RESEARCH PROTOCOL APPLICATION TO THE RESEARCH ETHICS COMMITTEE OF THE ROYAL ADELAIDE HOSPITAL

"The IMpact of Pre- HTN And Central HIGH blood pressure on atrial fibrillation and cardiovascular ouTcomes.(HIGH IMPACT- AF STUDY)"

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A. PURPOSE OF STUDY (GENERAL) AND AIMS (SPECIFIC)

Purpose of Study

Amongst the attributable factors, hypertension is the predominant risk leading to atrial fibrillation (AF) and premature cardiovascular events [1-3]. As compare to brachial blood pressure, central blood pressure and aortic stiffness assessment even in "normotensives", has shown improve predictability of cardiovascular outcomes including atrial fibrillation [4-7]. Conduit arterial stiffness is recognised as a surrogate for central high blood pressure [8, 9]. Cardiovascular risk stratification based on central blood pressure indices can be more relevant as it demonstrates the central pulsatile load an organ is exposed to and reveals early vascular remodelling of central arterial tree resulting in aortic stiffness. Non-invasively derived central hemodynamic indices have been demonstrated to predict cardiovascular outcomes in a variety of settings[10].

We propose a single blinded, randomised prospective trial to risk profile our AF patients according to their non-invasive assessment of peripheral or central blood pressure including aortic stiffness estimate. The impact of central blood pressure, on the atrial electrophysiological substrate and clinical outcomes will be analysed. In addition, the relationship between central high blood pressure and non-invasive indicators of end organ (cardiac, vascular, renal and retinal) injury will be explored.

Specific Aims

The specific aims of the project are:

1. To determine the prevalence of central high blood pressure and aortic stiffness amongst AF patients referred to Centre for Heart Rhythm Disorders (CHRD), University of Adelaide.
2. Prognostic impact of central high BP treatment to pre-defined targets as per age (Table-1) on clinical outcomes in AF patients categorised as pre-HTN or HTN during brachial blood pressure assessment with or without HTN induced end organ insult.
3. To assess the correlation between indices of central high blood pressure and end-organ damage including structural as well as electrophysiological changes of left atrium, LV diastolic dysfunction including LVH and HTN nephropathy.
4. To assess the role of central blood pressure indices including central blood pressure response to exercise and posture in risk profiling of arrhythmia patients over and above conventional brachial BP.
5. Defining AF as an index of end organ insult secondary to HTN.

B. BACKGROUND AND PRELIMINARY STUDIES:

Introduction

HTN poses a major risk in development of AF and premature cardiovascular events [1, 2, 3{Schnabel, 2009 #926, 11, 12]. However, definition of HTN is a moving target and "optimal" treatment goals are still not clear. Besides epidemiological studies advocate BP control of ≤120/80 mmHg from vascular risk standpoint, no strong outcome benefits of achieving such BP goals were reported by primary prevention studies in patients with

low risk of cardiovascular disease (CVD) [13-15]. Having said that, "SPRINT" strongly advocates aggressive BP control to improve outcomes in HTN patients with intermediate baseline risk of CVD (2%/ year) {Williamson, 2016 #931}, but guidelines are yet to incorporate lower BP treatment targets (≤ 120/80mmHg) in population at high risk of CV events [14]. In addition, stress induced HTN including white coat HTN and blood pressure response to exercise [16] are not very well defined in terms of treatment and outcome in guidelines.

Traditionally, clinical blood pressure assessment is performed by a sphygmomanometer applied at the brachial artery, providing measures of peripheral systolic and diastolic blood pressure [18, 19]. However, population studies revealed that up to one fifth of the participants characterised as "normotensives" based on their brachial blood pressure could have central high blood pressure leading to aortic stiffness [8]. Central blood pressure appraisal quantifies the aortic pressure and pulsatile load an organ is exposed to and has additional predictive value over and above conventional brachial blood pressure assessment in cardiovascular outcomes [17].

