

*ROYAL ADELAIDE HOSPITAL*

*DEPARTMENT OF MEDICINE*

*CENTRE FOR HEART RHYTHM DISORDER*

# Clinical Trial Protocol and Ethics Application

|  |
| --- |
| 1. **TITLE**

Clinical Effectiveness of Atrial Anti-tachycardia Pacing Therapy in Sick Sinus Syndrome with Previous Atrial Fibrillation Ablation (CEASE-AF) |
| 1. **INVESTIGATORS AND QUALIFICATIONS**

Professor Prashanthan Sanders, MBBS, PhD, FRACPDr. Dennis Lau, MBBS, PhD, FRACP Dr. Rajiv Mahajan, MD, PhD, FRACPDr. Dian Andina MunawarCONTACT DETAILProfessor Prashanthan Sanders, MBBS, PhD, FRACPPrash.sanders@adelaide.edu.auCVIU, Level 6, Theatre Block, Royal Adelaide HospitalDr. Dennis Lau, MBBS, PhD, FRACPDennis.lau@adelaide.edu.auCVIU, Level 6, Theatre Block, Royal Adelaide HospitalDr. Rajiv Mahajan, MD, PhD, FRACPRajiv.mahajan@adelaide.edu.au CVIU, Level 6, Theatre Block, Royal Adelaide HospitalDr. Dian Andina Munawar, MD.Dian.Munawar@adelaide.edu.auCVIU, Level 6, Theatre Block, Royal Adelaide Hospital |
| 1. **PURPOSE OF THE STUDY**

The purpose of the CEASE-AF study is to investigate the impact of anti-tachycardia pacing (aATP) algorithm with regards to the outcome of atrial fibrillation (AF) in the population of patients who had AF ablation procedure prior to this study. The use of aATP has been explored in patients with pacemakers. The efficacy of aATP therapy is modest with different studies demonstrating mixed results. Nevertheless, this algorithm appears to be effective in terminating atrial flutter that potentially degenerates to AF. Similarly, atrial preferential pacing (APP) had demonstrated promise but failed to show reduction in AF progression or reduction in AF burden in randomized control trial. A large proportion of atrial arrhythmias following AF ablation are re-entrant atrial flutter that may be amenable to APP and aATP therapy. We hypothesize that patients with pacemakers with previous history of AF ablation will benefit from APP and aATP therapy. |
| 1. **BACKGROUND AND PRELIMINARY STUDIES**

Atrial fibrillation (AF) is the most common arrhythmia associated with sinus node dysfunction (SND). Recent studies suggested that the risk of AF development was five-fold higher in SND, with the prevalence ranged from 45% to 53%.1-3 In the longer term, individuals with AF showed poor quality of life indices and associated with 1.5 to 2-fold probability of death.4 The role of cardiac pacing in management of SND has been well established. However, it is reported that the annual incidence of AF and chronic AF following pacemaker implantation is at least 5% and 3%, respectively, while lifetime cumulative incidences is approximately 30 to 40% and 20%, respectively.5 Over time evidence have emerged that excessive ventricular pacing is associated with increased risk of developing AF. Pacing algorithms that minimize ventricular pacing in patients with sinus node disease have been demonstrated to reduce the risk of AF progression and have become the standard of care.6 It is proposed that atrial ectopy may trigger AF and atrial preferential pacing may suppress atrial ectopy and therefore prevent AF episodes. In addition, atrial antitachycardia pacing (aATP) algorithm has been shown effective for a termination of atrial arrhythmia such as atrial tachycardia or atrial flutter.7 The aim of this study is to assess the efficacy of aATP algorithm in termination of atrial tachycardia and prevention of AF progression in patients with pacemakers and prior AF ablation. We propose a randomized controlled trial in patients with standard indication of permanent pacemaker implantation due to sinus node dysfunction (SND), pacemaker with aATP algorithm and previous history of AF ablation. |
| 1. **PARTICIPANTS – SELECTION AND EXCLUSION CRITERIA**

This study will recruit consecutive patients who had dual chamber pacemaker implanted at EP laboratory of Royal Adelaide Hospital. These patients will be evaluated for the eligibility to meet the following criteria:Inclusion criteriaPatients will be considered eligible for this study if they meet the following criteria:1. The patient has a dual chamber pacemaker capable of atrial anti-tachycardia based therapy,
2. Had AF ablation at least 3 months prior to recruitment,
3. AF/atrial arrhythmia burden >0.1% and <30%,
4. ≥ 18 years of age

