those who suffer from persistent AF.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/03/2019, North West - Greater Manchester Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ; Tel: +44 (0)207 104 8019; Email: nrescommittee.northwest-gmcentral@nhs.net), ref: 19/NW/0057

Study design
Observational; Design type: Cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Sinus node disease

Interventions

Study participants:
All study participants will be due to undergo a clinically indicated elective cardiac electrophysiology procedure or pacemaker implantation at one of the participating NHS hospitals. Participants will have been seen by their cardiologist in clinic and will have agreed to their procedure.

Participants will then be screened in one of the following ways:
1. Screening of the waiting list for electrophysiology studies (EPS), pacemakers, and cardiac ablation procedures. This will be performed by members of the direct care team, including the cardiology research practitioner; who undertakes this duty as part of their role. Initial approach to those identified as potentially eligible will be made by letter from the clinician responsible for their care. The letter will contain a brief description of the study, together with contact information for the research team.
2. Referral from a clinical Cardiology colleague within a participating centre. Patients seen at these clinics and who are identified as potentially eligible to participate will be asked by their treating clinical team for verbal permission to pass their contact details to the research team. The research team will then send out a letter with the patient information sheet.
3. Participants may also be recruited from poster advertisements in arrhythmia clinics at these sites. As these are elective procedures patients will have time to consider their participation in the study, likely to be anywhere up to 8 weeks, but not less than 24 hours.

Patients expressing interest will then be sent the study patient information sheet (PIS) and any additional supporting information to allow them to understand the study. The information sent will include contact details for the research team so that the patient can contact the research team to express an interest in participating in the study, or ask any questions they may have about the study. If no response is received within one week, the patient will be contacted by the research team by telephone to check they have received the information and establish interest. All potential participants will be advised that participation in the research is voluntary and declining participation will not affect their clinical care.

Patients who are willing to participate will be met at their pre-admission appointment by a member of the research team, patients will be informed this may extend the duration of the visit by up to 30 minutes. A member of the research team will answer any study questions and establish eligibility. The PI or designee should then obtain informed consent. Following written consent a research assessment will take place which will include medical history and clinical examination. Data will be collected from either medical records or by repeat questioning or examination by a medically qualified researcher or research nurse.

Should a participant not be able to be seen at the pre-admission assessment or only express interest at the visit, then another date suitable for the patient to visit could be arranged to consent and carry out baseline assessment. Alternatively a telephone discussion with the PI or designee could be carried out and consent taken before the procedure on the day of admission. If the patient has not had a 24hr ECG Holter monitor in the last 3 months this will be requested and carried out prior to their procedure. For this, patients will be required to briefly attend the hospital to have the monitor fitted, they will then need to wear it for 24hrs and return it to the hospital the following day. This will not delay their procedure. Patients will attend for their procedure as planned and no changes will be made to the clinically indicated procedure. In addition, the following will be carried out for each group in the study:

Groups (1) and (2) are AF ablation patients:
• Recording of additional cardiac electrograms using standard clinically available electrophysiology catheters

• Atrial pacing using catheters already in place for clinical procedure
• Predicted additional 30 min procedure time

(3) Control; SVT ablation patients:
• Intraprocedural recording of additional electrograms using standard clinically available electrophysiology catheters
• If AF has not been induced as part of the diagnostic electrophysiology assessment; induction of acute AF by pacing through catheters already in place for clinical procedure (no clinical risk from very short episodes of AF, this is often used as part of the electrophysiology assessment anyway)
• No additional predicted waiting time (research protocol to be done during post ablation waiting period)

(4) SND patients having pacemaker insertion:
• Femoral venous access and introduction of standard clinical electrophysiology catheters
• Intraprocedural recording of additional electrograms using standard clinically available electrophysiology catheters
• If AF has not been induced as part of the procedure, induction of acute AF by pacing through catheters
• Additional 30 min procedure time

The participant may be withdrawn from the study at the discretion of the operator prior to study protocol cardiac mapping. This would include concerns about participant safety due to problems with the clinical procedure e.g. inability of the patient to tolerate a prolonged procedure due to discomfort, procedural difficulties leading to a significantly longer clinical procedure and therefore increased risk of complications. These are predominantly day cases and patients will be monitored and discharged as clinically indicated for the procedure undertaken. Most participants will have a 24hr ECG Holter monitor requested at 3 months for clinical reasons, however, if this is not planned then one will be requested for research purposes. The procedure will be the same as before. Patients will receive standard follow up 3-4 months following the procedure as part of clinical care, but will not be seen by the research team again. They will have the contact details for the study team to contact should they have any further questions.

Sinus node disease will be defined as the presence of at least 2 of the following criteria:
1. CSNRT > 550 ms in the absence of reversible causes (eg rate limiting medication and cardiac ischaemia)
2. Post AF shock sinus recovery time >1200 ms in the absence of reversible causes (eg rate limiting medication and cardiac ischaemia)
3. ECG evidence of sinus pause >3 seconds when awake in the absence of reversible causes (eg rate limiting medication and cardiac ischaemia)
4. ECG evidence of sinus rates <45 bpm for more than 1 minute when awake in the absence of reversible causes (e.g. rate limiting medication and cardiac ischaemia)
5. Evidence of chronotropic incompetence on maximal exercise stress test (defined as reaching <80% of age-predicted maximal heart rate at maximal exercise) in the absence of reversible causes (eg rate limiting medication and cardiac ischaemia)

Intervention Type
Other

Primary outcome measure

The research is qualitative in nature. The primary outcome will be descriptive data characterising the role that SND plays in changing the electrical properties of the atrium that maintain atrial fibrillation, measured using cardiac electrogram at a single timepoint.

