Research Protocol

Study Title

Scientific title: The prevalence of true resistant hypertension in Dunedin based adults with resistant hypertension and the association between true resistant hypertension and obstructive sleep apnoea risk.

Lay title: Identification of adults with true high blood pressure resistant to drugs and its relationship with breath pauses during sleep.

Study Investigator(s)

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Introduction

This study is an observational study which aims to: 1) identify individuals with true resistant hypertension (TRHT) in a population of Dunedin based adults 60 years and younger, with resistant hypertension (RHT) as defined under the current guidelines (2017) of the American Heart Association and American College of Cardiology; 2) investigate the association between TRHT and high risk of obstructive sleep apnoea (OSA) in the sub group of individuals with TRHT.

Dunedin based adults, 60 years or younger, who meet the criteria for RHT (are on three or more pharmacological agents of different classes, including a diuretic), have been identified from the Ministry of Health Pharmaceutical Collection Warehouse (PCW)

database. Following a briefing by researchers about the study at a scheduled meeting of the local General Practitioners Association, researchers will gain agreement from General Practitioners to distribute a letter to patients. A letter of invitation to participate in the study will be co-signed by Dr. Skinner and Associate Professor Wilkins. Letters will then be distributed to General Practitioners, who will be asked to forward copies to their patients identified from the PCW database.

An initial appointment will then be arranged with each consenting adult. They will complete standardised health, OSA risk and activity questionnaires and have anthropometric measurements taken. The subset with RHT who also score ≥9 on the Epworth Sleepiness Scale (ESS) will be identified as 'at risk for OSA' and, will have, 24h ambulatory blood pressure monitoring (24hABPM) to confirm TRHT. For the subset with TRHT on the second appointment cardiorespiratory fitness will be measured using a six minute walk test (6MWT), and an echocardiogram will be completed. Sleep and physical activity monitoring for seven (24h) days/nights will then be undertaken using a wrist monitor to confirm sleep fragmentation. The outcome will be correlated with the ESS score to determine those at high risk of OSA.

As investigators will adhere to the new (2017) guideline for hypertension and include only those participants with TRHT, this will create a new knowledge dimension. The association between high risk of OSA and TRHT will be a key outcome measure. The outcomes from the echocardiogram, anthropometrics, activity parameters, and quality of life questionnaires will describe the population. The findings have potential to change the direction of research in the area, including opening the topic of TRHT to more debate and supporting modified guidelines for physicians and physiotherapists in managing the subpopulation with OSA and TRHT.

2. Background

Hypertension (HT) is a worldwide problem which affects at least one third of the adult population, numbering billions of people in the world.[1] Key determinants of the increasing prevalence of HT are increase in life expectancy, counterbalanced by factors such as an increase in both physical inactivity and obesity.[2] Cardiovascular disease is the greatest cause of morbidity and mortality in New Zealand and the prevalence of HT in the adult population is over 30%, with ethnic disparities.[3, 4] The Maori population is at a higher risk for HT compared to the other populations in New Zealand and has a higher use of antihypertensive medication - over 15% more than the New Zealand Europeans.[4]

There is an internationally accepted protocol for the diagnosis of HT (Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, JNC 7 Report 2003[5]). Despite the protocol itself being well established, a new guideline for the definition of Stage I hypertension was published in 2017 by the American College of Cardiology/American Heart Association (ACC/AHA).[6] The New Zealand Guidelines (2018) have been updated to comply with the new definition.[3]

Stage 1 hypertension is now defined as 130 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic, and Stage 2 hypertension as 140/90 mm Hg or higher,[6] thus bringing the 'prehypertension' group into the hypertension classification. Importantly management is centered around an assessment and treatment approach based on the cardiovascular risk rather than treating blood pressure as an isolated risk factor.[3, 6, 7] For Stage 1 HT, management focusses on lifestyle factors in particular, physical activity, diet and reducing stress, rather than pharmacological interventions.[3, 6-8]