Central Blood Pressure Evaluation - Non-invasive assessment

Historically, measurement of central blood pressure required central arterial catheterization for direct manometry. However, non-invasive assessment can be performed by echocardiography or a variety of cuff based devices using pressure or flow wave to calculate pulse wave velocity with central pressure indices [20]. The device based on principles of applanation tonometry or sphygmomanometer are routinely used to calculate PWV and the central arterial waveform[20].

Together, these clinical and experimental observations have led us to hypothesize a role for central blood pressure elevation in the pathophysiology and prognosis of AF.

Through this low risk study, we will explore the role of central blood pressure and aortic stiffness assessment in risk profiling of our AF patients. In addition, we will demonstrate the impact of aggressive central blood pressure control on AF and cardiovascular outcomes.

C. STUDY POPULATION

PAF patients, fulfilling the inclusion criteria will be recruited from Centre for Heart Rhythm Disorders (CHRD), Royal Adelaide Hospital (RAH), University of Adelaide and Cardiovascular Centre, Norwood (Professor P Sander's rooms).

The participants (125 in each arm), will be randomized to intervention or control arm during the recruitment phase over a study period of 24 months. Participants will be risk profiled according to their age (30-50, 50-70, > 70 yrs.) and baseline central blood pressure (pre-HTN, HTN with or without end organ insult) into three groups.

The control group will have conventional risk stratification as per brachial BP.

The following inclusion and exclusion criteria will be applied:

Inclusion Criteria

1. Age 20-80 years
2. Persistent and Paroxysmal AF patients
3. Able and willing to provide written informed consent

Exclusion Criteria

1. Age <20years
2. Contraindications to exercise stress test (EST)
3. Pregnancy
4. Active malignancy or severe illness
5. Active Inflammatory disorder
6. Severe Aortopathy
7. Advanced valvular heart disease including aortic insufficiency (AI)
8. Constrictive or restrictive cardiomyopathy
9. Contraindications to non-contrast CMR (*only in selected patients scheduled for PVI)*

Withdrawal Criteria

Participants may withdraw at any time from the study. Patient will be excluded from the study if she will become pregnant during follow up.

D. STUDY DESIGN, TIME LINE AND INTERVENTIONS

It is a single centre, single blinded, prospective, randomised control study to collect and compare data to risk stratify our AF patients according to their aortic stiffness severity and central or peripheral blood pressure. Participants will be randomised to intervention or control group.

Intervention group will have their anti-hypertensive therapy titrated as per central blood pressure targets (Table-1), while the control group will have their brachial blood pressure treated as per current treatment guidelines (BP ≤140/90 mmHg if risk of CVD is ≤ 1% per year or 130/80mmHg if CVD risk is ≥2% per year [21].

In addition, participants will be categorised according to their age (20-50yrs, 50-70yrs and >70yrs) and blood pressure into pre-HTN or HTN with or without end organ damage.

Off note that the reported "normal range" of central blood pressure is estimated invasively while the participants are monitored in a controlled environment and under the effect of mild sedation. To prevent any harm to our study participants, we will take a holistic approach to risk stratify our patients while instigating treatment based on central or brachial pressures in order to avoid symptomatic hypotension along with drug side effects. The risk profiling will include age of the participants, aortic pulse wave velocity, baseline BP, degree of HTN induced end organ injury, BP response to exercise and central or brachial pressure indices including pulse pressure.

In case if patient has presenting BP characterised as grade II or higher HTN, a graduated approach will be adapted to lower the BP gradually by keeping an eye on the side effects of anti-HTN treatment.

Table-1. Central Arterial Systolic Pressure (CASP) normal range as per age.