Exclusion criteriaPatients will be excluded from the study if one of the following criteria is met:1. Atrioventricular block with ventricular pacing >40 percent,
2. Atrial fibrillation episode >90 days. However, presence of prolonged episodes of atrial flutter will not be an exclusion corner,
3. Absence of indication for cardiac resynchronization or defibrillator,
4. Had < 12 months of life expectancy,
5. Cardiac surgery in the last six months, or expected during 10 months of study period,
6. A recent history of (< 1 year) or current malignancy, advanced heart failure (NYHA class IV), end-stage chronic obstructive pulmonary disease or other severe life-threatening comorbidities within 3 months of diagnosis, or
7. Unable to provide consent.

Redo AF ablation will not be performed in the first six month of randomization. The patient will be censored at the time of AF ablation (if performed after 6 months of randomization).The sample size was calculated based on the study that showed a recurrence rate of 48.6% after AF ablation in patients with paroxysmal AF and prolonged sinus pauses8 and a 49% relative reduction in the DDDR with all algorithm ON (MVP+APP+aATP) versus DDDR+MVP group, with a power of 80%, a confidence interval of 95%, and an assumed rate of loss to follow-up of 10%. Based on the calculation, it is planned to recruit 68 patients in each arm.  |
| 1. **STUDY PLAN AND DESIGN**

**Study design**:  Randomized controlled design – two groups (1:1 ratio)**Run-in phase** Following recruitment, patient will commence a 1-month run-in period during which all pacemakers were programmed with DDDR with MVP (Managed Ventricular Pacing) algorithm ON only in order to evaluate AF burden and ventricular pacing percentage. The patients who have more than 30% AF burden will be excluded from the study. Patients with ventricular pacing >40% on run-in phase will also be excluded. Randomization will be performed after the end of run-in period.**Randomization Period** Random allocation sequence will be conducted using computer software, stratified to balance out the presence/absence of AV-block. Concealment of each patient assignment was performed, and it will not be revealed until all baseline data had been collected. Eligible patients were randomly assigned in a 1:1 manner to (i) DDDR with MVP (control group) or (ii) MVP+APP+aATP group (figure 1). The patients will be followed for one-year. Assessment will be undertaken every six-month period. Throughout the study all patients and the other investigators remained blinded to the programmed pacing mode.**Pacemaker Programming**The enrolled patients will have a Medtronic dual chamber pacemaker with specific features (i) MVP (atrial pacing with backup ventricular pacing if AV conduction fails), (ii) APP (three atrial preferential pacing algorithms to prevent atrial tachyarrhythmias, and (iii) terminating atrial tachyarrhythmias by overdrive atrial pacing delivered at arrhythmia onset and during dynamic transition to slower and more organized atrial tachyarrhythmias (Reactive ATP or aATP). Pacemakers will be programmed to DDDR with a base rate of 60 bpm and an upper rate dependent on patient’s age and underlying heart disease. The algorithms included are as follow:1. Managed ventricular pacing

MVP is an atrial-based pacing mode that is designed to switch to a dual-chamber pacing mode in the presence of AV block. Specifically, MVP provides the following functions:* AAI(R) mode pacing when AV conduction is intact
* The ability to switch to DDD(R) pacing during AV block
* Periodic conduction checks while operating in DDD(R) mode, with the ability to switch back to AAI(R) mode when AV conduction resumes
* Back-up ventricular support for transient loss of AV conduction

If AV conduction is intact, the device remains in AAIR or AAI mode. While operating in AAI or AAIR mode, the parameters associated with single chamber atrial pacing are applicable.If 2 of the 4 most recent A-A intervals are missing a ventricular event, the device identifies a loss of AV conduction and switches to the DDDR or DDD mode. The device provides back-up ventricular pacing in response to dropped ventricular events until the loss of AV conduction is identified.After switching to DDDR or DDD mode, the device periodically checks AV conduction for an opportunity to return to AAIR or AAI mode. The first AV conduction check occurs 1 min after switching to DDDR or DDD mode. During the conduction check, the device switches to AAIR or AAI pacing mode for one cycle.* If the next A-A interval includes a sensed ventricular beat, the conduction check succeeds. The device remains in AAIR or AAI pacing mode.
* If the next A-A interval does not include a sensed ventricular beat, the conduction check fails, and the device switches back to the DDDR or DDD mode. The time between conduction checks doubles (2, 4, 8 … min, up to a maximum of 16 hours) with each failed conduction check.
1. Atrial Preference Pacing (APP)