Resistant hypertension (RHT) is a subset of HT. RHT is defined as 'blood pressure above the minimum level for hypertension despite concurrent use of three anti-hypertensive agents of different classes at optimal dose amounts, one of these being a diuretic'.[9] Use of four medications including a diuretic is also considered as 'resistant' regardless of blood pressure values.[9] An accurate account of compliance with medication and recorded blood pressure (BP) is important in the diagnosis of RHT to differentiate it from other categories of hypertension such as pseudo-hypertension, white coat hypertension and masked hypertension.[9] Twenty four hour ambulatory blood pressure monitoring (24h APMB) has been shown to be the most effective and valid tool for diagnosing true RHT (TRHT).[6] However, a key limitation of many studies that have investigated the management of RHT by focusing on lifestyle changes, such as an increase physical activity, have failed to diagnose TRHT within their cohorts.[10-12]

Obstructive sleep apnoea (OSA) in adults has been correlated with the degree of blood pressure elevation above normal and thereby with the increasing risk of hypertension (HT).[13] Thus, it is internationally accepted that OSA should be considered as a cause of both primary HT and secondary HT.[1, 6, 7] The evidence has shown that OSA is linked with uncontrolled high blood pressure, more precisely, OSA has a close and strong relationship with RHT[1] and is cited as the most common secondary cause.[14] Further, limited studies indicate, OSA has been associated with cardiac structure and function. [15] However, relatively few studies have identified an association between OSA and TRHT.

It follows that since the severity of OSA is associated with major modifiable risk factors such as obesity and hyperaldosteronism in patients with RHT,[16] reducing OSA through modifying the risk factor/s may be highly beneficial. Treatment for OSA is wide ranging and may include continuous positive airway pressure (CPAP).[17] However, the goal of CPAP intervention is more to reduce symptoms rather than addressing the cause.[18] Furthermore patient compliance is often low, due to the frustrations associated with the CPAP mask.[19] Rather than just focusing on symptomatic management of OSA, it is suggested that new therapeutic strategies, that address OSA and HT simultaneously, may be more effective.[16] In addition to CPAP management for OSA described above, increasing physical activity may be beneficial in treating both OSA[20] and BP[21] as compliance with a prescribed physical activity programme can lead to a reduction in BP, and thereby, a reduction in the number of antihypertensive medications required by patients with HT.[6, 7, 9, 22]

3. Aim of Study

To investigate the association between true resistant hypertension and high risk of obstructive sleep apnoea in a sub group of individuals diagnosed with resistant hypertension.

4. Objectives

To:

- determine the prevalence of true resistant hypertension (TRHT) measured by 24h ambulatory blood pressure monitoring in Dunedin based individuals with resistant hypertension (RHT);

- investigate the relationship between Epworth Sleepiness Scale scores and sleep fragmentation in the Dunedin based individuals identified with true resistant hypertension (TRHT);

- investigate the association between true resistant hypertension (TRHT) and high risk of obstructive sleep apnoea (OSA), in the Dunedin based individuals

5. Hypothesis

5a. Primary Hypothesis

H_A: In Dunedin based individuals aged 60 years and below, diagnosed with resistant hypertension, 24h ambulatory blood pressure monitoring will identify a subgroup with true resistant hypertension.

H_0: In Dunedin based individuals aged 60 years and below, diagnosed with resistant hypertension, 24h ambulatory blood pressure monitoring will not identify a subgroup with true resistant hypertension.

5b. Secondary Hypotheses

H_A: There is correlation between Epworth Sleepiness Scale (ESS) score, and levels of sleep fragmentation in the subgroup of individuals with true resistant hypertension

H_0: There is no correlation between Epworth Sleepiness Scale (ESS) score, and levels of sleep fragmentation in the subgroup of individuals with true resistant hypertension

H_A: There is an association between true resistant hypertension and high risk of OSA, in the subgroup of individuals.

H_0: There is no association between true resistant hypertension and high risk of OSA, in the subgroup of individuals.