CASP normal range			
Age (years)	**Average (mmHg)**	**Minimum (mmHg)**	**Maximum (mmHg)**
20–30	101	90	112
30–40	105	94	116
40–50	108	97	119
50–60	112	101	123
60–70	115	104	126
70–80	119	108	130
80–90	122	111	133

All AF patients will be assessed at baseline visits and at clinical follow-ups at RAH and Cardiovascular Centre, Norwood (Prof. P Sanders' rooms). Follow-up visits will be performed 3 monthly for the intervention group and six monthly for control as per treating electrophysiologist for 18-20 months (Tables 2 and 3). Participants will be risk stratified as per their central or brachial blood pressure indices into interventional and control group respectively.
The study will be approved by the ethics committee of RAH, University of Adelaide.
Central blood pressure indices and carotid-femoral PWV analysis will be performed as per IMPULSE-AF validation study protocol. (CALHN Ethics and Research Committee Approval: R2010712, HREC Reference: HREC/16/RAH/269).

Tables to illustrate follow up and intervention time lines for two groups

Table-2. Follow up and Investigations time line for Intervention Group
(AFSS= AF symptom scale, CBP= central blood pressure, CPI= central pressure indices, EST= exercise stress test, PWV= pulse wave velocity, RFTs= Renal function test)

0 months	3 months	6months	9months	12 months	15months	18-20 months
Demographics and cardiovascular (CV) risk profiling	CPI and PWV including lying and standing CBP	CPI and PWV including lying and standing CBP	CPI and PWV including lying and standing CBP	CPI and PWV including lying and standing CBP	CPI and PWV including lying and standing CBP	CPI and PWV including lyin and standing CBP
*CPI and PWV including lying and standing CBP (Sphygmocor)	AFSS, RFTS	AFSS, RFTS	AFSS, RFTs	AFSS, RFTs	AFSS, RFTs	AFSS, RFTs
Echo, EST, Holter 4-7 days , AFSS, Retinal examination, Serum and urinary analysis.	Holter 4-7 days	Holter 4-7 days	Echo, EST, Holter 4-7 days, Serum and urine analysis	Holter 4-7 days, Retinal examination	Holter 4-7 days	Echo, EST, Holter 4-7 day Retinal examination, Serum and uri analysis

*Offer treatment as per central BP targets. (Table-1).
Additional electro-anatomical mapping to estimate scar burden along with CMRI will be offered to patients listed for AF ablation. The CMR will be repeated after 12 months to assess AAD in a year as per IMPULSE AF protocol (CALHN Ethics and Research Committee Approval R2010712, HREC Reference: HREC/16/RAH/269)

Table-3. Follow up and Investigations time line for Control Group
(AFSS= AF symptom scale, BBP= Brachial blood pressure, CBP= central blood pressure, CPI= central pressure indices, EST= exercise stress test, PWV= pulse wave velocity, RFTs= Renal function test)

0 months	6months	11-13 months	18-20 months
Demographics and cardiovascular risk profiling	BBP treatment targets as per current guidelines	BBP treatment targets as per current guidelines	BBP treatment targets as per current guidelines
CPI, PWV (Sphygmocor) Brachial blood pressure (BBP) including lying and standing assessment, Retinal examination	Review for standard CV risk factor modification including AF and anti HTN treatment	Review for standard CV risk factor modification including AF and anti HTN treatment	Review for standard CV risk factor modification including AF and anti HTN treatment
Echo, EST, Holter 4-7 days, AFSS, Serum and urine analysis. Conventional cardiovascular risk factor (CVRF) management as per treating physician	Holter 4-7 days, AFSS, Conventional CVRF management as per treating physician	Echo, EST, Holter 4-7 days, AFSS, Retinal examination, Serum and urine analysis. CVRF management as per treating Physician	Echo, EST, Holter 4-7 days, AFSS, Retinal examination, Serum and urine analysis. CVRF management as per treating Physician
# Additional electro-anatomical mapping to estimate scar burden along with CMRI will be offered to patients listed for AF ablation. The CMR will be repeated after 12 months to assess AAD in a year as per IMPULSE AF protocol (CALHN Ethics and Research Committee Approval R2010712)			

Following assessments are standard for AF care and will be offered to all (control and intervention) participants.

a) Baseline Assessment

At baseline, following assessment will be performed for all participants:

