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Reduction in sympathetic tone in Obstructive sleep apnea patients: is fixed CPAP more effective than APAP? – a randomized, parallel trial protocol

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Abbreviations:

ABPM: ambulatory BP monitoring

AHI: apnea and hypopnea index

APAP: auto-adjusting continuous pressure

BP: blood pressure

CPAP: continuous positive airway pressure

DBP: diastolic blood pressure

ECG: electrocardiography

EEG: electroencephalography

EMG: electromyography

EOG: electrooculography

HRV: heart rate variability

ITT: intention-to-treat analysis

MBP: mean blood pressure

MSNA: muscle sympathetic nerve activity

OSA: obstructive sleep apnea

PPT: per protocol analysis

SBP: systolic blood pressure

Abstract (Word count: 288)

Introduction: Obstructive sleep apnea (OSA) is a prevalent chronic disease associated with fatal and non-fatal cardiovascular events. Hypertension is one of the major intermediary mechanisms leading to late cardiovascular events. Intermittent hypoxia and hypercapnia associated with nocturnal acute respiratory events stimulate chemo- reflexes which in turn result in sympathetic over-activity and finally blood pressure elevation. Continuous positive airway pressure (CPAP) is the primary treatment for OSA and induces a small but significant reduction in blood pressure. The use of auto-adjusting continuous pressure (APAP) modalities has increased in the last few years and several studies have suggested different ranges of blood pressure (BP) reduction when comparing fixed CPAP versus APAP. However, the pathophysiological mechanisms implicated are not fully elucidated. The variations in pressure through the night inherent to APAP use may induce persistent respiratory efforts and sleep fragmentation that might impair sympathovagal balance during sleep and result in smaller decreases in BP. Therefore, this study aims to compare muscle sympathetic nerve activity (MSNA) assessed by microneurography (the reference method for measuring sympathetic activity) after one month of APAP versus fixed CPAP in treatment-naive OSA patients.

Methods and analysis: adult subjects with newly diagnosed OSA (apnea hypopnea index > 20/h) will be randomized for treatment with APAP or fixed CPAP. Measurements of sympathetic activity by MSNA, heart rate variability and catecholamines will be obtained at baseline and after one month of treatment. The primary composite outcome will be the change in sympathetic tone measured by MSNA in bursts/min and bursts/100 heart beats.

Ethics and dissemination: The protocol was approved by the Ethics Committee (*Comite de Protection des Personnes Sud Est V*) and was registered on ClinicalTrials.gov (NCT03428516). The study started in March 2018 with primary completion expected in March 2019.

Trial registration number: NCT03428516

Keywords: obstructive sleep apnea, hypertension, continuous positive airway pressure, sleep medicine, sympathetic activity.

Strengths and limitations of the study:

- The analysis of vascular and cardiac sympathetic activity will be evaluated by complementary methods: microneurography of the peroneal nerve (the gold standard method), heart rate variability (HRV) and urinary catecholamines.
- The use of 24h ambulatory blood pressure (BP) monitoring is more sensitive when assessing therapeutic interventions than office BP and provides prognostic guidance.
- Subjects will be randomly allocated to one of the two positive airway pressure (PAP) modalities by a statistician not involved in the data collection. All other investigators, patients and assessment technicians will be blinded to the patient´s group.
- The same make and model of CPAP device will be used both in Fixed and APAP modes.
- The duration of exposure to treatment of one month is ample but might under-represent the chronic effects of PAP therapies on sympathetic activity.

Introduction

Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity and mortality (1-6). Hypertension is a leading cause of death worldwide and the main factor implicated in cardiovascular risk (7-9). There is a dose-response relationship between indices of OSA severity and hypertension (10, 11). Accordingly, one of the most common objectives when treating OSA is blood pressure (BP) reduction in order to prevent or reduce late cardiovascular events.

Obstructive sleep apnea (OSA) is characterized by partial (hypopnea) or complete (apnea) upper airway collapses during sleep (12). Sympathetic activation is the main intermediary mechanism for BP elevation in OSA patients (11, 13). The repetitive occurrence of respiratory events leading to intermittent hypoxia and hypercapnia results in stimulation of central and peripheral chemoreflexes enhancing sympathetic activity and, subsequently increasing vascular tone and promoting blood pressure elevation (14). Chronic sympathetic activation induces vascular remodeling and, frequently, uncontrolled or resistant hypertension (15). In OSA patients, night-time sympathetic over-activation is associated with the non-dipping pattern of BP and the high sympathetic tone persists during wakefulness (16). In the early course of the disease, even non-hypertensive subjects exhibit increased BP and muscle sympathetic nerve activity in response to chronic intermittent hypoxia (13, 17).

Continuous positive airway pressure remains the gold standard therapeutic option for the treatment of severe OSA. Several systematic reviews and meta-analyses (18-24) have demonstrated limited but significant improvements in BP (a reduction of about 2 mmHg in 24-h mean BP). Better results are achieved in specific phenotypes with more severe OSA, higher BP at baseline and adherent to PAP therapies (use of CPAP ≥ 4 hours/night) (19, 25-27).

Auto-adjusting CPAP (APAP) changes the pressure delivered throughout the night depending on events detected, with the goal of applying the minimal effective pressure (28-31) thus reducing side effects and improving adherence. The average overnight applied pressure is significantly lower with APAP for the same range of improvement in the apnea-hypopnea index (AHI) (32). However, the continuous variations in pressure associated with the functioning of APAP devices potentially induce micro-arousals, and change sleep

macrostructure in some patients (31,33,34). This might limit the decrease in sympathetic activity during the night when treating OSA and consequently result in a smaller reduction of BP.

Studies have demonstrated controversial results on the impact of the two pressure modalities (fixed versus auto-adjusting) on blood pressure reduction (table 2). Although some authors reported superiority with fixed pressure (35, 36), other clinical trials reported no significant difference between APAP and CPAP (37-39). A recent study that evaluated 208 patients with a longer than usual follow up of 2 years demonstrated comparable reductions in sleepiness and blood pressure with similar OSA-related costs for both treatments (37). Karasulu *et al* (40) and Patruno *et al* (41) have demonstrated lower reduction in cardiac sympathetic activity using heart rate variability (HRV) in OSA patients and obese OSA patients during APAP treatment compared with fixed CPAP. However, neither study was randomized and Patruno evaluated only a specific population of obese patients with severe OSA, which limits the generalizability of the results. In a small study of adult males, without antihypertensive treatment, Marrone *et al* (34), evaluated BP changes after treatment with APAP versus CPAP. As a secondary outcome, they reported sympathetic activity by measurement of catecholamines. Norepinephrine decreased significantly after treatment in the APAP group but not in the CPAP group and normetanephrine decreased significantly in both groups. Overall, there is a lack of well-designed studies evaluating the mechanisms underlying specific BP responses under APAP versus fixed CPAP. In this context, the aim of the present study is to compare vascular sympathetic tone after one month of treatment with fixed versus auto-adjusting pressure by microneurography in newly diagnosed OSA patients.

