Difference in Cardiovascular Biomarkers Between Obesity Hypoventilation Syndrome and Obese Obstructive Sleep Apnoea

1. Background

Obesity hypoventilation syndrome is characterised by obesity (BMI>30) and alveolar hypoventilation during sleep and wakefulness (awake paCO2>45mmHg).[i] The majority of patients with OHS (90%) have concurrent obstructive sleep apnoea (OSA).[ii] The remaining 10% have non-obstructive sleep hypoventilation characterised by apnoea-hypopnoea index of <5 per hour.

The prevalence of OHS in the general population is unknown. It has been estimated to be around 0.3-0.4% and is expected to rise to mirror the obesity epidemic.[iii] The rates of obesity in Australia have risen to 20% from 28% in the last 10 years.[iv]

It is well recognised that OSA is associated with increased incidence of cardiovascular disease.[v] Compared to OSA patients without daytime hypercapnia, OHS is associated with more cardiovascular consequences, health care utilisations and health care costs.[vi] The high mortality rate is supposedly as a result of cardiovascular morbidity. The impact of therapy on cardiovascular complications and mortality is uncertain. Even when sleep disordered breathing is treated, mortality in those with OHS remains significantly worse than OSA alone.[vii]

The pathophysiology underlying the associations between OSA and cardiovascular disease are not fully established. Proposed mechanisms include elevated sympathetic drive, large swings in intra-thoracic pressure, increased oxidative stress and vascular inflammation.[viii] The discrepancies in the cardiovascular profiles of OHS versus OSA are even less well understood.

Cardiovascular biomarkers play an important role in the diagnosis of cardiac disease (troponin in myocardial injury and B-type natriuretic peptide in heart failure). Their high sensitivity assays have been demonstrated to be predictive of adverse cardiovascular events.[ix]

Cardiovascular disease has a long asymptomatic phase of development. Assessment of endothelial function and arterial stiffness allows early assessment and track progression of cardiovascular disease. Pulse wave analysis is a simple and non-invasive technique that has been widely employed in both epidemiological and interventional studies.

Impaired cerebral vasoreactivity is another indicator of endothelial dysfunction and increased arterial stiffness. Dynamic changes in carbon dioxide, a potent and reversible vasodilator, and oxygen tension during respiratory challenges can be used to produce changes in cerebral blood flow. Cerebral vasoreactivity and cerebrovascular reserve can be assessed indirectly by measuring cerebral perfusion during respiratory challenges.[x]

Near infrared spectroscopy (NIRS) device offers non-invasive real-time monitoring of regional tissue oxygenation. Near infrared light easily penetrates the skull and can be used to assess cortical oxygenation (rSO2) and cerebral perfusion using stickers paced on the patient's forehead. Impaired cerebrovascular function may be related to poorer daytime neurocognitive function. [xi]

This study aims to demonstrate the differences in the above-mentioned cardiovascular markers that reflect poorer outcomes in patients with OHS and concurrent OSA when compared to weight matched OSA patients without hypercapnia.

2. Hypothesis:

Patients with OHS and concurrent OSA have significantly more abnormal cardiovascular biomarkers, increased arterial stiffness and reduced vasoreactivity when compared to weight and age matched OSA patients without hypercapnia.

3. Study Objectives

3.1 Primary Objective:

1. To ascertain whether OHS patients have reduced vasoreactivity to ventilatory manoeuvers when compared to weight and age matched OSA patients without hypercapnia.

3.2 Secondary Objectives:

1. To compare the arterial stiffness between OHS patients with OSA patients without hypercapnia.

2. To ascertain whether OHS patients have higher biomarkers indicative of poorer long-term cardiovascular outcome when compared to OSA patients without hypercapnia.

4. Study Design

4.1 Design

This is a cross-sectional study comparing two patients groups:
1. Patients with obesity hypoventilation syndrome
2. Patients with obstructive sleep apnoea without hypercapnia.

4.2 Expected Participant Numbers

10 patients with obesity hypoventilation syndrome and 10 patients with obstructive sleep apnoea without hypercapnia, matched for age and weight.

4.3 Duration of the Study

Participant recruitment dates: May 2018 to May 2020.

4.4 Centres

Currently recruitment will only occur at RPAH (through Respiratory Failure Clinic or referrals from Metabolic Obesity Service).