The device includes three atrial preventive pacing algorithms designed to eliminate some of the onset mechanisms of atrial tachyarrhythmias and to reduce the incidence of atrial tachyarrhythmias. These atrial pacing features comprise the atrial pacing preference algorithm, for maintenance of a pacing rate just above the intrinsic rate, the atrial rate stabilization algorithm, designed to avoid short-long intervals following a premature atrial contraction, and the post-mode switching overdrive pacing algorithm designed to inhibit early re-initiation of atrial tachyarrhythmia following a mode switching episode.Atrial Preference Pacing (APP) is available when the device is operating in the DDDR, DDD, AAIR, AAI, or MVP (AAIR<=>DDDR or AAI<=>DDD) mode. APP is a programmable feature that is designed to maximize atrial overdrive pacing when the patient is not experiencing an atrial tachyarrhythmia. The device responds to changes in the atrial rate by accelerating the pacing rate until reaching a steady paced rhythm that is slightly faster than the intrinsic rate. After each non-refractory atrial sensed event, the device decreases the atrial-pacing interval by the programmed Interval Decrement value. This progression continues until the pacing rate exceeds the intrinsic rate, resulting in an atrial-paced rhythm. It sustains this increased rate for the number of beats programmed for a Search Beats parameter, then decreases the pacing rate slightly (by 20 ms) to search for the next intrinsic beat. This results in a dynamic, controlled, stair-step increase or decrease in the pacing interval, resulting in a pacing rate slightly above the intrinsic rate. The Maximum Rate parameter sets an upper rate limit for APP. The Interval Decrement in CEASE-AF study was set at 50 ms. After 10 Search Beats, i.e. consecutive atrial paces at the current atrial preference pacing rate, the pacing rate interval was increased by 20 ms to decelerate the pacing rate. The Maximum Rate induced by atrial preference pacing was set at 95 bpm.The atrial rate stabilization algorithm is available when the device is operating in the DDDR, DDD, AAIR, AAI modes. When it is enabled, at each atrial event, for example a premature atrial contraction (PAC), the device calculates a new pacing interval, which is equal to the current pacing interval increased by the Interval Percentage Increment, and if this interval ends before the device senses an atrial event, the device delivers an atrial pace and recalculates its interval using the current atrial interval. After a PAC, the calculated escape interval stabilizes the atrial rate and gradually slows it to the intrinsic rate, sensor indicated rate or lower rate. This prevents the ‘short/long’ sequences of atrial cycle lengths that have been observed to precede the onset of some spontaneous atrial tachyarrhythmias. The Interval Percentage Increment, i.e. the pacing interval increment per beat, measured as a percentage of the preceding interval was set at 25% in our study. The Maximum Rate induced by atrial rate stabilization algorithm was set at 95 bpm. The post-mode switching overdrive pacing algorithm is available when the device is operating in the DDDR or DDD modes. When it is enabled, at the termination of a mode switch, i.e. an atrial tachyarrhythmia episode, post-mode switching overdrive pacing causes the device to continue to pace in DDIR mode at the higher of the programmable Overdrive Rate or sensor-activated rate for a programmable Overdrive Duration. In our study the Overdrive Rate was set at 80 beats per minute and the Overdrive Duration was required to be ≤ 5 minutes.1. Reactive atrial Anti-tachycardia pacing