Methods and analysis

Study design

This study is a prospective, single-site, randomized, double-blind, parallel, one month-controlled trial.

Objectives

Primary research objective

The main objective is to compare change in vascular sympathetic tone measured by Muscle Sympathetic Nerve Activity (MSNA) microneurography after one month of APAP versus after one month of fixed CPAP in treatment-naive moderate to severe OSA patients.

The primary composite outcome will be the change in sympathetic tone measured by MSNA in bursts/min and bursts/100 heart beats between baseline and after one month of treatment.

Secondary research objectives

The secondary objectives will be to compare the following variables before and after treatment:

- Ambulatory BP monitoring (24h ABPM): mean blood pressure (MBP), systolic blood pressure (SBP) and diastolic blood pressure DBP, during 24h periods as well as daytime and night-time measurements.

- Urinary catecholamines (24h collection): epinephrine, norepinephrine, and dopamine.

- Heart Rate Variability as an indicator of cardiac sympathovagal balance.

Population

Consecutive adult outpatients attending a tertiary hospital sleep center (*Grenoble Alpes University Hospital* – France), with an established diagnosis of obstructive sleep apnea by full-night polysomnography (apnea-hypopnea index > 20/hour), and willing to receive positive airway pressure treatment, will be enrolled in the study. The inclusion and exclusion criteria are presented in table 1. Written informed consent will be obtained from all participants by a sleep physician study investigator (supplementary file).

Materials

Muscle Sympathetic Nerve Activity (MSNA)

Multiunit postganglionic muscle sympathetic activity will be recorded from the peroneal nerve (Figure 1). A reference electrode and a collecting electrode will be inserted percutaneously to record the discharges of the muscle sympathetic fibres contained in the peroneal nerve. Dorsiflexion of the first toe will confirm the correct placement of the

electrode. Neural activity will be amplified, band-pass filtered, rectified and integrated to create a sympathetic neurogram for real-time inspection. The raw, unfiltered neurogram will be recorded at 40 kHz for processing using our algorithm for identification of sympathetic nerve signals (42). All signals will be digitized and stored (Windaq, DATAQ Instruments, or PowerLab, ADInstruments) for subsequent analysis.

MSNA will be expressed as burst frequency (bursts·min^{-1}) and burst frequency normalized to heart beat (bursts per 100 beats).

During the measurement of MSNA, a standard 3-lead electrocardiogram will continuously record heart rate. Beat-by-beat arterial BP will be non-invasively measured throughout the study session via finger photoplethysmography (CNAP 500, CNSystems, Austria) and calibrated against oscillometric brachial pressure.

Blood flow

Popliteal blood velocity will be recorded using a 4-MHz Doppler probe (Multidop T2, DWL) at the popliteal fossa of the contralateral leg to the sympathetic nerve recording.

Several parameters will be extracted from the above measurements: sympathetic vascular tone, blood pressure and blood flow. Furthermore, we shall calculate vascular resistance and vascular sympathetic tone and blood pressure gains, as previously described (14, 43).

Blood Pressure

Ambulatory BP monitoring (ABPM) will use Spacelabs 90207® devices (Spacelabs International, Redmond, Washington, USA). The measurements will be made using an oscillometric method and programmed every 15 minutes during the day and every 30 minutes at night. The following ABPM parameters will be studied: mean SBP, mean DBP and mean HR over 24 hours, the same mean values during the daytime (7.00 am to 10.00 pm) and at night-time (10.00 pm to 7.00 am). The normal night-time physiological dipping BP is expected to be > 10%. The summary values in the ABPM report for each patient will be used in the data analysis. This is an average by subject and by recording session (at baseline and 1 month). Data relating to the average daytime and night-time systolic BP (SBP), diastolic BP (DBP), and mean BP (MBP) will be recorded. SBP values of > 260 mmHg or < 70 mmHg and

DBP > 150 mmHg or < 40 mmHg will be automatically eliminated. Daytime hypertension is defined as daytime SBP > 135 mmHg and/or DBP > 85 mmHg, and night-time hypertension as SBP > 120 mmHg and/or DBP > 70 mmHg.

Clinical BPs (SBP and DBP) will be measured by mercury sphygmomanometer on three occasions in line with the European Society of Hypertension–European Society of Cardiology and American College of Cardiology/ American Heart Association guidelines (9, 44). Mean arterial BP (MABP) will be calculated as DBP + 1/3(SBP-DBP).

Each recording will be validated only if the following quality criteria are met: cuff size adapted to the diameter of the arm, calibration of the device, full 24 hours' duration of recording comprising at least 48 valid measures and no more than two missing time slots.

Catecholamine measurements

24h urine samples will be collected, acidified with acetic acid and stored at -20°C until analysis. Catecholamines (epinephrine, norepinephrine, and dopamine) will be measured in one millilitre of urine by high-performance liquid chromatography with electrochemical detection (Coularray Detector, ESA Dionex, Chelmsford, USA).

Polysomnography

Full night polysomnography will be performed at our sleep laboratory. The following physiological variables will be monitored: electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), electrocardiography (ECG), oral and nasal airflows, chest and abdominal respiratory effort through inductance plethysmography, snoring, body position, oxyhemoglobin saturation by pulse oximetry and heart rate. Continuous recordings will be taken with electrode positions C3/A2-C4/A1-Cz/01 of the international 10–20 Electrode Placement System, along with eye movements, chin electromyogram and ECG with a modified V2 lead. Airflow will be measured with nasal pressure prongs together with the sum of oral and nasal thermistor signals. Respiratory effort will be monitored using abdominal and thoracic bands. Oxygen saturation will be measured using a pulse oximeter. Respiratory events will be classified according to the American Academy of Sleep Medicine's guidelines (45). An apnea is defined as the complete cessation of airflow for at least 10 seconds and hypopnea as a reduction of at least 30% in the nasal pressure signal associated

with either oxygen desaturation of ≥3% or an EEG arousal from sleep, both lasting for at least 10 seconds. Apneas will be classified as obstructive, central or mixed according to the presence or absence of respiratory effort. The classification of hypopneas as obstructive or central will be based on the thoraco-abdominal band signal and the shape of the nasal respiratory pressure curve (flow limited aspect or not). The AHI is defined as the number of apneas and hypopneas per hour of sleep. Sleep will be scored manually according to AASM criteria (45).