5. Study Participants

5.1 Inclusion Criteria (OHS Group)

- BMI>30kg.m^{-2}
- Daytime respiratory failure with a $PaCO_2$>45mmHg
- Age years and over
- Willingness to provide informed consent and willingness to participate and comply with the study requirements

5.2 Exclusion Criteria (OHS Group)

- Presence of any other condition that may contribute to hypoventilation including neuromuscular disease, chest wall abnormalities, respiratory depressant medications, COPD or an FEV1/FVC ratio of <0.7
- Uncontrolled medical or psychiatric conditions
- Any recent myocardial infarction (past 6 weeks)
- Any pre-existing CVA/TIA
- Any decompensated heart failure
- Long term positive airway pressure therapy prior to enrolment
- Women lactating or pregnant
- Not proficient in English
- Inability to provide informed consent

5.3 Inclusion Criteria (OSA Group)

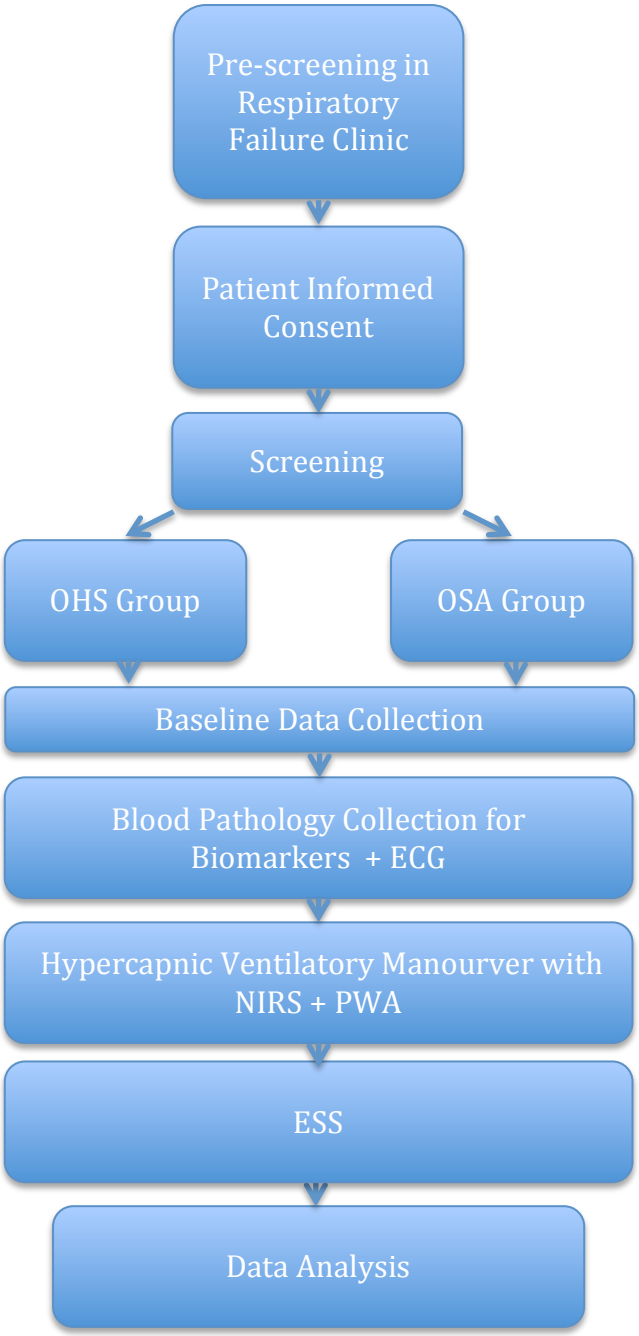
- AHI>30
- BMI>30kg.m^{-2}
- Age 18 years and over
- Willingness to provide informed consent and willingness to participate and comply with the study requirements

5.4 Exclusion Criteria (OSA Group)

- Presence of hypercapnia (paCO2 >45mmHg)
- Uncontrolled medical or psychiatric conditions
- Any recent myocardial infarction (past 6 weeks)
- Any pre-existing CVA/TIA
- Any decompensated heart failure
- Long term positive airway pressure therapy prior to enrolment
- Women lactating or pregnant
- Not proficient in English
- Inability to provide informed consent