If the device detects an atrial tachyarrhythmia episode, aATP therapy will be delivered. Treatments for such episodes are intended to interrupt the atrial tachycardia and restore patient’s normal sinus rhythm. The device can deliver up to 3 aATP therapies to treat an AT/AF or a Fast AT/AF episode. aATP therapies become available when the duration of sustained atrial tachyarrhythmias exceeds the programmed value of episode duration before aATP delivery - which in this study will be set at 0 minute.When an AT/AF or Fast AT/AF episode is detected, the device delivers the first sequence of the ATP therapy. After the first ATP sequence, it continues to monitor for the presence of the atrial tachycardia episode. If it redetects the atrial tachycardia episode, the device and repeats this cycle until the episode is terminated or all sequences in the therapy are exhausted.In the CEASE-AF study, reactive ATP makes it possible for the device to repeat programmed sets of atrial ATP therapies in two different situations. Rhythm Change, one type of Reactive ATP, subdivides the AT/AF detection zone into smaller regions. This type is enabled to allow the device to detect changes in the atrial arrhythmia on the basis of both regularity and cycle length. The atrial tachyarrhythmias zone is subdivided into a series of narrower regions: specifically the atrial tachyarrhythmia Interval for regular rhythms is divided into 5 regions of 50 ms length from 100 ms to 350 ms and the atrial tachyarrhythmia interval for irregular rhythm is divided into 3 regions, the first from 100 ms to 200 ms, the second from 200 ms to 300 ms and the third from 300 ms to 350 ms. Each region is supplied with a separate set of the atrial aATP therapies enabled for atrial tachyarrhythmia episodes. If the rhythm shifts into a different region because of a change in cycle length or regularity, the device delivers therapies from those available in the new region. The second type of reactive ATP is Time Interval feature, which allows to schedule additional therapies for atrial arrhythmias regardless of rhythm changes. . In the CEASE-AF the Reactive aATP Time Interval allow to re-arm aATP sequences when the Sustained Duration value reaches a multiple of 2 hours. The device will be programmed to suspend all atrial therapies if an atrial episode exceeded the Duration to Stop parameter, which was programmed at 72 hours.The aATP therapies that can be delivered by the pacemaker are Burst+ or Ramp. Burst+ therapy sequences consist of a programmed number of AOO pulses followed by two premature stimuli that are delivered at shorter intervals. Ramp therapy sequences consist of a programmable number of AOO pulses delivered at decreasing intervals.The Burst+ and Ramp pacing intervals are based on programmed percentages of the atrial tachycardia cycle length, which is calculated as the median of the last 12 atrial intervals prior to therapy delivery. The median atrial tachycardia cycle length can vary from one sequence in a therapy to the next, and the ATP pacing intervals vary accordingly. The first pulse of each aATP sequence is delivered at a chosen percentage of the current atrial tachyarrhythmia cycle length. Subsequent pulses are delivered at progressively shorter intervals. The A-A Minimum ATP Interval parameter limits the pacing intervals at which the Burst+ and Ramp pacing pulses are delivered. If some calculated intervals are shorter than the programmed A-A Minimum ATP Interval, the pulses are delivered at the A-A Minimum ATP Interval. If the median of the last 12 A-A intervals is shorter than the programmed A-A Minimum ATP Interval, the device does not deliver Burst+ or Ramp therapies until the atrial rate slows.Parameters for Burst+ therapy were the Number of S1 pulses in each burst sequence (15), the Pacing interval of the S1 burst pulses, as a percentage of the pre-therapy atrial cycle length (84%), the Pacing interval of the S2 stimulus following the burst as a percentage of the pre-therapy atrial cycle length (81%), the S2-S3 interval equals the S1-S2 interval minus this decrement value (20 ms), the Pacing interval decrement per sequence (10 ms), the Number of sequences in the Burst+ therapy (10).The Parameters for Ramp therapy were Number of pulses in the first Ramp sequence (12), the Pacing interval of the first Ramp pulse as a percentage of the pre-therapy atrial cycle length (91% in Rx1 and 81% in Rx2), the Pacing interval decrement per pulse for the remaining Ramp pulses in each sequence (10 ms), the number of sequences in the Ramp therapy.**AF detection** The device detects atrial tachyarrhythmias by examining the atrial rate and the relationship between atrial and ventricular events. The device confirms initial AT/AF episode detection if the criteria are met (table 2).After confirmation of detection, the atrial tachyarrhythmia episode is considered to be sustained; thereafter the device monitors the cardiac rhythm for changes or episode termination and can respond to detected episodes by delivering tachyarrhythmia therapies. Once the device detects an atrial tachyarrhythmia, the episode is considered to be ongoing until episode termination. **Clinical parameters**A complete medical history will be recorded to obtain co-existing risk factor. The variables that will be obtained are as follows:* + 1. Baseline characteristics
* Age
* Gender
* Body mass index
* Symptom: including history of syncope, NYHA functional class
* Diagnosis: including the presence of other bradyarrhythmia (such as AV block) and other supraventricular tachyarrhythmias
* History of other concomitant disease: including coronary artery disease, heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), stroke or transient ischemic events, hyperthyroid
* Risk factors: including hypertension, diabetes mellitus, hyperlipidemia, obesity (body mass index), presence of sleep apnea (symptom and treatment)
* History of medication: including antiarrhythmic agents (beta-blocker, calcium-channel blocker, digoxin, flecainide, amiodarone), renin- angiotensin-aldosterone system blocker (angiotensin converting enzyme-inhibitor (ACE-I), angiotensin receptor blocker (ARB)), anti-coagulants
	+ 1. Electrocardiography will be performed to document:
* PR interval
* QRS duration
* Bundle branch block
	+ 1. Echocardiography parameter to document:
* Left ventricular function, shown by ejection fraction (%)
* Cardiac chamber dimension, including:
* Left ventricular dimension (End diastolic diameter (EDD) and end systolic diameter (ESD)
* Left atrial dimension
* Morphology and function of cardiac valves
* Diastolic function
	+ 1. Blood test, to determine:
* Fibrotic marker such as TGF-, TIMP, or MMP9
* Inflammatory marker such as hs-CRP
	+ 1. Device interrogation – measured by device programmer to determine:
* Basic interrogation: Including atrial and ventricular threshold, impedance, measured P wave and R wave,
* Cumulative percentage of atrial and ventricular pacing,
* AF burden will be assessed as (i) sum of the daily time spent in atrial tachyarrhythmias stored in the device memory divided by the follow-up duration), (ii) incidence of persistent AF (at least seven consecutive days with 22 h of device-recorded AF per day or at least 1 day with an episode of AF lasting at least 22 h—and interrupted with an electrical or chemical cardioversion), and (iii) incidence of AF with pre-specified daily durations (5 min, 1 h, 6 h, 1 day, 2 days, 7 days and 30 days). The rhythm will be adjudicated as AF if it lasts at least 6 minutes.9
* Electrical changes was assessed by measuring:
* sinus node recovery time (SNRT), defined as the recovery interval in excess of the sinus cycle (following a determined period of atrial pacing – 600 ms and 500 ms) to beginning of sinus complex
* corrected sinus node recovery time (cSNRT), defined as the recovery interval in excess of the average sinus cycle length (SNRT minus average sinus cycle length).10
* Wenkebach block point, defined as 2:1 AV block in which atrial beat conducting to ventricle shows progressive prolongation of AV interval,11 obtained by programming to increase heart rate in AAI mode in 10 beats incremental steps at 30 seconds intervals.12
 |
| 1. **OUTCOMES**