Procedures

At the baseline visit, MSNA, ABPM, calf blood flow, HRV and catecholamines will be measured. Then, during a one week titration phase optimal CPAP pressure will be obtained over eight nights at home using an auto CPAP device (RESMED^{TM}) to obtain a fixed CPAP pressure value. The optimal pressure (95th percentile) will be determined by one expert researcher, based on visual evaluation of the raw data recordings from nights with no significant leaks. A minimum of continuous pressure use for 4 hours per night will be required. The pressure determined during the titration nights will be used as the therapeutic pressure in the fixed CPAP mode, whereas in APAP the pressure level will be adjusted between a minimal pressure of 6 cmH_2O and a maximum of 16 cmH_2O. After the titration phase, patients will be randomized to treatment with either APAP or fixed CPAP. Finally, following one month of treatment, MSNA, ABPM, calf blood flow, HRV and catecholamines will be measured for comparison with baseline. Figure 2 shows the study schema.

Statistical considerations

Sample size

We powered the study based on the MSNA outcome. To date no previous study has compared these two PAP modalities using MSNA as primary outcome. Since there are no reliable MSNA data available, we hypothesized the impact of CPAP to be 8±5 bursts/min in the fixed CPAP group and 5±5 bursts/min in the APAP group. Assuming an alpha error of 5%, a statistical power of 80%, in unilateral situation, 34 patients per arm will need to be enrolled in the study.

In a group sequential design, firstly an interim analysis will be performed on data from the first 24 patients (12 per arm) with a nominal p value of 0.0081 required to demonstrate a significant difference between groups. If at the interim analysis, the observed p value for the primary outcome is greater than the nominal p value inclusions will continue until the final sample of 68 patients is reached. Conversely, if significance is observed, the patient inclusion can stop and no further inclusions will be needed.

Randomization

After titration of fixed CPAP (lasting 8 nights), patients will be randomized to either fixed CPAP or APAP treatment. Randomization will be conducted by a statistician independent of the study using a computer-generated random numbers list (6 patients per block). This list will be transmitted to one of the investigators who will be responsible for installation of the device but not for the follow-up and evaluation of the patients. All other investigators, patients and outcome assessment technicians will be masked to the patient's group.

Statistical methodology and analyses

The analysis will be done following the Intention to treat method. Continuous variables will be expressed as median (25th/75th percentiles) or mean (SD), while categorical variables will be reported as absolute numbers and percentages for both groups. Baseline comparisons between groups will be made using a Student test or Mann-Whitney test, depending on validation of normal distribution. For discrete variables, a Chi-square test will be used. Normality will be assessed using the Shapiro-Wilk test. If significant differences are observed between arms, a multivariable regression will be performed.In case of missing data, an imputation strategy will be applied according to the percentage of missing values. If less than 5% of missing value are observed, simple imputation will be performed, based on the median for quantitative variables or on the most frequent values for qualitative variables. If the proportion of missing values is between 5 and 20%, multiple imputations will be performed.

Data management and statistical analyses will be performed using SAS® (version 9.4, SAS Institute, Cary, NC, USA).

Ethics

The current study will be conducted in accordance with the Declaration of Helsinki and the recommendations for Good Clinical Practice. The protocol was approved by the French Regional Ethics Committee (Comite de Protection des Personnes Sud Est V N^{o} IRB: 0006705 on 19 February 2018). Written informed consent will be signed by all study participants before enrollment in the study. Patients have the right to withdraw from the study without incurring any prejudice at any time. The protocol is registered on the ClinicalTrials.gov website (NCT03428516).

Patient and Public Involvement

Patients, collaborators and sponsors were not directly involved in the design, recruitment and conduction of the study. Dissemination plans of the results include presentations at conferences and publication in peer-reviewed journals. Updates of the randomized trial will be available at ClinicalTrials.com. All patients will be informed that the dissemination of results will be accessible on request.

Sponsor and funding

The sponsor of the study is Grenoble Alpes University Hospital, France. The principal investigator is Renaud Tamisier. Erika Treptow is supported by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES) – Brazil. ResMed, "*Agir pour les maladies chroniques"* and the French National Research Agency in the framework of the "Investissements d'avenir" program (ANR-15-IDEX-02) will provide unrestricted funding. The collaborators and sponsors were not involved in the design of the study and will not influence the execution, analysis and publication of results.

Discussion

CPAP remains the first-line therapy for OSA patients. In order to determine the optimal pressure that will maintain airway patency during sleep, a titration made during full night polysomnography is required. However, this is costly, demands technical expertise and may result in a delay in the initiation of treatment. Furthermore, night-time AHI can be variable, depending on position, sleep architecture, overnight rostral fluid shifts and alcohol intake, which may influence the determination of the optimal effective pressure if performed during only one night (46, 47). Therefore, over the last few years there has been an exponential increase of the use of APAP for automatic titration prior to long-term treatment at home. This simplified procedure is associated with comparable outcomes (48) and a significant cost reduction (49).

Currently, in many countries especially in Europe, APAP is by far the most commonly used device for OSA treatment and gives a slight increase in PAP adherence (50). However, the increase in APAP use is accompanied by unresolved scientific questions: is APAP as effective as fixed CPAP in reducing cardiovascular risk? Is it safe to use APAP in patients with comorbidities? Do APAP and CPAP have the same efficacy in normalizing sleep in patients with OSA? The proposed study will focus on the cardiovascular response to these different PAP modalities. To achieve this, we shall use complementary reference tools to evaluate sympathetic activity in patients using fixed CPAP or APAP. Vascular and cardiac sympathetic activity will be explored in addition to circulating catecholamine levels.

Since its first description in 1967 (51) vascular sympathetic activity measured by microneurography has provided insights into our understanding of the pathophysiology of hypertension, cardiac failure and sleep apnea (16, 52). This method allows the recording of impulses in peripheral nerves and is the gold standard for measurement of vascular sympathetic activity. When applied by experienced professionals, MSNA is reproducible and allows evaluation between subjects before and after an intervention, with minor risks and side effects (43, 53). It has been demonstrated that intermittent hypoxia is a major contributor to inducing sympathetic activation in healthy humans and patients with OSA (13, 17, 54) and that treatment with CPAP lowers MSNA (55). One of the strengths of the present study is that, in addition to MSNA, we will measure heart rate variability and urinary catecholamines to assess cardiac and whole body sympathetic activity respectively.

