

Auto-titrating versus Fixed Continuous Positive Airway Pressure in Obesity Hypoventilation Syndrome

1. Background

Obesity hypoventilation syndrome is characterised by obesity (BMI>30) and alveolar hypoventilation during sleep and wakefulness (awake $\text{paCO}_2 > 45 \text{ mmHg}$).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}

Positive airway pressure with either nocturnal non-invasive bilevel positive airway pressure (Bi-level) or continuous positive airway pressures (CPAP) has been shown to be more effective than lifestyle modification in improving clinical symptoms and polysomnographic parameters. Initial treatment with Bi-level or CPAP in newly diagnosed OHS resulted in similar improvements in ventilatory failure, quality of life and adherence. While therapy with Bi-level appeared to result in better respiratory functional improvements than CPAP (six-minute walk test and FEV1), it is not clear whether this produces greater long-term benefits.^v

In OSA, there is increasing employment of auto-titrating CPAP (APAP). APAP is engineered to automatically provide a positive pressure to the upper airway in response to apnoea, hypopnea, airflow limitation or snoring. The positive pressure required may change throughout the night due to the subject's different body positions and stages of sleep, and over time related to changes in weight or nasal

resistance. APAP has a theoretical benefit over fixed CPAP in position-dependent or REM-predominant OSA. Both APAP and fixed CPAP have been shown to produce similar improvements in apnoea-hypopnoea index and quality of life. However, compared to fixed CPAP, APAP is associated with higher compliance and a greater reduction in sleepiness, but less improvement in minimum oxygen saturation.^{vi} APAP has been used as an alternative method to conventional polysomnographically-directed CPAP titration, with studies demonstrating no significant difference in the optimal CPAP levels achieved.^{vii} This allows patients to go on adequate therapy without the need for a potential lengthy wait for a second in-lab pressure determination polysomnogram.

The American Academy of Sleep Medicine has recommended against the use of APAP titration or treatment in certain co-existing conditions, including congestive heart failure, chronic lung diseases, and obesity hypoventilation syndrome.^{viii} However, this recommendation is based on consensus, and to date, there has been no supporting evidence against the use of APAP in stable OHS with concurrent OSA.

2. Hypothesis:

Therapy with an APAP device is not inferior to fixed pressure CPAP therapy with respect to improvements in ventilatory failure, sleep quality, quality of life and cardiovascular biomarkers in OHS with severe OSA. Compliance with either device is not significantly different.

3. Study Objectives:

Primary Objective:

1. To compare improvements in capillary blood gases (pH and paCO_2) after 3 months of fixed CPAP therapy versus 3 months of APAP therapy in stable OHS-OSA ($\text{AHI} > 30$).

Secondary Objectives:

1. To compare changes in sleep quality, nocturnal oximetry, quality of life and cardiovascular biomarkers after 3 months of fixed CPAP therapy versus 3 months of APAP therapy in stable OHS-OSA ($\text{AHI} > 30$).
2. To compare treatment compliance of fixed CPAP versus APAP during the 3 months trial period.

4. Study Design

4.1 Design

This is a randomised control trial with double blinding. Patients are randomised to one of two treatment arms:

1. Autotitrating CPAP (APAP)
2. Fixed CPAP (fCPAP)

4.2 Expected Participant Numbers

The intention is to recruit 40 patients with obesity hypoventilation syndrome with 20 randomised to each treatment arm.