6. Study Design

The study is a descriptive observational study. The design has been selected to identify those with true resistant hypertension (TRHT) in a population of Dunedin based adults with resistant hypertension (RHT) and to investigate the risk of obstructive sleep apnoea (OSA) in the subset identified with TRHT. The anthropometric characteristics (body mass index (BMI), neck circumference, waist to hip ratio), cardio respiratory fitness (6MWT); quality of life (SF-36); and echo cardiogram parameters of the sub population with TRHT and high risk of OSA, will be determined to describe the study population.

7. Study Setting/ Location

The study is categorised as a single centre study at the University of Otago. The location will be the School of Physiotherapy, University of Otago (325 Great King Street, Dunedin North). Specific investigations, and interpretation of data downloaded from 24hABPM and Echo-cardiography recordings, will be carried out in the Dunedin School of Medicine Cardiology Research Laboratory, on 9th floor of the Dunedin Public Hospital.

8. Study Population

The population will comprise adults with resistant hypertension (RHT), based in the Dunedin region, aged 60 years and younger, who have been diagnosed with high blood pressure and are on three or more pharmacological agents of different classes including a diuretic. The population has been drawn from the Ministry of Health Pharmaceutical Collection Warehouse, via the Best Practice Advocacy Centre (bpac),[23] New Zealand.

The total number of adults with hypertension and being pharmacologically managed with three or more antihypertensive medications (estimated RHT) in New Zealand is 100,340; Southern District Health Board, 8425; and in the Dunedin region, 3184. The number of adults 60 years age or below in the Dunedin region with RHT is 559.[24]

9. Eligibility Criteria

Inclusion criteria

- Age: 18-60 years inclusive
- Gender: all
- Able to communicate/follow instructions in English
- Based in Dunedin region
- Diagnosed with hypertension
- Prescribed three of more antihypertensive medications including a diuretic (RHT definition[9]).

Exclusion criteria

- Diagnosed with hypertension prescribed two or less antihypertensive medications
- Adults above the age of 60 years
- Diagnosed/known renal disease
- Females who are pregnant

10. Study Outcomes

Primary Outcome

The prevalence of TRHT in a population with RHT and the association of TRHT with high risk of OSA.

Secondary Outcome(s)

The correlation between increased Epworth Sleepiness Scale score and sleep fragmentation in the subset with true resistant hypertension.

11. Study Procedures

a. Recruitment of participants

Adults (18-60y) in the Dunedin region, [anonymized] on three or more pharmacological agents of different classes, and the general practices [anonymized] they are enrolled at, have been identified from the Ministry of Health Pharmaceutical Collection Warehouse, via the Best Practice Advocacy Centre (bpac),[23] New Zealand. The number of adults on the list is 559[24], [the list of names will remain de-identified to the research team as letters will be forwarded by General Practitioners].

Following a briefing by researchers about the study at a scheduled meeting of the local General Practitioners Association, researchers will gain agreement from General Practitioners to distribute a letter to their patients identified from PWC database. The letter of invitation to participate in the study will be co-signed by Dr. Skinner and Associate Professor Wilkins. Inclusion criteria will be adults 18-60 years, who meet the definition for RHT[9], have no known renal disease and are able to communicate in English. Based on the population with RHT in Dunedin region a sample size n=83, with 95% confidence interval and 10% margin of error, is required. The recruitment target is n=100 with the dropout rate of up to 20%.

A list of individuals who consent to participate in the study will be created and each will be matched with a random serial number generated by the computer (using MS Excel). NIH number/name and contact details will be included on the database but remain deidentified other than to the research group. The random ID number will be used in the study.

The proposed recruitment period is August 2018 to April 2019; 9 months

Step 1
For individuals identified with RHT.
August 2018 - invitation to participate in the study;
August 2018 – March 2019: initial recruitment, initial measurements, 24hABPM

Step 2
For the sub group identified with TRHT and high ESS score.
September 2018 – April 2019: Echo cardiogram, cardiorespiratory fitness test (6MWT) and 24h day/night activity monitoring for one week

October 2019 September 2020 – write up and publication

11b. Randomisation

The study is a descriptive observational trial.

