RESEARCH PROTOCOL APPLICATION to the

RESEARCH ETHICS COMMITTEE of

THE ROYAL ADELAIDE HOSPITAL

1. **TITLE:**

   Cardiac implantable electronic devices related chronic thromboembolic pulmonary hypertension – an evaluation of thromboembolic risk in paced patients

2. **INVESTIGATORS AND QUALIFICATIONS:**

   A. Principal investigator

   Professor Prashanthan Sanders, MBBS (Hons) PhD FRACP FESC FHRS

   Director, Cardiac Electrophysiology and CHRD, RAH, University of Adelaide

   B. Investigators and Qualifications

   Dr Dian Andina Munawar, MBBS

   Electrophysiology Fellow, CHRD RAH, UOA

   Dr Dennis Lau MBBS PhD FRACP

   Consultant Electrophysiologist, University of Adelaide

3. **PURPOSE OF STUDY (general) and AIMS (specific)**

Previous case studies have shown that intracardiac lead thrombus can cause pulmonary embolism (PE). **(1)** However, the incidence of new or worsening pulmonary hypertension after cardiovascular implantable electronic devices (CIED) lead placement has not been well investigated. Pulmonary hypertension after CIED implantation will subsequently result in right heart failure and increase morbidity and mortality. This study is aimed to:

I. Determine the incidence and factors associated with development of pulmonary hypertension and right ventricular dysfunction in patients with CIEDs.

II. Determine the role of anticoagulation in the prevention of pulmonary hypertension in patients with CIEDs.

4. BACKGROUND AND PRELIMINARY STUDIES:

Cardiovascular implantable electronic devices (CIED) have been implanted transvenously for nearly last five decades. Although these devices have been demonstrated to be lifesaving with a good safety profile, these patients are at risk of developing venous complications. Venous abnormalities on venous angiograms or doppler are seen in up to 23% of patients 1 year after transvenous permanent pacemaker implantation.(1-3) Symptomatic venous thrombosis is less common and complicates only 0-6% of all pacemaker implants.(1, 2, 4-7) Possible causative factors include foreign body reaction, endothelial trauma and lead-related venous flow obstruction and turbulence.(8) Thrombosis can cause local morbidity such as swelling and pain and can also be a source of pulmonary embolism.(9, 10). Although venous thrombosis may be easily recognized, intracardiac lead related thrombi may often be asymptomatic and remain under recognized.(11) An intracardiac echocardiography based study has demonstrated the high prevalence of intracardiac lead related thrombi.(11) Similarly, an autopsy based study has shown that 14% of patients with pacemakers had right atrial pacemakerl ead thrombosis at an average of 4 years post implantation.(12) Furthermore, case studies have shown that intracardiac lead thrombus can cause pulmonary embolism (PE) and develop subsequent right heart failure.(13-16) Although symptomatic PE is uncommon, asymptomatic PE occurs with a greater frequency. Ventilation-perfusion defects have been demonstrated to occur in 15% of patients within 14 days of pacemaker implant.(17)

A recent study of data from an international prospective registry shows that only 74.8% of patients with pulmonary hypretension (PH) have previously confirmed PE (18), suggesting a role of sub-clinical pulmonary emboli in development of CTPH. PE results in increased pulmonary vascular resistance due to unresolved embolic obstruction, fibrosis and remodeling of pulmonary arterial branches. This may further present clinically as right heart failure.(19) Right heart failure is the most common cause of hospitalization in patients with pulmonary hypertension and is associated with a 14% in-hospital mortality rate.(20)

Although there are case reports demonstrating PM lead related thromboembolism(1, 3, 7, 11-14, 16, 21), there is a paucity of data evaluating the development of pulmonary hypertension following pacemaker implantation. In view to this, we hypothesize the development of CTPH secondary to subclinical pulmonary emboli. We propose to perform a retrospective study to analyze the development of CTPH in chronically paced patients.

5. SUBJECTS SELECTION AND EXCLUSION CRITERIA

Data will be obtained from an existing clinical database within the Centre for Heart Rhythm Disorders. This will include case sheets, echocardiograms and device interrogation reports. From this, we will establish a cohort of records of patients with CIEDs who underwent at least two echocardiograms (first within 6 months and the second greater than 1 year following implant). Similarly, a group of age-matched patients from patients without CIED who underwent echocardiogram will be established to serve as controls.

6. STUDY PLAN AND DESIGN

Data will be taken from the records from Centre for Heart Rhythm Disorders. No contact will be made with the participants as there will be no participant involvement.

Clinical notes and serial echocardiograms will be reviewed for both the study and control groups.

Clinical parameters

1. Sex
2. Age
3. Height
4. Weight
5. Body surface area
6. Body mass index
7. Atrial fibrillation
    - Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by incoordinated atrial activation with consequent deterioration of atrial mechanical function. (22) On electrocardiogram, AF is characterized by replacement of regular P waves with fibrillatory waves that vary in morphology and an irregularly irregular R-R interval
    - Paroxysmal AF is defined as recurrent AF that spontaneously terminates within 7 days. Persistent AF is defined as AF that fails to spontaneously resolve within 7 days or requires cardioversion. Chronic AF refers to persistent AF that has lasted for over a year.