4.3 Duration of the Study

Study duration: 3 months

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

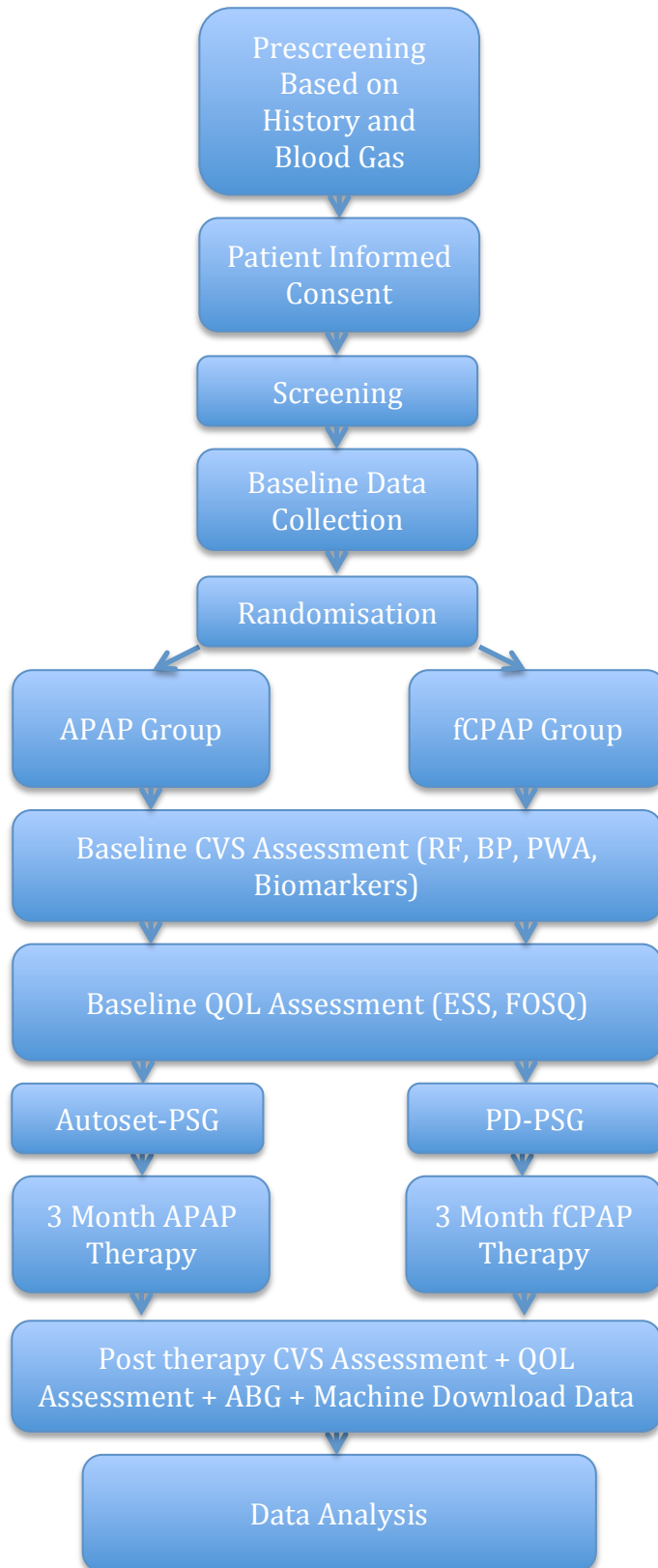
- BMI > 30 kg.m⁻²
- Daytime respiratory failure with a PaCO₂ > 45 mmHg (OHS group)
- pH is in the normal range at admission (7.35-7.45)
- Treatment naïve of long-term positive airway pressure device i.e. the patient has not been using CPAP in the past 12 months.
- AHI >= 30 events per hour

5.2 Exclusion Criteria

- 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 conditions
- Any pre-existing heart failure with reduced ejection fraction
- Any pre-existing CVA/TIA
- Decompensated right heart failure
- Women lactating or pregnant
- Not proficient in English
- Inability to provide informed consent
- PaCO₂ > 60 mmHg

6. Study Procedures

6.1 Study Flow Chart



6.2 Investigation Plan

Interventions	Enrolment Visit	Night 0	Visit 1	Night 1	Visit 2	Visit 3
Participant Consent	✓					
Sleep Study		✓		✓		
Inclusion/Exclusion Criteria			✓			
Randomisation			✓			
Patient Data Collection¹ and Physical Examination			✓			
Blood Collection²			✓			✓
12 Lead ECG			✓			✓
Capillary Blood Gas			✓		✓	✓
Pulse Wave Analysis³			✓			✓
Questionnaires⁴			✓			✓
Oximetry on CPAP					✓	
Adverse Event or SAE Assessment					✓	✓
Compliance Download					✓	✓

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

- Participants will be randomised if they meet the inclusion and exclusion criteria
- Participants' data and baseline questionnaires and investigations will be performed

Night 1

- Participants will undergo a CPAP titration study
- Participants randomised to the fCPAP will be titrated according to a standardised protocol to identify optimal CPAP pressure settings.
- Participants randomised to APAP will use their allocated APAP device during the night of titration study whereby the PAP device will determine the administered pressure while oximetry, transcutaneous CO₂ and PAP device flow signals are recorded.
- All participants will have mask fitting and CPAP education as per usual standard of care. All participants will be loaned a Resmed Airsense 10 or Philips DreamStation device and appropriate mask interface for the duration of the study.
- fCPAP group participants will have their PAP device set to a fixed pressure as determined by their respective pressure determination study while the APAP group participants will have their PAP device set to auto set pressure range of 8cmH₂O to 20cmH₂O.

Visit 2

- 1 month follow up (after APAP or fCPAP initiation)
- Awake ABG and participant's PAP compliance will be assessed.

- Participants' loaned PAP device will also be fitted with a oximetry device, which they will be asked to wear for one night to record nocturnal oxygen saturation whilst using their PAP device.
- Participants will be withdrawn from the study if paCO₂ has risen by >10mmHg and placed on Bilevel therapy (with appropriate titration study and clinical review i.e. usual care) or poor compliance (average hours of use less than 2 hours per night). These instances will be recorded as therapy failure.