11c. Study procedure

Step I – Initial recruitment

Potential participants will be invited to contact Dr Skinner with enquiries and to indicate their interest in participating in the study. The Principal investigator (PI), the PhD candidate, will provide each participant with an appointment time for the initial assessment where written informed consent will be obtained first. The session will be at the School of Physiotherapy. A summary of the stages of the study is outlined in Figure 1.

Step II – Assessment and measurements

Appointment 1:
The PI will obtain the participant's demographic data (age; gender; ethnicity); general health and habits, physical activity level (initial assessment form – Appendix 1), quality of life (SF-36: Appendix 2) and OSA risk (ESS: Appendix 3), using self-administered questionnaires. Participants will use a tablet computer to complete this section which will take approximately 20 minutes. Data will then be downloaded onto the study data base (MS Excel).

The PI will then take the participant's resting blood pressure (office blood pressure – (BP)), heart rate, and peripheral saturation using standardised, calibrated equipment (NT1A Pulse oximeter, New Tech, Hamburg, Germany and Omron automatic digital blood pressure monitor, HEM 7322, Netherlands) and in accordance with the

ACC/AHA 2017 guidelines.[6] Next, the PI will take the anthropometric (body weight, height and circumferences of neck, waist, hip,) measurements of the participant using standard guidelines[25] and equipment; electronic weighing scale (kg) and stadiometer (cm), measuring tape (scale in cm); with two decimal point accuracy. The equipment will be calibrated as required. This section of the procedure will take about 15 minutes. The variables, body mass index (BMI) and waist to hip ratio will be calculated using simple formulas on MS Excel.

The subset with RHT who also score ≥9 on the Epworth Sleepiness Scale (ESS) will be identified as 'at risk for OSA', and will be fitted with 24h ambulatory blood pressure monitor on the non-dominant upper arm, at the Cardiology Research Laboratory, on 9th floor in Dunedin Hospital. The participant will be advised to undertake daily activities/sleep as usual over the next 24 hours.

Appointment 2:
On the following day the device will be removed at the same setting, the Cardiology Research Laboratory, and data downloaded to confirm TRHT or not. Where THRT is confirmed the participant will have an echo cardiogram to confirm baseline left ventricular function (results to be interpreted by co-investigator cardiologist).

After the echocardiogram, the PI will conduct a Six Minute Walk Test (6MWT) following the standardised test and safety procedures. Then an activity monitor (ActiGraph GT3XPB, Pensacola, Florida[26]) will be calibrated and placed on the non-dominant wrist to be worn for seven days/nights to determine the participant's true levels of functional activity during the day and during sleep. The participants will select the most convenient way to return the Activitrax monitor, either in person or by post. Data will be downloaded and analysed for activity levels, and sleep parameters, by the PI. Objective measurements of daytime activity (step count, time in low/moderate/vigorous physical activity, sedentary time and sleep, including total sleep time, awakenings, average awakenings, sleep efficiency, sleep onset, latency and wake after sleep onset) will be derived from the Actigraph calculator for the period.

The PI who will then determine the correlation between Epworth Sleepiness Scale score and sleep fragmentation and subsequently identify those with high risk of OSA in the subset with TRHT.

Note: Participants not found to have TRHT will meet with the co-investigator (Primary Supervisor) to discuss the outcomes and will be advised to visit their GP to discuss the report on findings for 24hABPM, risk of OSA (obtained from the questionnaire, ESS ≥9[27]), and self-reported physical activity level). The participants with objective signs of OSA scored from the data downloaded from the activity monitor but not with TRHT

will be referred by the co-investigator cardiologist, to the physician at the Sleep Clinic for further sleep analysis.
Individuals who have TRHT and high risk of OSA will be invited to participate in a second study (Figure 1): a feasibility study to investigate the outcomes of a supervised physical activity programme on blood pressure levels.