Moreover, we will provide a better understanding of BP responses under the two PAP therapies and possibly identify the type of patients who would benefit the most from APAP.

Conclusions

The sympathetic APAP-CPAP protocol is key randomized controlled trial that will assess, for the first time, different PAP modalities that might differ in terms of the decrease in sympathetic activity they induce in patients with OSA. The results of the APAP-CPAP study should provide further clarification as to the cardiovascular benefits of an effective treatment for patients with OSA. In addition, the findings might have important implications for individualized therapeutic strategies by identifying the best phenotypes to be treated by a given PAP therapy.

Author contributions

ET participated in the design of the study, wrote the article based on the study protocol, will include patients, and collect and analyze data into the protocol.

JLP and PL designed the study, wrote the study protocol, critically revised the manuscript and will include patients into the protocol.

SB participated in the design of the protocol, established the statistical analysis plan, and calculated the sample size.

CB revised the manuscript and will include patients into the protocol.

MD revised the manuscript and will include patients into the protocol.

HW participated in the design of the study and critically revised the manuscript.

RT designed the study, wrote the study protocol and article, critically revised the manuscript and will include patients, and collect and analyze data.

The submitted manuscript has been approved by all authors.

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Competing interests

R Tamisier reports travel grants from Agiradom (a Home Healthcare provider) and research grants from Resmed.

Ethics approval

The protocol was approved by the French Regional Ethics Committee (*Comite de Protection des Personnes Sud Est V*) on 19 February 2018 and is registered on ClinicalTrials.gov (NCT03428516).

Patient consent

Written informed consent will be signed by all study participants before enrollment in the study (see supplement materials).

Tables

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients aged 18 to 80 years	Pregnancy
OSA (AHI ≥20 events/ h)	Person deprived of liberty or subject to a legal protection measure.
Daytime sleepiness	Patient with heart failure
Naive of any pressure treatment for OSA	Patient with central sleep apnea index above 20% of AHI
Able to provide written informed consent	Patient with unstable comorbidities that could influence the results
Not a vulnerable person or legally protected adult	

OSA, obstructive sleep apnea; AHI, apnea hypopnea index

Table 2. Literature on the impact of CPAP versus APAP on BP

Author (ref.)	Year	Sample Size	Study design	Duration	Intervention	Findings
Bloch KE (37)	2017	208	Randomized, parallel	2 years	APAP (5-15 cmH_2O) vs CPAP (90^{th} percentile during titration)	Reduction in MBP, SBP and DBP by 3-4 mmHg (ITT) and 4-6 mmHg (PPT), similar in APAP x CPAP *
Pépin JL (35)	2016	322	Randomized, parallel	4 months	APAP (minimal interval of 5 cmH_2O) vs CPAP (95^{th} percentile during titration)	CPAP was more effective in reducing 24h DBP than APAP * †
Marrone O (38)	2011	17	Randomized, parallel	2 months	APAP (5-18 cmH_2O) vs CPAP (fixed pressure determined during titration)	Treatment reduced SBP during sleep and DBP during both sleep and wakefulness. Similar reductions in BP were demonstrated in both groups *
Patruno V (36)	2007	31	Randomized, parallel	3 months	APAP (4-15 cmH_2O) vs CPAP (fixed pressure determined during titration)	Significant reduction in SBP (from 144 ± 10 to 132 ± 8 mm Hg; $p < 0.001$) and DBP (from 88 ± 4 to 79± 6 mmHg; $p < 0.001$) in the CPAP group but not in the APAP group (SBP, 142 ± 12 to 136 ± 6 mm Hg; DBP, 87.5 ± 4 to 86 ± 4 mm Hg) †
West SD (39)	2006	98	Randomized, parallel	6 months	APAP vs APAP for 1 week and then CPAP (95^{th} percentile during titration)or CPAP (determined by an algorithm)	No difference between groups in MBP *

CPAP, continuous positive pressure; APAP, auto-adjusting continuous positive pressure; BP, blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ITT, intention-to-treat analysis; PPT, per protocol analysis.
* Ambulatory Blood Pressure Monitoring (24h) † Office blood pressure measurements.

Figure legend

Figure 1. Settings, acquisition, recording and reporting of muscle sympathetic nerve activity (MSNA)**.** Measurement of MSNA is obtained by placement of an un-insulated tungsten register electrode in the peroneal nerve in the popliteal fossae or close to the fibula head. The objective is to reach post ganglionic efferent sympathetic neurons. Potential voltage signal is recorded between the nerve electrode and a reference electrode placed on the external side of the knee. The acquired electrical signal is then amplified, band-filtered (700 to 2000 Hz), rectified and integrated. Sympathetic burst, which correspond to nerve firing, are detected and scored using an automatic software in order to minimize subjective interpretation of the signal MSNA results may be expressed in number of bursts per min or per 100 heart beats, Burst/min and bursts/100 hb respectively or using the sum of areas under the curve of all burst in arbitrary integration units per minute or per 100 heart beats, AUI/min and AUI/100 hb respectively.

Figure 2. Study protocol

MSNA, Muscle Sympathetic Nerve Activity; HRV, heart rate variability; CPAP, fixed continuous positive pressure; APAP, auto-adjusting continuous positive pressure.

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Supplementary file

Patient consent forms: French and English versions.

Supplementary material – Consent form (original French version)

FORMULAIRE DE CONSENTEMENT ECLAIRÉ

Diminution du tonus sympathique chez les patients avec une apnée obstructive du sommeil: La CPP fixe est-elle plus efficace que la CPP auto ajusté?

Titre court : APAP CPAP

Promoteur de l'étude : CHU de Grenoble – DRCI (Direction de la Recherche Clinique et Innovation) : CHU de Grenoble, CS 10217, 38043 Grenoble Cedex 09 - Tel : 04 76 76 56 09 Fax : 04 76 76 52 21

Investigateur principaL : Pr. Renaud Tamisier

Investigateurs du CHU de Grenoble participant à cette étude :

Pr Jean-Louis Pépin, Pr Renaud Tamisier, Pr Patrick Levy, Dr Marie Destors, Dr Erika Treptow, Dr. Holger Whorle: Physiologie Sommeil et Exercice - Pôle Locomotion Rééducation et Physiologie; Dr Cecile Bosc : Centre Santé et Sommeil.