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
01/11/2018

Completion date
30/04/2024

Eligibility

Key inclusion criteria
Patients undergoing first EP study and/or catheter ablation or undergoing pacemaker implantation for sinus node disease with no prior AF.
For the study groups:
1. Documented atrial fibrillation without sinus node disease
2. Documented atrial fibrillation with sinus node disease
3. SVT without AF and with normal sinus node function (control)
4. Sinus node disease without atrial fibrillation, requiring pacemaker implantation (control)
Sinus node disease will be defined as the presence of at least 2 of the following criteria: CSNRT > 550 ms in the absence of reversible causes, Post AF shock sinus recovery time >1200 ms in the absence of reversible causes, ECG evidence of sinus pause >3 seconds when awake in the absence of reversible causes, ECG evidence of sinus rates <45 bpm for more than 1 minute when awake in the absence of reversible causes, evidence of chronotropic incompetence on maximal exercise stress test (defined as reaching <80% of age predicted maximal heart rate at maximal exercise) in the absence of reversible causes (eg rate limiting medication and cardiac ischaemia). AF is defined as persistent atrial fibrillation in accordance with the European Society of Cardiology definition as AF that lasts for longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or DC cardioversion, after 7 days or more but has not been present continuously for 1 year or longer (long standing persistent AF).

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria EXPLICITLY state otherwise.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit

65 Years

Sex
Both

Target number of participants
Planned Sample Size: 40; UK Sample Size: 40

Key exclusion criteria
1. Age < 18 or > 65
2. BMI > 35
3. Diabetes mellitus
4. Intubated/ventilated patients
5. Existing intravascular implanted cardiac device or prior device extraction
6. Prior cardiac surgery
7. Previous cardiac ablation for AF
8. Ischaemic heart disease
9. Uncontrolled type 2 or 3 hypertension
10. Structural heart disease
11. Infiltrative or inherited cardiomyopathy
12. Left ventricular systolic ejection fraction < 50%
13. Inability or unwillingness to discontinue antiarrhythmic medication
14. Pregnancy or participation in CTIMP

Post-procedure exclusion/withdrawal criteria:
1. Inability of the patient to tolerate a prolonged procedure due to discomfort, procedural difficulties leading to a significantly longer clinical procedure and therefore increased risk of complications

Date of first enrolment
19/07/2019

Date of final enrolment
30/04/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Manchester University NHS Foundation Trust
Cobbett House
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Liverpool Heart And Chest Hospital NHS Foundation Trust
Thomas Drive
Liverpool
United Kingdom
L14 3PE

Study participating centre
University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
Whitechapel
London
United Kingdom
E1 1BB

Study participating centre
Manchester University NHS Foundation Trust
Cobbett House
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Royal Papworth Hospital NHS Foundation Trust
Papworth Everard
Cambridge
United Kingdom
CB23 3RE

Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation; Grant Codes: FS/18/47/33669

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan

1. Peer reviewed scientific journals
2. Conference presentation
3. There are no plans to publish or share the protocol or statistical analysis plan at this stage

Intention to publish date

30/04/2025

Individual participant data (IPD) sharing plan

Study documentation will be completed and stored in accordance with the Medical Research Council's guidelines for Good Clinical Practice in clinical trials (MRC, 1998) and other applicable local guidelines.
Personal Identifiable Data will be collected from participants by the research team and kept at the individual hospital with access restricted to the treating clinical team and study team only. Patients will be assigned a unique study identification number on enrolment and all data will be pseudo-anonymised using this number. The key that links the case number to the patient will be password protected and encrypted on an NHS computer which will be password protected and accessible by only the research team.
During the study, the anonymised dataset will be transferred to the CI at the University of Manchester where it will be stored on the secure network. Each subject will have been assigned a unique, sequential study number on entering the dataset. The key document linking the dataset to participant details will be stored on secure NHS computers accessible only by the research team.
Study data will be a mixture of electronic records (for example intracardiac electrical recordings) and paper records (for example medical notes, Holter monitors). These data will be stored at the NHS hospital treating the patient. The data will be shared with the CI from the participating centres after anonymisation. The preferred method of sharing will be anonymised electronic data (for example intracardiac maps, holter monitor documents, tabulated patient data), which will be transferred using NHS-NHS secure email, encrypted password protected University hard drives or encrypted password protected University laptops. Where it is necessary to send paper records (for example a copy of the holter monitor as this is sometimes unavailable in electronic format), this will be anonymised and sent to the CI at Manchester University NHS Foundation Trust by mail.
Data from the study will be used for presentation at academic conferences and for publication in peer-reviewed journals, this will include numerical data and pictures of intracardiac electrical maps. Data will be shared in accordance with the 2017 ICMJE guidelines:
Individual de-identified participant data will be shared. The data shared will be individual participant data that underlies any published results, after deidentification. The data will become available beginning 9 months and ending 36 months after publication. Data will be shared with researchers providing a methodologically sound proposal, the data shared will be that data required to meet the aims in the proposal. Proposals will be directed to the corresponding author on the publication, data will be available on the University of Manchester data repository (currently Mendeley data).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Protocol file	version V4	06/11/2019	21/08/2020	No	No
HRA research summary			28/06/2023	No	No