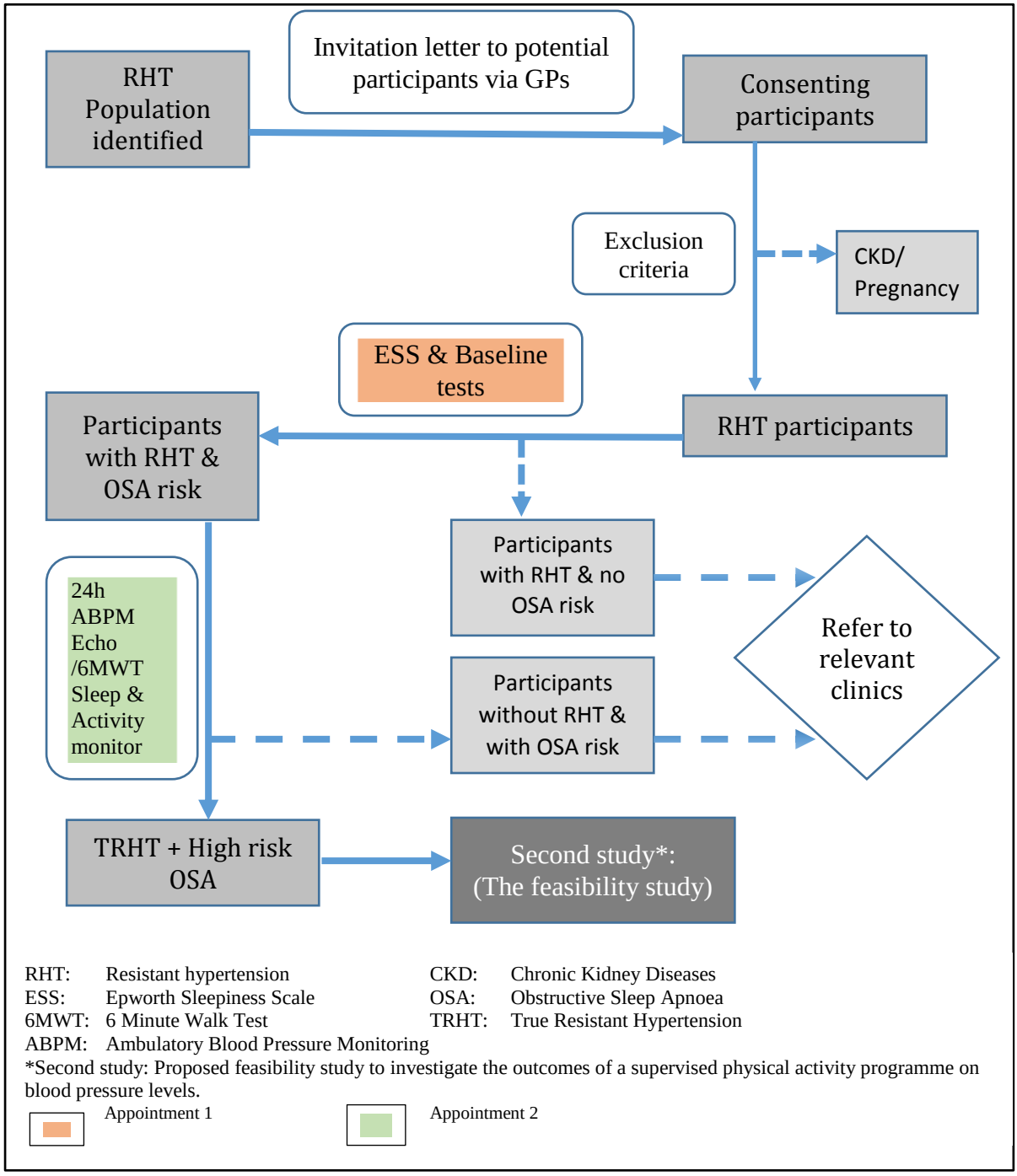

Figure 1: Flow diagram Study 1 outlining measurements and data gathered at appointment 1 and appointment 2

11d. Measurement tools

The research nurse at the cardiology research laboratory will conduct the 24hABPM and echocardiography under supervision of the co-investigator/cardiologist in the project. Other measurements will be taken by the PI, who has experience in measuring anthropometry and cardiovascular parameters.