Le Dr ……..m'a proposé de participer à l'étude APAP CPAP. Il m'a expliqué en détail les objectifs et le déroulement de celle-ci, ainsi que les bénéfices, les risques et les contraintes.

Une notice d'information m'a été remise et j'ai eu suffisamment de temps pour la lire et prendre la décision d'accepter ou non de participer à l'étude. J'ai pu poser toutes les questions que je souhaitais et j'ai obtenu des réponses satisfaisantes. J'ai bien compris que ma participation à l'étude est volontaire et que je peux à tout moment retirer mon consentement, quelles que soient mes raisons, sans engager ma responsabilité et sans que cela modifie la qualité des soins qui me seront donnés, ni l'attention de mon médecin.

J'ai bien pris connaissance que cette recherche sera conduite en conformité avec le Code de la Santé Publique.

J'ai eu l'assurance que les décisions qui s'imposent pour ma santé seront prises à tout moment, conformément à l'état actuel des connaissances médicales.

J'ai compris que je ne dois pas participer à une autre recherche en même temps que celle-ci.

En cours d'étude, tout élément nouveau me concernant et pouvant modifier mon consentement me sera communiqué.

J'accepte que les données de mon dossier médical qui se rapportent à l'étude soient accessibles aux responsables de l'étude et aux représentants des autorités de santé. A l'exception de ces personnes, qui traiteront les informations dans le plus strict respect du secret médical, mon anonymat sera préservé.

J'ai pris connaissance que cette recherche a reçu l'avis favorable du Comité de Protection des Personnes et l'autorisation de l'ANSM le.

Le promoteur de la recherche (CHU de Grenoble) a souscrit une assurance de responsabilité civile en cas de préjudice auprès de la société.

J'accepte que les données enregistrées à l'occasion de cette étude fassent l'objet d'un traitement informatisé par le service de Physiologie Sommeil et Exercice du CHU de Grenoble, responsable de l'analyse statistique. Je peux accéder, directement ou par l'intermédiaire d'un médecin de mon choix, à l'ensemble de mes données médicales. Mon droit d'accès, de rectification et d'opposition prévu par la loi " informatique et libertés "

s'exerce à tout moment, auprès du médecin en charge de la recherche.

Mon acceptation de participer à l'étude ne dégage pas les médecins et les organisateurs de l'étude de leur responsabilité. Je conserve tous mes droits garantis par la loi.

J'ai reçu une copie du présent document et j'ai été informé qu'une copie serait également conservée par l'investigateur et le promoteur dans des conditions garantissant la confidentialité et j'y consens.

Je certifie avoir lu ce document ainsi que la notice d'information et accepte de participer, librement, à cette recherche, dans les conditions qui m'ont été précisées.

En cas d'événements indésirables ou de problèmes, ou si j'ai d'autres questions au cours de ma participation, je pourrai contacter le médecin en charge de la recherche au numéro de téléphone suivant : ……

Nom / Prénom du patient :	Nom du médecin :
……..	……..
……..	……..
Date : ……./……./…….	Date : ……./……./…….
Signature du patient :	Signature du médecin :

1

Supplementary material – Consent form (English version)

Reduction of Sympathetic tone in OSA patients:

Is CPAP more effective than APAP? – a randomized, parallel clinical trial protocol

Short title : APAP-CPAP

Study Sponsor: CHU de Grenoble – DRCI (Direction de la Recherche Clinique et Innovation) : CHU de Grenoble, CS 10217, 38043 Grenoble Cedex 09 - Tel : 04 76 76 56 09 Fax : 04 76 76 52 21

Principal investigator: Renaud Tamisier

Members of Grenoble Alpes University Hospital participating in this study :

Pr Jean-Louis Pépin, Pr Renaud Tamisier, Pr Patrick Levy, Dr Marie Destors, Dr Erika Treptow, Dr. Holger Whorle: Physiologie Sommeil et Exercice - Pôle Locomotion Rééducation et Physiologie (Physiology, Sleep and Exercise – Centre for locomotion, Reeducation and Physiology); Dr Cecile Bosc: Centre Santé et Sommeil (Health and Sleep Center).

Dr. .....has proposed that I participate in the study APAP-CPAP study. I have received detailed explanations about the objectives and procedures of the study, as well as its benefits, risks and constraints.

I have received an information sheet and I've had enough time to read it and to make the decision to participate, or not, in the study. I've had the opportunity to ask all my questions and I've received satisfactory answers. I understood that my participation in the study is voluntary and that I can, at any time, withdraw my consent, whatever my reasons, without incurring any responsibility and without any modification in the treatment received.

I have been informed that this study will be conducted according to the French Code of Public Health, and have been assured that all study procedures will be made in accordance with the current medical recommendations.

I have understood that I should not participate in any other biomedical research protocol

during the period of this study.

During the study, I will be informed of any event concerning my health that could influence my consent.

I accept that the data in my medical file(s) related to the study will be accessible to the study´s collaborators and to representatives of the health authorities. With the exception of these people, who will deal with my data in respect of professional secrecy, my anonymity will be preserved.

I have been informed that this research has been approved by the Regional Biomedical Ethics committee (Comité de protection de Personnes) and authorized by the French National Agency for the Safety of Medicines and Health Products.

The sponsor of the study (Grenoble Alpes University Hospital) has contracted an additional insurance of civil responsibility in case of harms.

I accept that the data concerning me acquired during this study will be registered by the Department of Physiology, Sleep and Exercise of Grenoble Alpes University Hospital, which is responsible for the statistical analysis. I have the right to access, directly or through a physician of my choice, the set of information and medical data concerning me. At any time I will have the right of access and correction of computerized data according to the law on "*informatique et libertés*" through the physician responsible for the research.

My acceptance to participate in the study does not discharge the organizers and investigators of the study from their responsibilities. I retain all my rights guaranteed by law.

I have received a copy of the current consent sheet and I was informed that one copy will be retained by the investigator and another by the sponsor under conditions guaranteeing confidentiality.

I certify that I have read this document as well as the patient information sheet and I freely accept to participate in the study according to the conditions specified.

In case of any undesirable events or problems, or if I have any other questions during my participation of the study, I may contact the physician responsible for the research through the telephone number +33 (0)4 76765516.