The focus of this study is to evaluate the impact of aATP algorithm in the reduction of AF burden. Examination of clinical symptom as well as the structural and electrical function will be performed after run-in phase (1 month after pacemaker implantation procedure) and during each follow up visit (every three months). * + - 1. Primary end point
1. AT/AF burden at 12 month follow up – defined as cumulative number of hours of AT/AF divided by follow-up period in days (hours/day), calculated based on data in the device storage over the study terms. The rhythm will be adjudicated as AF if it lasts at least 6 minutes.9 All recorded data will be adjudicated manually by a committee of experienced electrophysiologists.13
	1. Secondary endpoint
2. ATP efficacy – defined as the incidence of successful terminations based on the device counters.
3. Number of subjects who develop:
4. Paroxysmal AF – defined as self-terminating AF, usually within 48 h, may continue for up to 7 days and spontaneous conversion.9,14
5. Persistent AF – defined as AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC).9,14
6. Permanent AF – defined as the presence of the arrhythmia that is accepted by the patient and physician.9,14
	1. Tertiary endpoint
7. Assessment of quality of life with AF questionnaire (according SF-36 questionnaire scale). 15
8. Exercise capacity that will be evaluated using exercise test (using BRUCE protocol) measured by maximum METs achieved. 16
9. Fibrotic and inflammatory markers evaluation, measured by blood test.
10. Electrical changes, measured by device interrogation.
	* 1. SNRT
		2. cSNRT
		3. Wenkebach block point
11. Structural changes that will be evaluated by echocardiography.
12. Left ventricular function, shown by ejection fraction (%) measured by Simpson technique.
13. Right ventricular function, shown by Tricuspid annular planar systolic excursion (TAPSE), Right Index Myocardial Perfomance (RIMP), 2D Right Ventricular Fractional Area Change (2D RV FAC), and basal free wall S’ velocity measured by tissue Doppler imaging.
14. Cardiac chamber dimension, including:
15. Left ventricular dimension (End diastolic diameter (EDD) and end systolic diameter (ESD)
16. Right and left atrial dimension
17. Morphology and function of cardiac valves