Table 1: Measurements, measuring equipment and tools

Measurements	**Equipment/Tool**
Socio demographic data/ health status and habits/ adherence to medications	Self-administered questionnaire (Appendix I)
Office blood pressure Herat rate and peripheral oxygen saturation	Digital BP monitor (Omron automatic digital blood pressure monitor, HEM 7322, Netherlands) NT1A Pulse oximeter, New Tech, Hamburg, Germany
Height	Stadiometer[23]
Weight	Electronic weighing scale[23]
Neck, hip, waist circumference	Measuring tape (cm)[23]
Risk of OSA	ESS scale[27, 28] (Appendix II)
Quality of life	SF-36 (Appendix III)
Exercise readiness	PARQ+ 2017 (appendix IV)
Cardiorespiratory fitness	6MWT (Appendix V)/ Borg Rating of Perceived Exertion Scale[10]
24h ABPM	ABPM (90207, Spacelabs, Snoqualmie, Washington, USA[10])
Functional activity [step count, time in low/moderate/vigorous physical activity, sedentary time]	ActiGraph GT3XPB, Pensacola, Florida[26].
Objective sleep measurements [total sleep time, awakenings, average awakenings, sleep efficiency, sleep onset, latency and wake after sleep onset]	ActiGraph GT3XPB, Pensacola, Florida[26].
Echocardiography [Interventricular septal end diastole and end systole (IVSd and IVSs), Left ventricular internal diameter end diastole and end systole (LVIDd and LVIDs), Left ventricular posterior wall end diastole and end systole (LVPWd and LVPWs), Left ventricular ejection faction (LVEF%), Right ventricular end diastole (RVDd), Aortic root diameter (Ao Root Diam), Left atrium diameter (LA Diam), Mitral and Aortic valve regurgitations (MR and AR)]	Cardiac ultrasound machine

11e. Safety considerations/Patient safety

This study can be categorised as a minimal risk observational study, based on the guidelines of Health and Disability Ethics Committees (HDEC). No invasive clinical or non-clinical procedures or equipment and are involved in the proposed study. Activity involving equipment available in a gymnasium setting will be applied, (Table 1). Only the calibrated equipment and standardised tests outlined above will be used in the study.

All measuring equipment is categorised as low risk (Class I) according to Therapeutic Goods Administration (TGA) guidelines (2011), referred to in Appendix I of the HDEC application. The measurement procedures have no or minimal risk, e.g. falling or tripping whilst walking or usual muscle soreness/joint pain the day after the 6MWT. The measurements will be recorded in a research laboratory in the School of Physiotherapy and/or Dunedin School of Medicine Cardiology Research Laboratory located on the 9th floor the Dunedin Hospital building. Thus, there is no significant risk involved with the procedures or measurements made.

All researchers hold at a minimum a current First Aid certificate and AED emergency equipment is available in each location. The risk of an adverse event is, thus, low. However should an adverse event or accident occur, the participant will be covered by ACC under the Accident Compensation legislation. The study population is not a vulnerable population according to Appendix 2 of the HDEC application guidelines.

11f. Data monitoring

Data will be recorded using both hard copy and electronically. The electronic data will be saved on the PIs password protected computer, while the hard copies will be kept under lock and key in the research primary supervisor's office. A back up computer file will be maintained and the computer will be password protected.

Only the investigators (4 in number plus a research assistant) will be able to access the data and no third party will be involved in collection, entering or the processing data. In accordance with the requirement, data will be kept for 10 years and after that it will be discarded according to the standard procedures.

The participants can withdraw from the study any time with no disadvantage to their health care. However, the data obtained up to the point of withdrawal will be used in the study, as per detail in in the participant information sheet. Throughout the study and in the publications, or in any other material open to public, no individual data relating to a participant/s will be identified.

12. Statistical Considerations and Data Analysis

12a. Sample size and statistical power

A statistician was consulted to confirm the calculation of the sample size based on the population with RHT in Dunedin region (559). Thus, the sample size is n=83, with 95% confidence level and 10% margin of error. The recruitment target is set at n=100 and with the dropout rate of up to 20%, the estimated sample size (n=83) is expected to be able to be fulfilled.