- Weight and height recorded to calculate BMI.
- Demographics and conventional cardiovascular risk factors profiling by recording fasting glucose, lipid profile, age, gender, smoking history, systolic, diastolic, and pulse pressure.
- Brachial and aortic blood pressure (BP) assessment in a supine position after a resting period of 10 min by a mercury sphygmomanometer. Sphygmocor device will be applied to the right forearm over brachial artery to determine the central blood pressure indices as described previously (IMPULSE-AF protocol). Brachial blood pressure will be assessed by recording phase I and V of Korotkoff sounds to determine the brachial systolic and diastolic BP, respectively.
- Conventional 12-lead resting electrocardiograms (ECG) will be recorded and interpreted according to the Minnesota code (Mc).

- Exercise stress test as per Bruce Protocol to assess exercise capacity.
- Blood will be drawn following a 12-hour fast to determine plasma lipids, fasting glucose, hs CRP and renal function.
- Trans-thoracic Echo (TTE) will be performed to assess Biventricular systolic and diastolic function along with left atrial size.
- 4 to 7days Holter monitoring to evaluate AF recurrence and arrhythmia burden

b) Exercise Tolerance Assessment

Exercise tolerance assessment as a part of AF management will be determined by Bruce protocol with gradual increase in treadmill gradient and velocity every 3 mins to achieve maximal target heart rate as per age by the following formula [220-Age for males, 220-Age x0.8 for females]. Where necessary, the test will be tailored as per individual age and effort tolerance with a view to assess the maximum workload performance with in period of 8-12 minutes. An experience doctor or an exercise physiologist will supervise the test. Continuous monitoring of 12 leads ECG and blood pressure will be performed. Data will be recorded continuously and stored digitally for analysis later on by an experienced exercise physiologist. Central pulse wave morphology and velocity will be determined pre and post exercise (+5minutes) by Sphygmocor device.

c) Holter Recording

4- 7 days Holter recordings will be obtained to determine recurrence of AF along with its burden. Briefly, a 3-lead electrocardiogram is recorded continuously by way of five electrodes positioned on the upper torso. Upon completion of the recording period, data will be imported into MediLog Darwin analysis software and automatically analysed by using R-wave detection.

E. STUDY INTERVENTIONS IN ADDITION TO STANDARD OF CARE IN AF PATIENTS

a) Non-invasive central blood pressure assessment

Non-invasive evaluation of central blood pressure indices and carotid-femoral PWV analysis will be performed as per IMPULSE-AF validation study protocol (CALHN Ethics and Research Committee Approval: R2010712, HREC Reference: HREC/16/RAH/269)

Non-invasive central blood pressure assessment will be performed at baseline, and at follow-up using the SphygmoCor applanation tonometry device (Fig 1). Central blood pressure indices, including central systolic, diastolic and pulse pressures with augmentation index will be recorded. Carotid-femoral pulse wave velocity (PWV) will be performed by applanation tonometry as per IMPULSE AF study protocol. The test is painless and typically takes10-15 minutes.

In control patients, central blood pressure measurement will be performed as a single clinical assessment during their first visit after randomisation.

b) Atrial Fibrillation Severity Scale (AFSS)

Atrial Fibrillation Severity Scale (AFSS) will be used to quantify AF symptomatic burden. The AFSS is a validated scale with range of 3.25 [single

episode with minimal symptoms lasting for minutes] to 30 [continuous highly symptomatic episode lasting for 48 hours]. The scale also includes AF event frequency (scored 1-10), duration (scored 1.25-10) and global episode severity (scored 1-10). In addition, the AFSS assesses symptom severity via an associated symptom-specific continuous subscale (range, 0 [no symptoms] to 35 [severe symptoms]).