Surname / First Name of participant : Surname of investigating physician in :

1	……..	……
2	……..	……
3	Date : ……./……./…….	Date : ……./……./…….
4	Participant´s signature :	Physician´s signature :
5		
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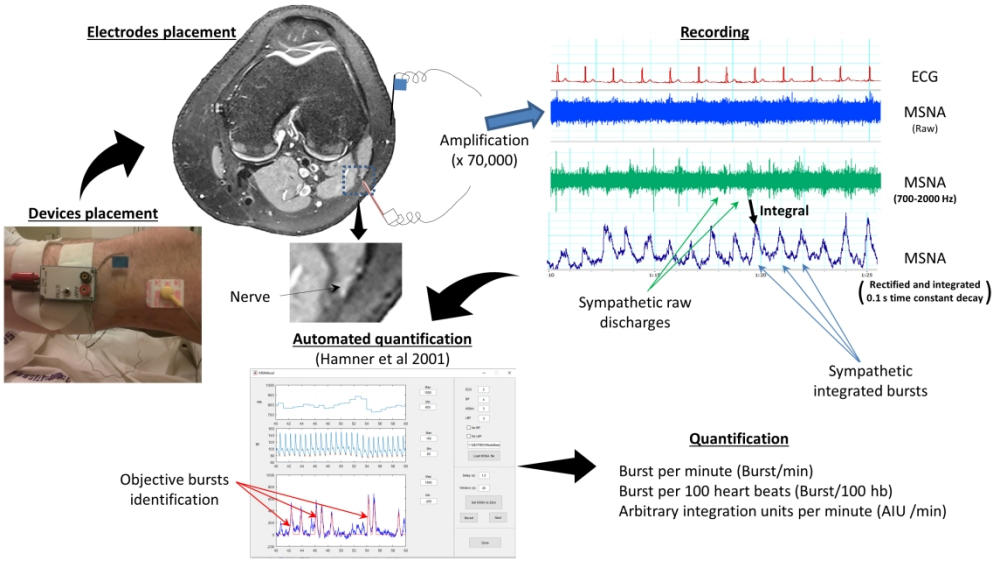

Figure 1. Settings, acquisition, recording and reporting of muscle sympathetic nerve activity (MSNA). Measurement of MSNA is obtained by placement of an un-insulated tungsten register electrode in the peroneal nerve in the popliteal fossae or close to the fibula head. The objective is to reach post ganglionic efferent sympathetic neurons. Potential voltage signal is recorded between the nerve electrode and a reference electrode placed on the external side of the knee. The acquired electrical signal is then amplified, band-filtered (700 to 2000 Hz), rectified and integrated. Sympathetic burst, which correspond to nerve firing, are detected and scored using an automatic software in order to minimize subjective interpretation of the signal MSNA results may be expressed in number of bursts per min or per 100 heart beats, Burst/min and bursts/100 hb respectively or using the sum of areas under the curve of all burst in arbitrary integration units per minute or per 100 heart beats, AUI/min and AUI/100 hb respectively.

254x142mm (300 x 300 DPI)

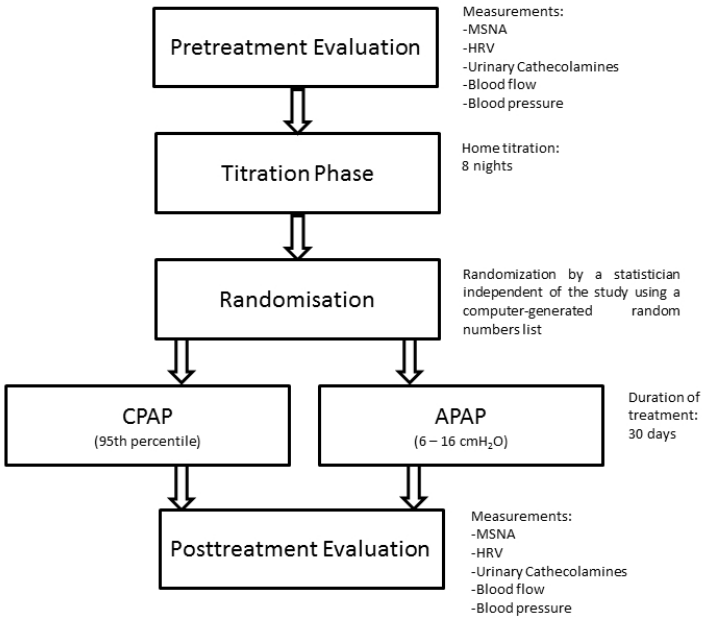

Figure 2. Study protocolMSNA, Muscle Sympathetic Nerve Activity; HRV, heart rate variability; CPAP, fixed continuous positive pressure; APAP, auto-adjusting continuous positive pressure.

254x190mm (96 x 96 DPI)

BMJ Open

Reduction in sympathetic tone in Obstructive sleep apnea patients: is fixed CPAP more effective than APAP? – a randomized, parallel trial protocol

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diagnostics, Respiratory medicine
Keywords:	obstructive sleep apnea, Hypertension < CARDIOLOGY, continous positive airway pressure, SLEEP MEDICINE, sympathetic activity

Reduction in sympathetic tone in Obstructive sleep apnea patients: is fixed CPAP more effective than APAP? – a randomized, parallel trial protocol

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Word count: 3104

Number of figures and tables: 2 figure and 2 tables

Abbreviations:

ABPM: ambulatory BP monitoring

AHI: apnea and hypopnea index

APAP: auto-adjusting continuous pressure

BP: blood pressure

CPAP: continuous positive airway pressure

DBP: diastolic blood pressure

ECG: electrocardiography

EEG: electroencephalography

EMG: electromyography

EOG: electrooculography

HRV: heart rate variability

ITT: intention-to-treat analysis

MBP: mean blood pressure

MSNA: muscle sympathetic nerve activity

OSA: obstructive sleep apnea

PPT: per protocol analysis

SBP: systolic blood pressure

Abstract (Word count: 299)

Introduction: Obstructive sleep apnea (OSA) is a prevalent disease associated with cardiovascular events. Hypertension is one of the major intermediary mechanisms leading to long-term cardiovascular adverse events. Intermittent hypoxia and hypercapnia associated with nocturnal respiratory events stimulate chemo-reflexes, resulting in sympathetic over-activity and blood pressure (BP) elevation. Continuous positive airway pressure (CPAP) is the primary treatment for OSA and induces a small but significant reduction in BP. The use of auto-adjusting continuous pressure (APAP) has increased in the last years and studies showed different ranges of BP reduction when comparing both modalities. However, the pathophysiological mechanisms implicated are not fully elucidated. Variations in pressure through the night inherent to APAP may induce persistent respiratory efforts and sleep fragmentation that might impair sympatho-vagal balance during sleep and result in smaller decreases in BP. Therefore, this double blind randomized controlled trial aims to compare muscle sympathetic nerve activity (MSNA) assessed by microneurography (reference method for measuring sympathetic activity) after one month of APAP versus fixed CPAP in treatment-naive OSA patients.