8. Hypertension
    - Blood pressure of over 140 mmHg systolic and 90 diastolic based upon an average of readings over 2 or more visits after an initial screen (23)
9. Obstructive sleep apnea
    - Sleep apnea is defined by reduction of >90% in airflow measured by a nasal pressure transducer for at least 10 seconds accompanied by (a) a clear reduction of >50% in a valid measure of breathing during sleep or (b) clear reduction of breathing amplitude that is associated with either oxygen desaturation of >3% or arousal. Sleep apnea is defined as obstructive if there is sustained respiratory effort in the chest or abdominal bands. (24)
10. Diabetes
    - Diagnosed by a random BGL of >11, a OGTT BGL of >11, fasting glucose of >7
11. Congestive heart failure
    - Presence of clinical signs of heart failure or left ventricular ejection fraction less than 40%
12. Ischemic heart disease
    - A positive stress test or a coronary angiogram showing greater than 50% stenosis of at least one coronary artery.
13. Anticoagulation status
    - Warfarin, aspirin, novel anticoagulants

CIED parameters

1. Venous access route,
2. Number of leads- this will include any abandoned lead,
3. Type of leads- silicon or polyurethane or composite,
4. Defibrillator or pacing lead,
5. Size of leads.

Echocardiographic parameters

1. Right atrial size

- Right atrial size is calculated using the area-length method, the RA area is calculated by measuring its chamber circumference on apical four chamber view

2. Right ventricular size and function
    - Right ventricular size is calculated by measuring the chamber's minor and major axis using the apical four chamber (A4C) view.
    - RV fractional area change in A4C view.
3. Estimated pulmonary arterial pressure
    - In the absence of right ventricular outlet tract obstruction or pulmonary stenosis, the right ventricular systolic pressure (RVSP) and pulmonary artery systolic pressure (PASP) are equal. RVSP will be calculated using peak tricuspid regurgitation velocity and mean right atrial pressure.
    - Right atrial pressure (RAP) is estimated by observation of the calibre and reactivity of the inferior vena cava with respiration.
    - Tricuspid regurgitation velocity (TRV) is estimated by measurement of pulse wave Doppler at tricuspid regurgitation area
4. Presence of lead thrombus
5. Left atrial size
    - Same as RA size calculation.
6. Left ventricular size and function
    - Left ventricular end-diastolic and end-systolic volumes will be measured from apical four and two chamber views using the Modified Simpson's biplane method.

From there, left ventricular volume and ejection fraction can be calculated.

7. OUTCOMES

The development of increased pulmonary or right atrial pressures, right atrial or ventricular enlargement and changes in right ventricular function will be studied in the CEID and control groups. Furthermore, whether anticoagulation is protective against development of these

changes will be evaluated. The manuscript will be submitted for consideration of publication in a peer reviewed journal.

8. ETHICAL CONSIDERATIONS

The study is retrospective in nature. Inform consent would not be obtained as it would not be practical to obtain consent from the large number of potential participants in this research and there will not be any identifiable data that could compromise the privacy of an individual or their treating clinician. This research does not pose any risk to individuals involved but could identify issues relevant to improving care delivery for patients with CIED.

9. SPECIFIC SAFETY

Not applicable.

10. DRUGS/DEVICES

Not applicable.

11. ANALYSIS AND REPORTING OF RESULTS

Normally distributed continuous data will be expressed as mean ± standard deviation and tested with unpaired t-tests between groups. Skewed distributions will be expressed as median and inter-quartile and means tested using Mann-Whitney U.

This is a retrospective study and will be based on data collected from case sheets, echocardiograms and pacemaker interrogation reports. No contact will be made with any patient.

The data will be stored at the Centre of Heart Rhythm Disorders.

On completion, the manuscript will be submitted for publication in a pear review journal.

12. REFERENCES

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13. OTHER RELEVANT INFORMATION

Nil.

14. RESOURCE CONSIDERATIONS

A)

1. *Staffing (own and other Departments):* Research students
2. *Facilities (own and other Departments):* Cardiovascular centre

3. *Goods and services:* No additional cost is expected as the study is only a retrospective data collection. However, if need be, it will be covered by the departmental funds.
4. *Investigations to be undertaken (involvement of other Functional Units):* None
5. *Any other cost implication of the protocol:* No cost incurred related to the study
6. *Support available (financial and other) or requested to offset costs of project:* This study will be initially funded by available research funds. It is anticipated that after collection of preliminary data, competitive funding will be sought.
7. The research aspects of the study will not lead to any increased cost to the patients or to Medicare.

B)

Medical Records required: Yes.

14. FINANCIAL STATEMENT

There is no commercial involvement and no financial interest with respect to any of the investigators as a result of this study.