c) *Serum and Urine Analysis*
Venous blood samples (10ml) will be drawn from an antecubital vein after 10 minutes of supine rest and within five minutes following peak exercise to analyse atrial natriuretic peptide, serum markers of endothelial function (asymmetric dimethyl arginine, nitrate/nitrite), coagulation inflammation and fibrosis (C-reactive protein(CRP), tissue growth factor beta (TGF-B) and tumour necrosis factor (TNF)). Samples will be collected in appropriate tubes, centrifuged and plasma stored at -80°c. A preferably early morning urine sample will be collected to quantify albumin creatinine ratio (ACR).

d) *Recording of additional Electrophysiological (EP) parameters during AF ablation:*
Some of the study AF patients will be scheduled for pulmonary vein isolation (AF ablation) on clinical grounds at the Royal Adelaide Hospital. Conventionally, electro-anatomic mapping of the left atrium is performed by using the 3D mapping system during AF ablation. The following additional electrophysiological parameters will be recorded from the ablation catheter for these patients to characterise electro-anatomical atrial remodelling: effective refractory period, linear catheter conduction time, conduction velocity, proportion of fractionated electrograms, and bipolar voltage from the electroanatomic mapping system. This will add an extra 15mins to the procedure time without any additional requirements.

e) *Non-contrast cardiac MRI (CMR) assessment of aortic distensibility.*
In sub-group of 20-30 patients, scheduled for PVI (AF ablation) a non-contrast CMR will be performed to assess aortic distensibility (AAD) as per IMPULSE AF study Protocol (CALHN Ethics and Research Committee Approval: R2010712, HREC Reference: HREC/16/RAH/269). A repeat CMR will be performed to appraise (AAD) in a year's time.

f) *Retinal photography and analysis*
Retinal photographs will be acquired from AF patients at baseline and during their follow up appointments yearly. Retinal vascular calibre will be measured from photographs using a validated computer program[22]. Retinal arteriolar and retinal venular calibre equivalents will be measured, and correlated with changes in central or peripheral blood pressures[22]. The acquisition of retinal image takes couple of minutes and it is a painless procedure that does not require any specific preparation.

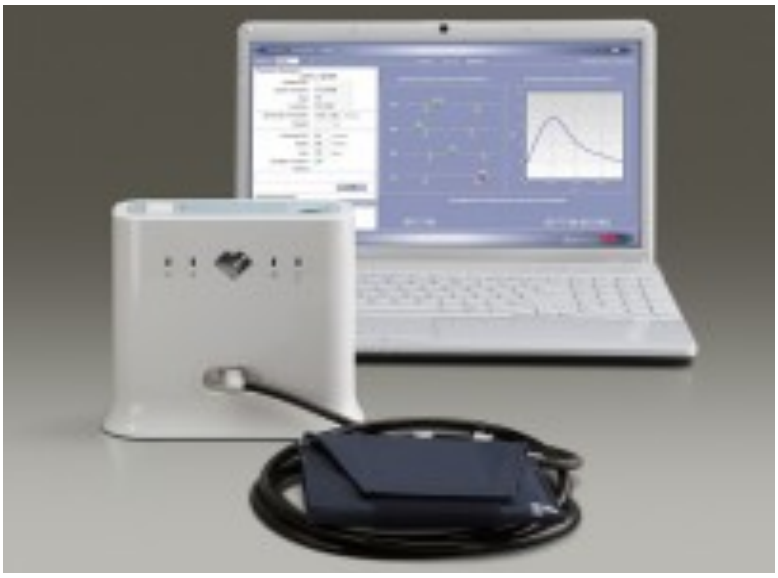

Fig. 1. Sphygmocor applanation tonometry device
(http://atcormedical.com/sphygmocor.html)

F. OUTCOMES OF THE STUDY

Primary outcomes to be evaluated include:

- Association and Impact of central blood pressure control on AF outcomes (recurrence and AF burden).