Methods and analysis: adult subjects with newly diagnosed OSA (apnea hypopnea index > 20/h) will be randomized for treatment with APAP or fixed CPAP. Measurements of sympathetic activity by MSNA, heart rate variability and catecholamines will be obtained at baseline and after 30 days. The primary composite outcome will be the change in sympathetic tone measured by MSNA in bursts/min and bursts/100 heart beats. Sample size calculation was performed with bilateral assumption. We will use the t-Student test to compare changes of sympathetic tone between groups.

Ethics and dissemination: The protocol was approved by The French Regional Ethics Committee and registered on ClinicalTrials.gov (NCT03428516). The study started in March 2018 with primary completion expected to March 2019. Dissemination plans of the results include presentations at conferences and publication in peer-reviewed journals.

Trial registration number: NCT03428516

Keywords: obstructive sleep apnea, hypertension, continuous positive airway pressure, sleep medicine, sympathetic activity.

Strengths and limitations of the study:

- The analysis of vascular and cardiac sympathetic activity will be evaluated by complementary methods: microneurography of the peroneal nerve (the gold standard method), heart rate variability (HRV) and urinary catecholamines.
- The use of24h ambulatory blood pressure (BP) monitoring is more sensitive when assessing therapeutic interventions than office BP and provides prognostic guidance.
- A statistician not involved in the data collection will randomly allocate subjects to one of the two positive airway pressure (PAP) modalities. All other investigators, patients and assessment technicians will be blinded to the patient´s group.
- The same make and model of CPAP device will be used both in Fixed and APAP modes.
- The duration of exposure to treatment of one month is ample but might under-represent the chronic effects of PAP therapies on sympathetic activity.

Introduction

Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity and mortality (1-6). Hypertension is the main intermediary mechanism implicated in cardiovascular risk (7-9). There is a dose-response relationship between indices of OSA severity and hypertension (10, 11). Accordingly, one of the most common objectives when treating OSA is blood pressure (BP) reduction in order to prevent or reduce long-term cardiovascular adverse events.

OSA is characterized by partial (hypopnea) or complete (apnea) upper airway collapses during sleep (12). Sympathetic activation is the main intermediary mechanism for BP elevation in OSA patients (11, 13). The repetitive occurrence of respiratory events leading to intermittent hypoxia and hypercapnia results in stimulation of central and peripheral chemoreflexes enhancing sympathetic activity and, subsequently increasing vascular tone and promoting blood pressure elevation (14). Chronic sympathetic activation induces vascular remodeling and, frequently, uncontrolled or resistant hypertension(15). In OSA patients, nighttime sympathetic over-activation is associated with the non-dipping pattern of BP and the high sympathetic tone persists during wakefulness (16). In the early course of the disease, even non-hypertensive subjects exhibit increased BP and muscle sympathetic nerve activity in response to chronic intermittent hypoxia (13, 17). Muscle sympathetic nerve activity (MSNA) is one of the reference methods for measuring sympathetic activity and understanding the pathophysiology of neurogenic hypertension (18). Moreover, MSNA changes across time or after intervention are corresponding with arterial blood pressure changes in prehypertension (19).

In different models of hypertension only intermittent hypoxia, which is the main stimuli in OSA, causes neurogenesis modulation in hippocampus (20). In human, intermittent hypoxic exposure induces after 2 and 4 weeks an increase in daytime MSNA (13, 17). This increase in sympathetic tone was suggested in the early 90ies as a mechanism of hypertension in OSA (16, 21). Therefore, MSNA measurement is of particular interest in showing the effect of OSA treatment as a surrogate marker of cardiovascular outcomes. Although several studies have demonstrated the beneficial effects of OSA treatment by continuous positive airway pressure (CPAP) in sympathetic activation (14, 22-24), this

measurement has never been evaluated in patients under Auto-adjusting continuous pressure (APAP). MSNA consists of a technique of microneurography minimally invasive that measures the sympathetic nerve activity of the peroneal nerve.

CPAP remains the gold standard therapeutic option for the treatment of moderate and severe OSA. Several systematic reviews and meta-analyses (25-31) have demonstrated limited but significant improvements in BP (a reduction of about 2 mmHg in 24-h mean BP). Better results are achieved in specific phenotypes with more severe OSA, higher BP at baseline and adherent to PAP therapies (use of CPAP ≥ 4 hours/night)(26, 32-34).

APAP changes the pressure delivered throughout the night depending on events detected, with the goal of applying the minimal effective pressure (35-38) thus reducing side effects and improving adherence. The average overnight applied pressure is significantly lower with APAP for the same range of improvement in the apnea-hypopnea index (AHI) (39). However, the continuous variations in pressure associated with the functioning of APAP devices potentially induce micro-arousals, and change sleep macrostructure in some patients (38, 40, 41). This might limit the decrease in sympathetic activity during the night when treating OSA and consequently result in a smaller reduction of BP.

Studies have demonstrated controversial results on the impact of the two pressure modalities (fixed versus auto-adjusting) on blood pressure reduction (table 1). Although some authors reported superiority with fixed pressure (42, 43)other clinical trials reported no significant difference between APAP and CPAP (44-46). A recent study that evaluated 208 patients with a longer than usual follow up of 2 years demonstrated comparable reductions in sleepiness and blood pressure with similar OSA-related costs for both treatments (44). Karasulu *et al*(47)and Patruno *et al*(48) have demonstrated lower reduction in cardiac sympathetic activity using heart rate variability (HRV) in OSA patients and obese OSA patients during APAP treatment compared with fixed CPAP. However, neither study was randomized and Patruno evaluated only a specific population of obese patients with severe OSA, which limits the generalizability of the results. In a small study of adult males, without antihypertensive treatment, Marrone *et al*(41),evaluated BP changes after treatment with APAP versus CPAP. As a secondary outcome, they reported sympathetic activity by measurement of catecholamines. Norepinephrine decreased significantly after treatment in

the APAP group but not in the CPAP group and normetanephrine decreased significantly in both groups. Overall, there is a lack of well-designed studies evaluating the mechanisms underlying specific BP responses under APAP versus fixed CPAP. In this context, the aim of the present study is to compare vascular sympathetic tone after one month of treatment with fixed versus auto-adjusting pressure by microneurography in newly diagnosed OSA patients.