The cohort with true resistant hypertension and high risk of OSA is unknown for the Dunedin based population with RHT. An 18% response rate will be sufficient to achieve the target sample size (n=100) for the study.

12b. Statistical methods

Simple statistics (mean, standard deviation, range) will be used to describe the demographic data and the measurements (anthropometry /blood pressure/ /sleep/activity/cardiac parameters) of the population with RHT in Dunedin region and in the sub population with TRHT and high risk of OSA. The data for anthropometrics, blood pressure, activity and cardiac parameters will be compared with accepted international guidelines,[25] and questionnaires will be interpreted using standard descriptors.

The relationship between the anthropometry parameters, blood pressure, ESS score, cardiorespiratory fitness, and activity and sleep levels with TRHT will be determined using regression analysis.

The statistical package for social sciences (SPSS) version 25.0 or above for Windows (IBM SPSS version 25.0 or above), NY, USA[10] will be used for the data analysis.

13. Ethical Considerations

The study to be conducted will conform fully with the principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of New Zealand. The study has been registered on the Australian New Zealand Clinical Trials Registry (ANZCTR). Ethical clearance will be obtained from the HDEC, New Zealand prior to commencing the study.

No identifiable information will be used in the study. For the identification of the cohort, the adults in the Dunedin region, who meet the criteria for RHT, on three or more pharmacological agents of different classes, including diuretic, have been identified (by bpac from the Ministry of Health Pharmaceutical Collection Warehouse and categorised to the various general practices. Letters supplied will be sent to those identified from their General Practitioner by linking names and addresses to national health numbers)

Each participant will be allocated a random ID number generated using Microsoft Excel, by the PI, for use in the study.

Only the investigators (4 in number) will be able to access the data and the list of consenting participants. A research assistant may be involved in the study to assist the baseline collection of data and measurements. Hard copies will be stored securely in a locked filing cabinet, by the Primary Supervisor and the electronic data will be accessed under password protection for the period of 10 years.

No data will be individually represented and no individuals will be identifiable in the published data. Simple statistics will be used to publish the demographic data and no participant will be able to be identified by any other party or in any other publication.

14. Outcomes and Significance

Benefits for the participants

The participants will be able to receive a report (Ambulatory blood pressure, echocardiogram, risk of obstructive sleep apnoea (ESS score), physical activity level, anthropometry such as BMI, Hip to waist ratio) on their cardiovascular health. If they indicate ‘yes’ on the consent form, a copy will also be forwarded to their GP.

Participants not found to have TRHT will meet with the co investigators (Primary supervisor) to discuss the outcomes and will be advised to visit their GP to discuss the report on the findings for 24hABPM, risk of OSA (obtained from the questionnaire, ESS ≥9), and self-reported physical activity level. The participants with a high risk of OSA will be referred by the co-investigator cardiologist, to the physician at the Sleep Clinic for further sleep analysis.

Participants who are identified with both TRHT and high risk of OSA, in the study, will be invited to participate in a second study, a single group non randomised intervention

study to determine the effects of a 12 week physical exercise program on 24h ABPM. The exercise as part of lifestyle modification is recommended to manage TRHT.[7]

Significance

Cardiovascular risk factors including OSA, are common in people with RHT, yet the particular relationship between RHT and OSA has not been adequately investigated because studies have not identified those with TRHT.[9, 10] by using24h AMBP which is the gold standard [6, 9] to diagnose TRHT. Further to that the new guideline used to diagnose hypertension (2017)[6] has lowered the threshold high blood pressure value. The investigators will adhere to the new guideline [6] for hypertension and include only those with TRHT, in the study, thus creating a new knowledge dimension.

Relatively few studies have identified the association between OSA and TRHT. Reducing OSA through modifying the risk factor/s would be highly beneficial. The predominant recommendation for management of OSA is to control obstruction and reduce the risk of developing hypertension, however CPAP manages symptoms and does not reduce HT. Therefore, new therapeutic strategies such as exercise and lifestyle modifications will be helpful to improve blood pressure in this group.

15. References

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