6. Study Procedures

6.1 Study Flow Chart



6.2 Investigation Plan

Interventions	Enrolment Visit	Night 0	Visit 1
Participant Consent	✔		
Sleep Study		✔	
Capillary Blood Gas		✔	
Inclusion/Exclusion Criteria			✔
Patient Data Collection[1] and Physical Examination			✔
Blood Collection[2]			✔
12 Lead ECG			✔
ScO2 Assessment during Ventilatory Manoeuvers[3]			✔
Pulse Wave Analysis[4]			✔
Pulse Wave Velocity[5]			✔
Questionnaire[6]			✔

Enrolment Visit

- Potential patients at Respiratory Failure and Sleep Clinics will be identified based on their history and earlobe blood gas.
- Information about regarding the study given, and patient offered to enroll in study
- Witnessed written consent if patient agrees to enrol

Night 0

- Overnight diagnostic sleep study will be performed at RPAH Sleep Disorders Unit

Visit 1

- Patients will be assessed suitability to continue in study based on inclusion and exclusion criteria
- Participants who satisfy criteria will be undergo listed investigations

1. Patient data collection – demographic information, medical history, current medications, height and weight, spirometric measurements, results of awake capillary blood gas, results of the diagnostic sleep study

2. Venous blood sampling (blood biomarker collection) for:
    a. High sensitivity troponin T (hsTnT)
    b. N-terminal pro b-type natriuretic peptide (NT-proBNP)
    c. CRP/renal function
    d. HbA1c and fasting glucose
    e. Lipid profile, Leptin

3. Cerebral oxygenation (ScO2) and arterial stiffness assessment during hypercapnic and hypoxic ventilatory response manoeuver using near infrared spectroscopy (NIRS)
    a. Participants will be connected to a rebreathing system comprised of a closed loop of pipes attached to a mouthpiece/facemask that allows control of inspired gases and measurement of end-tidal CO2 (EtCO2), respiratory rate, minute ventilation, inspired PO2 and SpO2.
    b. All studies will be started after 5 minutes of rest in a sitting position. Participants will be given a 15 minute break between each ventilatory manoeuver.
    c. Hypercapnic hyperoxic response manoeuver:
        i. Participants will breathe through a circuit connected to a 5 Litre reservoir bag (containing 6% CO2, 26% O2 and the balance N2) via a one-way inhalation only valve.
        ii. Participants will be asked to hyperventilate for 2 minutes prior to normal tidal breathing.

iii. The manoeuver will be terminated if: a) 5 minutes is reached; b) participants EtCO2 reaches 10% (76mmHg); c) participant complains of discomfort; d) adequate data is obtained.

d. Hypercapnic hypoxic response manoeuver:
    i. Participants will breathe through a circuit connected to a 5 Litre reservoir bag (containing 6% CO2, 6% O2 and the balance N2) via a one-way inhalation only valve.
    ii. Participants will be asked to hyperventilate for 2 minutes prior to normal tidal breathing.
    iii. The manoeuver will be terminated if: a) 5 minutes is reached; b) participants EtCO2 reaches 10% (76mmHg) or SpO2 falls below 80%; c) participant complains of discomfort; d) adequate data is obtained
e. Hypoxic isocapnic response manoeuver:
    i. Participants will breathe through a circuit connected to a 5 Litre reservoir bag (containing 6% CO2, 6% O2 and the balance N2) via a one-way inhalation only valve.
    ii. Participants will be asked to undergo normal tidal breathing.
    iii. A CO2 absorbent (soda lime) will be used to prevent CO2 accumulation
    iv. The manoeuver will be terminated if: a) 5 minutes is reached; b) when SpO2 falls below 80%; c) participant complains of discomfort; d) adequate data is obtained
f. Changes in cerebral oxygenation using a NIRS device (NIRO 200) in addition to minute ventilation, SpO2 and PETCO2 will be recorded in real time. The recordings will continue for 5 minutes after termination of each ventilatory manoeuver to ensure the cerebral oxygenation (ScO2) nadir is captured.

4. Central arterial pressure waveform analysis will be performed using a SphygmoCor XCEL at baseline (during 5 minute resting period) and at termination of ventilatory manoeuver. Augmentation index, augmented pressure and reflected wave magnitude will be recorded from both readings.

5. Carotid-femoral pulse wave velocity measurements will be performed using SphygmoCor XCEL. A cuff is placed around the femoral artery of the patient to capture the femoral waveform and a tonometer is used to capture the carotid waveform. The velocity is determined by dividing the distance between the two sites by the pulse transit time.