The manuscript will be submitted for consideration of publication in a peer-reviewed journal. |
| 1. **ETHICAL CONSIDERATIONS**

Managed ventricular pacing (MVP), atrial preferencial (APP) and atrial anti-tachycardia pacing (aATP) algorithm has been demonstrated to be safe in several studies.6,7,17 |
| 1. **SPECIFIC SAFETY**

 N/A |
| 1. **DRUGS/DEVICES**

 Dual chamber pacemaker has been implanted for the patients based standard indication according to HRS guideline 2012.18 The subjects will be recruited after the procedure.  |
| 1. **ANALYSIS AND REPORTING OF RESULTS**

All data will be analyzed according to the intention-to-treat principle. The nominal data will be presented as number of events (n) and percentage (%). Normally distributed continuous data will be expressed as mean ± standard deviation. The difference between groups will be analyzed using chi-squared comparisons for the nominal data and the normal continuous data tested with unpaired t-tests between groups. Skewed distributions will be expressed as median and inter-quartile and means tested using Mann-Whitney U. Data will be collected from case sheets, echocardiograms and pacemaker interrogation reports. The data will be stored at the Centre of Heart Rhythm Disorders. The principal investigators will have access to the research data, and will collectively own the data and results of the research. Data (whether positive or negative findings) will be analysed and published. All patient information will be de-identified.On completion, the manuscript will be submitted for publication in a pear review journal |
| 1. **REFERENCES**

1. Lamas GA, Lee K, Sweeney M, et al. The mode selection trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. American heart journal 2000;140:541-51.2. Santini M, Alexidou G, Ansalone G, Cacciatore G, Cini R, Turitto G. Relation of prognosis in sick sinus syndrome to age, conduction defects and modes of permanent cardiac pacing. Am J Cardiol 1990;65:729-35.3. Alonso A, Jensen PN, Lopez FL, et al. Association of sick sinus syndrome with incident cardiovascular disease and mortality: the Atherosclerosis Risk in Communities study and Cardiovascular Health Study. PloS one 2014;9:e109662.4. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. International journal of cardiology 2013;167:1807-24.5. Nielsen JC. Mortality and incidence of atrial fibrillation in paced patients. J Cardiovasc Electrophysiol 2002;13:S17-22.6. Boriani G, Tukkie R, Manolis AS, et al. Atrial antitachycardia pacing and managed ventricular pacing in bradycardia patients with paroxysmal or persistent atrial tachyarrhythmias: the MINERVA randomized multicentre international trial. Eur Heart J 2014;35:2352-62.7. Gillis AM, Koehler J, Morck M, Mehra R, Hettrick DA. High atrial antitachycardia pacing therapy efficacy is associated with a reduction in atrial tachyarrhythmia burden in a subset of patients with sinus node dysfunction and paroxysmal atrial fibrillation. Heart Rhythm 2005;2:791-6.8. Inada K, Yamane T, Tokutake K, et al. The role of successful catheter ablation in patients with paroxysmal atrial fibrillation and prolonged sinus pauses: outcome during a 5-year follow-up. Europace 2014;16:208-13.9. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2010;12:1360-420.10. Narula OS, Samet P, Javier RP. Significance of the sinus-node recovery time. Circulation 1972;45:140-58.11. Levy S, Roudaut R, Bouvier E, Obel IW, Clementy J, Bricaud H. Alternate ventriculoatrial Wenckebach conduction. Circulation 1980;61:648-52.12. Haywood GA, Ward J, Ward DE, Camm AJ. Atrioventricular Wenckebach point and progression to atrioventricular block in sinoatrial disease. Pacing and clinical electrophysiology : PACE 1990;13:2054-8.13. Padeletti L, Purerfellner H, Adler SW, et al. Combined efficacy of atrial septal lead placement and atrial pacing algorithms for prevention of paroxysmal atrial tachyarrhythmia. Journal of cardiovascular electrophysiology 2003;14:1189-95.14. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Heart rhythm : the official journal of the Heart Rhythm Society 2011;8:157-76.15. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.16. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. Ann Clin Res 1971;3:323-32.17. Padeletti L, Purerfellner H, Mont L, et al. New-generation atrial antitachycardia pacing (Reactive ATP) is associated with reduced risk of persistent or permanent atrial fibrillation in patients with bradycardia: Results from the MINERVA randomized multicenter international trial. Heart Rhythm 2015;12:1717-25.18. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Heart Rhythm 2012;9:1737-53. |
| 1. **OTHER RELEVANT INFORMATION**