Visit 3

- 3 month follow up (after APAP or fCPAP initiation)
 - All baseline tests will be repeated
 - Data download will be performed on PAP device to obtain information on compliance, AHI on PAP and 90th centile APAP pressure (in APAP group)
 - An exit interview will be performed
 - Further pressure determination study will be organised for participants in the APAP group
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
 - d. HbA1c, fasting glucose
 - e. Lipid profile
 3. Central arterial pressure waveform analysis will be performed using a SphygmoCor XCEL.
 4. Epworth Sleepiness Score (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ) and Severe Respiratory Insufficiency Questionnaire (SRI) (attached)

6.3 Study Procedure Risks

Positive airway pressure therapy:

- Failure to provide adequate therapy (worsening hypercapnia or persistent and frequent obstructive respiratory events)
- Nasal congestion
- Oral or nasal dryness
- Eye irritation from mask leak
- Claustrophobia
- Skin irritation or pressure sores
- Poor sleep quality or continued tiredness
- Headaches
- Aerophagia – bloating, fullness, gassy

Complications arising from positive airway pressure device therapy are non-severe. It is the standard of care for obesity hypoventilation syndrome. Risks of therapy will be minimised by adequate patient education and mask fitting session.

Blood sampling:

- Pain
- Bruising

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.

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 be documented in the participant's 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 Randomisation Procedure

Patients will be randomised to either fixed CPAP or APAP using a computer-generated randomised sequence.

6.8 End of Study Treatment/Withdrawal Procedure

At the end of visit 3 (3 months follow up), participants of both treatment arms will exit the study. Downloaded compliance data would be used in addition to their sleep study results for application of an appropriate NSW-Enable funded positive airway pressure device, or a script will be provided for purchase of an appropriate positive

airway pressure device if the patient is deemed not eligible for a funded machine as per NSW-Enable criteria. This is usual standard of care.

They will continue to receive their regular follow up for management of their sleep disordered breathing as deemed necessary by their treating clinician.

Participants who withdraw from treatment early will return to the care of their treating clinician and receive usual clinical care.

Participants who fail CPAP therapy (increasing hypercapnia of $>10\text{mmHg}$ at 1 month or 3 months) will be withdrawn from the study. They will undergo further bilevel titration study, reviewed by their treating clinician and commenced on bilevel therapy as per usual clinical care.

All participants will complete an exit interview at end of study to assess their experience of trial participation, CPAP treatment and blinding adequacy.

7. Outcomes

Comparison of APAP with fCPAP in the following:

Primary Outcome:

Change in awake PaCO₂ at 3 months post initiation of therapy

Secondary Outcomes:

- a) Change in cardiovascular markers with CPAP therapy
- b) Change in quality of life and sleepiness
- c) Nocturnal oximetry on therapy
- d) Treatment compliance
- e) Optimal CPAP level. Residual Apnoea-Hypopnoea Index on APAP device.

8. Statistical Considerations

Prior to treatment, the baseline measurements 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. Linear mixed models will be used to examine the fixed effects of group (APAP or fCPAP), time (baseline, 1 and 3 months after commencing treatment) and their interaction, on capillary blood gas analysis, cardiovascular outcomes, quality of life measurements and compliance. Mixed effects modeling will be used to control for differences in compliance.

Using a margin for non-inferiority of 5mmHg paCO₂, a Type I error of 5%, a Type II error of 20%, the sample size required is over 200. There is insufficient data on secondary outcomes to perform power analysis. As this is designed as a pilot study, a total of 40 patients will be studied with 20 patients randomised to each treatment arm.

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. Blinding and Unblinding

Participants will be blinded to which device they are allocated. Markings indicating mode of therapy (APAP or fCPAP) will be concealed on their loaned machine (either Philips Dreamstation or Resmed Airsense 10).

The principle investigator will be blinded regarding treatment allocation. The blinding will continue during data analysis by the principle investigator. The respiratory physiotherapists who will provide education, CPAP download will have knowledge to treatment allocation, but are not directly involved in data analysis. An exit interview will be performed at the end of the trial to assess the adequacy of blind procedure.

Unblinding will be performed at the end of the trial, or on an individual basis in the case of a treatment failure (rise in paCO_2 of $>10\text{mmHg}$).

12. 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).

13. 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.

14. 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.

15. Conflict of Interest

None to declare

16. Outcomes and Significance

The study aims to answer whether APAP is a safe alternative in the treatment of OHS-OSA. If APAP therapy does not have any safety concerns when compared to standard of care fixed CPAP, then it may be safely used as a treatment alternative, which might be preferred or tolerated better by a proportion of patients with OHS-OSA. It will also potentially allow initiation of APAP therapy on newly diagnosed stable OHS patients without the need for an urgent pressure determination study.

17. Dissemination of Results and Publication Policy

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

18. References:

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