6. Epworth Sleepiness Score (ESS)

6.3 Study Procedure Risks

Blood sampling:

- Pain
- Bruising

Ventilatory manoeuvers:

- Transient breathlessness
- Headache
- Transient paresthesia
- Transient dizziness

Central pulse wave analysis:

- Transient arm discomfort
- Transient arm paresthesia

6.4 Participant Recruitment and Screening

Patients will be recruited from the Royal Prince Alfred Hospital Sleep Disorders Unit in Camperdown, NSW, Australia. Newly referred patients to the RPAH Respiratory Failure and Sleep clinic for assessment who are likely to meet eligibility will undergo an earlobe blood gas prior to their scheduled diagnostic polysomnogram. The earlobe blood gas is part of routine care and will assist in identifying obese patients with

hypercapnia. Patients scheduled for a diagnostic polysomnogram for possible OHS who satisfy the inclusion and exclusion criteria will be eligible for the trial. Patients who are shown to be normocapnic on their early morning blood gas but with evidence of severe obstructive sleep apnoea on their overnight PSG will be screened as a potential participant in the obstructive sleep apnoea group.

6.5 Participant Enrolment

Potential participants will be enrolled into the study after the informed consent process has been completed and the participant has been assessed to meet all the inclusion criteria and none of the exclusion criteria. Study participants will receive a study enrolment number and this will documented in the participants' medical records and on all study documents.

6.6 Information and Consent

The research team outlined in the ethics application will introduce and provide a summary of the study and invite participation. A staff member not involved in the study will then witness written consent if given (Patient Informed Consent Form).

6.7 End of Study

Once the investigations are complete, the participants will exit the study. OHS patients will be offered to enrol in a randomised therapeutic trial of comparing autotitrating CPAP versus fixed CPAP trial (see other protocol). Standard clinical care will continue for their sleep-disordered breathing for OSA patients and OHS patients who do not wish to participate in or meet the inclusion/exclusion criteria for the randomised therapeutic trial.

7. Outcomes

Primary Outcome:

Change in ScO2 in relation to change in PETCO2 with comparison between the two groups (OHS and OSA)

Secondary Outcomes:

a) Comparison of arterial stiffness between OHS and OSA groups (based on pulse wave velocity and augmentation index from pulse wave analysis)

b) Comparison of CRP, hs-TnT, NT-proBNP, ECG abnormalities between OHS and OSA groups

8. Statistical Considerations

As this is a pilot study and there is insufficient data to perform power analysis.
20 patients will be studied in total: 10 in the OHS group and 10 in the OSA group.
The baseline characteristics of both groups will be expressed as mean and SD or percentages with 95% CIs and compared using Student's t-test and X2 analysis, respectively.

9. Ethical Considerations

The trial will require ethics approval by RPA Research Ethics and Governance Committee prior to study commencement. The trial will be listed with the Australian New Zealand Clinical Trials Registry.

The responsible investigators will ensure that the study is completed in accordance with the guidelines set out in the National Statement on Ethical Conduct in Human Research and the CPMP/ICH Note for Guidance on Good Clinical Practice.

10. Safety Considerations

Any adverse events will be recorded. These will be reported to their respective treating physician and the Ethics Committee (HREC) informed.

11. Data Management

All raw sleep study data is routinely stored in DVD format or on external hard drives and kept in the Sleep Unit, Level 11, Building 75, RPAH. All data collected from each visit will be de-identified and stored on a computer hard drive and external hard drive within the Respiratory and Sleep Medicine Department. The de-identified information will be accessed for analysis of results that will be subject to statistical procedures.

The data will be retained for 4 years (1 year after end of trial).

12. Trial Sponsorship and Financing

RPAH Sleep Disorders Unit will cover cost of equipment and pathology tests performed during study visits. The principle investigator's funding is assisted by University of Sydney research scholarship (NeuroSleep). The sleep studies will be performed as per standard care and is covered under Medicare.

13. Investigator Obligations

The principle investigator will be responsible for safe storage of data and protection of participant confidentiality. They will be responsible for any adverse event reporting.

14. Conflict of Interest

None to declare

15. Outcomes and Significance

The study will contribute to a better understanding of the discrepancy in cardiovascular health among the OHS patient population when compared to OSA patient population.

16. Dissemination of Results and Publication Policy

We aim to publish the research findings. Results will also be available to the research participants.

17. References:

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