Nil |
| 1. **OTHER ETHIC COMMITTEES TO WHICH THE PROTOCOL HAS BEEN SUBMMITTED**

Nil |
| 1. **DATE OF PROPOSED COMMENCEMENT**

July 2016 |
| 1. **DATE OF EXPECTED COMPLETION**

December 2017 |
| 1. **RESOURCE CONSIDERATION**

 The staffing and facilities required for the undertaking of this research protocol will de derived entirely from within the Cardiovascular Investigation Unit (CVIU) and Centre for Heart Rhythm Disorders (CHRD). In particular, the senior cardiologists, rostered electrophysiology fellows, technicians, and staffs involved would all be employees of RAH. Moreover, the principal investigators will be present during the pacemaker programming, who will also be responsible for the collection and recording of data. Dr. Munawar will undertake this project as a part of her PhD studies. The financing of this research protocol will be initially funded by available research funds. It is anticipated that after collection of preliminary data, competitive funding will be sought. Access to patient medical records will be necessary during the study in order to assess for cardiovascular risk factors. Such access will be strictly limited to study personnel, with prior written consent of each patient involved in the study. |
| 1. **FINANCIAL AND INSURANCE ISSUES**

 There are no financial interests in the outcome of the study project. This is not a commercially sponsored trial involving a drug or device. Procedures performed in CVIU will be covered by standard Royal Adelaide Hospital indemnity agreements. |
| 1. **SIGNATURES OF INVESTIGATORS**

**Professor Prashanthan Sanders, MBBS, PhD, FRACP****Dr. Dennis Lau, MBBS, PhD, FRACP****Dr. Rajiv Mahajan, MD, PhD, FRACP****Dr. Dian Andina Munawar, MD****Dr. Sharath Kumar, MD****Dr. Kashif Khokhar, MD****Mr. Thomas Agbaedeng, BSc** |
| 1. **APPENDIX**

**FIGURE 1. Trial Schema**

|  |
| --- |
| Participant fulfills inclusion / exclusion criteriaIf eligible, participant signs information consent form. |
| **RUN-IN PERIOD (1 MONTH)**MVP ONParticipant will be screened prior to randomization |
| **RANDOMISATION** |
| **Group A****Enrollment** **MVP on*** Medical history
* SF-36/MLWHF Questionnaire
* ECG
* Trans Thoracic Echo (TTE)
* Blood samples
* Exercise test
 | **Group C****Enrollment** **MVP + APP + ATP on*** Medical history
* SF-36/MLWHF Questionnaire
* ECG
* Trans Thoracic Echo (TTE)
* Blood samples
* Exercise test
 |
| **Clinic visit month 6*** SF-36/MLWHF Questionnaire
* Trans Thoracic Echo (TTE)
* Device interrogation
* Blood samples
* Exercise test
 | **Clinic visit month 6*** SF-36/MLWHF Questionnaire
* Trans Thoracic Echo (TTE)
* Device interrogation
* Blood samples
* Exercise test
 |
| **Clinic visit month 12*** SF-36/MLWHF Questionnaire
* Trans Thoracic Echo (TTE)
* Device interrogation
* Blood samples
* Exercise test
 | **Clinic visit month 12*** SF-36/MLWHF Questionnaire
* Trans Thoracic Echo (TTE)
* Device interrogation
* Blood samples
* Exercise test
 |