Secondary Outcomes:

- Prevalence of central high blood pressure and aortic stiffness in AF patients with normal brachial BP.
- Association of brachial and central blood pressure indices including aortic stiffness to end organ insult and electro-anatomical remodeling of atria in AF patients.
- Correlating central blood pressure treatment target goals to proportionate decrease in events [Nephropathy (20% increase in ACR or 15-20% drop in estimated glomerular filtration rate (eGFR)), Left ventricular hypertrophy (LVH)/mass, LV diastolic dysfunction. Left atrial area and conduit vascular remodeling.
- Defining exaggerated BP response to exercise and postural change in our AF cohort and relating it with outcomes.
- Number of anti-HTN required to achieve BP targets.
- Adverse events secondary to anti-HTN drugs including symptomatic postural BP drop of >20mmHg, acute kidney injury and electrolytes imbalance requiring hospitalization.

G. ETHICAL CONSIDERATIONS

Clinical Equipoise

The study is a low risk, single blinded randomised trial to evaluate the impact and treatment of central high blood pressure on AF and CV outcomes. Central high blood pressure will be estimated by validated cuff based device (Sphygmocor) non-invasively. Vascular remodelling secondary to HTN, leads to aortic stiffness, which is a modifiable risk factor. At present, it is known that various anti-hypertensive agents can have significantly different effects on central aortic pressures despite similar brachial blood pressure valuation [23]. Agents such as inhibitors of the renin-angiotensin system and amlodipine could be started in individuals with increased aortic stiffness. As such, the investigators regarding the conduct of this study identify no specific ethical concerns.

Informed Consent

All patient participants will undergo a formal process of informed consent prior to study participation. Patients will be blinded with regard to their randomised group and will be treated for peripheral or central high blood pressure accordingly.

Drugs

No additional pharmaceuticals will be administered for the study protocol, with the exception of anti-HTN to achieve treatment target goals re central or brachial blood pressure. Side effects of anti HTN medication will be recorded by conventional clinical approach of reviewing the symptoms, documentation of postural drop in BP and monitoring of renal function tests during follow up or as required clinically.

Specific Safety Consideration

No significant increase in radiation dose is anticipated for the acquisition of electrophysiological data for the study because we are going to use 3D mapping to position the catheters in atria. The non-invasive assessment of blood pressure is not associated with any known risk. Retinal photography does not require any mydriatics.

H. ANALYSIS AND REPORTING OF RESULTS

Sample size calculation

Assuming the recurrence risk is 40% for AF in control, we estimate 90 patients in each group would give us 80% power to detect the 20% difference between groups at 5% significance level. Anticipating dropout rate of 28% over the course of the study, we would like to recruit 126 patients in each group.

Statistical Analysis

Continuous variables will be reported as mean with standard deviation (SD). Results will be expressed as mean +/- SEM with p value of <0.05 considered statistically significant. Intra-class correlation analysis, Student's *t*-test and Bland– Altman plots will be used to assess the agreement between the peripheral and central blood pressure recordings. Pearson's method will be used for correlation analysis for the differences between the mean values of the blood pressure indices in two groups.

Other ad hoc summary or analysis may be performed as necessary. The results of this study are expected to be published in an internationally recognised Cardiology journal.

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OTHER RELEVANT INFORMATION

None

DATE OF PROPOSED COMMENCEMENT.

December 2017

RESOURCE CONSIDERATIONS

Staffing (own and other Departments)

The study will be carried out at Centre for Heart Rhythm Disorders (CHRD) Royal Adelaide Hospital, and at cardiovascular centre (CVC) Norwood. Professor Sanders will be the principle investigator. Dr Kashif Khokhar, Dr Adrian Elliott, Dr Mehardad Emami and Dr Andien Munawar will be the investigators coordinating recruitment and analysis of results.

Facilities (own and other Departments)

a) Goods and services
   Nil

b) Investigations to be undertaken (involvement of other Functional Units)
   Cardiac MRI is to be undertaken in the department of Cardiovascular Magnetic Resonance Imaging for a sub-group of our patients. Retinal photography will be performed in collaboration with the Ophthalmology unit using existing equipment.

Any other cost implication of the protocol

Nil

FINANCIAL STATEMENT

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