**Table 1.** The programming of aATP in our study is shown in table 1:

|  |  |  |  |
| --- | --- | --- | --- |
| **Therapy sequence** | **Rx1** | **Rx2** | **Rx3** |
| Therapy | **Ramp** | **Ramp** | **Burst+** |
| Initial pulse N° | 12 | 12 | 15 |
| A-S1 | 91% | 81% | 84% |
| S1S2 |  |  | 81% |
| S2S3 |  |  | 20 ms |
| Dec Interval | 10 ms | 10 ms | 10 ms |
| Sequence N° | 10 | 10 | 10 |
| **aATP programming**Episode duration before aATP: 0 minute Rhythm based rearming: ON Time to stop therapy: 72 hours aATP output : 4 times atrial threshold (min 3.0 V and max 6.0 V) |

**Table 2.** AF detection criteria and programming

|  |
| --- |
| A. AF detection criteria1. There are at least 2 atrial sensed events per ventricular interval for a sufficient number of ventricular intervals (which will be set at 32).
2. The median of the 12 most recent sensed atrial intervals is shorter than the programmed AT/AF (or Fast AT/AF) interval. In CEASE-AF study, it will be set at 350 ms (171 bpm)
 |
| B. AF detection programmingNumber of detection zones: 1 Atrial interval: 350 ms or according to patient characteristics. |

 |

1. Lamas GA, Lee K, Sweeney M, et al. The mode selection trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. American heart journal 2000;140:541-51.

2. Santini M, Alexidou G, Ansalone G, Cacciatore G, Cini R, Turitto G. Relation of prognosis in sick sinus syndrome to age, conduction defects and modes of permanent cardiac pacing. Am J Cardiol 1990;65:729-35.

3. Alonso A, Jensen PN, Lopez FL, et al. Association of sick sinus syndrome with incident cardiovascular disease and mortality: the Atherosclerosis Risk in Communities study and Cardiovascular Health Study. PloS one 2014;9:e109662.

4. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. International journal of cardiology 2013;167:1807-24.

5. Nielsen JC. Mortality and incidence of atrial fibrillation in paced patients. J Cardiovasc Electrophysiol 2002;13:S17-22.

6. Boriani G, Tukkie R, Manolis AS, et al. Atrial antitachycardia pacing and managed ventricular pacing in bradycardia patients with paroxysmal or persistent atrial tachyarrhythmias: the MINERVA randomized multicentre international trial. Eur Heart J 2014;35:2352-62.

7. Gillis AM, Koehler J, Morck M, Mehra R, Hettrick DA. High atrial antitachycardia pacing therapy efficacy is associated with a reduction in atrial tachyarrhythmia burden in a subset of patients with sinus node dysfunction and paroxysmal atrial fibrillation. Heart Rhythm 2005;2:791-6.

8. Inada K, Yamane T, Tokutake K, et al. The role of successful catheter ablation in patients with paroxysmal atrial fibrillation and prolonged sinus pauses: outcome during a 5-year follow-up. Europace 2014;16:208-13.

9. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2010;12:1360-420.

10. Narula OS, Samet P, Javier RP. Significance of the sinus-node recovery time. Circulation 1972;45:140-58.

11. Levy S, Roudaut R, Bouvier E, Obel IW, Clementy J, Bricaud H. Alternate ventriculoatrial Wenckebach conduction. Circulation 1980;61:648-52.

12. Haywood GA, Ward J, Ward DE, Camm AJ. Atrioventricular Wenckebach point and progression to atrioventricular block in sinoatrial disease. Pacing and clinical electrophysiology : PACE 1990;13:2054-8.

13. Padeletti L, Purerfellner H, Adler SW, et al. Combined efficacy of atrial septal lead placement and atrial pacing algorithms for prevention of paroxysmal atrial tachyarrhythmia. Journal of cardiovascular electrophysiology 2003;14:1189-95.

14. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Heart rhythm : the official journal of the Heart Rhythm Society 2011;8:157-76.

15. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.

16. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. Ann Clin Res 1971;3:323-32.

17. Padeletti L, Purerfellner H, Mont L, et al. New-generation atrial antitachycardia pacing (Reactive ATP) is associated with reduced risk of persistent or permanent atrial fibrillation in patients with bradycardia: Results from the MINERVA randomized multicenter international trial. Heart Rhythm 2015;12:1717-25.

18. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Heart Rhythm 2012;9:1737-53.