Methods and analysis

Study design

This study is a prospective, single-site, randomized, double-blind, parallel, one month-controlled trial.

Objectives

Primary research objective

The main objective is to compare change in vascular sympathetic tone measured by Muscle Sympathetic Nerve Activity (MSNA) microneurography after one month of APAP versus after one month of fixed CPAP in treatment-naive moderate to severe OSA patients.

The primary composite outcome will be the change in sympathetic tone measured by MSNA in bursts/min and bursts/100heart beats between baseline and after one month of treatment.

Secondary research objectives

The secondary objectives will be to compare the following variables before and after treatment:

- Ambulatory BP monitoring (24h ABPM): mean blood pressure (MBP),systolic blood pressure(SBP) and diastolic blood pressure DBP, during 24h periods as well as daytime and night-time measurements.

- Urinary catecholamines (24h collection): epinephrine, norepinephrine, and dopamine.

- Heart Rate Variability as an indicator of cardiac sympathovagal balance.

Population

Consecutive adult outpatients attending a tertiary hospital sleep center (*Grenoble Alpes University Hospital* – France),with an established diagnosis of obstructive sleep apnea by full-night polysomnography (apnea-hypopnea index > 20/hour), daytime sleepiness (Epworth Sleepiness Scale > 10) (49) and willing to receive positive airway pressure treatment, will be invited to participate in the study. The inclusion and exclusion criteria are presented in table 2. Written informed consent will be obtained from all participants by a sleep physician study investigator (supplementary file).

Materials

Muscle Sympathetic Nerve Activity (MSNA)

We will obtain MSNA from nerve recordings using standard tungsten microelectrodes inserted into the peroneal nerve into the popliteal area, after localization by electric surface stimulation (Figure 1). Signals will be filtered (700-2000 Hz), amplified (x 70,000) and full-wave rectified. The rectified signal will be integrated (0.1 second moving window) for display and for recording (Nerve Traffic Analyzer, Model 662c-3, University of Iowa, Bioengineering Dept., Iowa City, IA). Electrode position in muscle fascicles will be confirmed by pulse synchronous bursts of activity occurring 1.2-1.4 s after the ECG QRS complex, reproducible activation during the second phase of the Valsalva maneuver, elicitation of afferent nerve activity by mild muscle stretching and the absence of response to startle. Doppler popliteal vascular flows (DWL500EZ) will be measured during time periods concomitant from measurement of MSNA, HR (3-lead ECG) and arterial blood pressure. Beat-by-beat arterial BP for vascular doppler leg resistance calculations will be measured using the CNAP® system the same time period. All these signals will be digitalized and recorded for off-line analysis on Powerlab system. These measurements will be performed before and after PAP therapy on morning sessions, fasten since 12 AM from foods and any beverage except water, during room air breathing. We will average nerve activity, heart rate and arterial BP over 5-minute windows of data collection at baseline and post-PAP therapy. Sympathetic bursts will be identified using a specific algorithm described by Hamner and colleagues (50) using Matlab software (The Mathworks Inc., Natick, MA USA). For purposes of quantification MSNA will be

reported in at least five minutes periods and expressed as burst frequency (bursts/min and bursts/100 heart beats).

Blood flow

Popliteal blood velocity will be recorded using a 4-MHz Doppler probe (Multidop T2, DWL) at the popliteal fossa of the contralateral leg to the sympathetic nerve recording.

Several parameters will be extracted from the above measurements: sympathetic vascular tone, blood pressure and blood flow. Furthermore, we shall calculate vascular resistance and vascular sympathetic tone and blood pressure gains, as previously described (14, 51).

Blood Pressure

Ambulatory blood pressure monitoring (ABPM) will be measured in the dominant arm over 24 hours at 15 min intervals during daytime and every 30 minutes nighttime (ABP monitor 90207, Spacelabs Healthcare, Issaquah WA). Blood pressure acquisition began at a morning session and ended 24 hours later. The following ABPM parameters will be studied: mean SBP, mean DBP and mean HR over 24 hours, the same mean values during the daytime (7.00 am to 10.00 pm) and at night-time (10.00 pm to 7.00 am). The normal night-time physiological dipping BP is expected to be > 10%. The summary values in the ABPM report for each patient will be used in the data analysis. This is an average by subject and by recording session (at baseline and 1 month). Data relating to the average daytime and night-time systolic BP (SBP), diastolic BP (DBP), and mean BP (MBP) will be recorded. SBP values of > 260 mmHg or < 70 mmHg and DBP > 150 mmHg or < 40 mmHg will be automatically eliminated. Daytime hypertension is defined as daytime SBP > 135 mmHg and/or DBP > 85 mmHg, and night-time hypertension as SBP > 120 mmHg and/or DBP > 70 mmHg (52).

Clinical BPs (SBP and DBP) will be measured by mercury sphygmomanometer on three occasions in line with the European Society of Hypertension–European Society of Cardiology and American College of Cardiology/ American Heart Association guidelines(9, 53). Mean arterial BP (MABP) will be calculated as DBP + 1/3(SBP-DBP).

Each recording will be validated only if the following quality criteria are met: cuff size adapted to the diameter of the arm, calibration of the device, full 24 hours' duration of recording comprising at least 48 valid measures and no more than two missing time slots.

Catecholamine measurements

24h urine samples will be collected, acidified with acetic acid and stored at -20°C until analysis. Catecholamines (epinephrine, norepinephrine, and dopamine) will be measured in one millilitre of urine by high-performance liquid chromatography with electrochemical detection (Coularray Detector, ESA Dionex, Chelmsford, USA).

Polysomnography

Full night polysomnography will be performed at our sleep laboratory. The following physiological variables will be monitored: electroencephalography (EEG), electrooculography (EOG),electromyography (EMG), electrocardiography (ECG), oral and nasal airflows, chest and abdominal respiratory effort through inductance plethysmography, snoring, body position, oxyhemoglobin saturation by pulse oximetry and heart rate. Continuous recordings will be taken with electrode positions C3/A2-C4/A1-Cz/01 of the international 10–20 Electrode Placement System, along with eye movements, chin electromyogram and ECG with a modified V2 lead. Airflow will be measured with nasal pressure prongs together with the sum of oral and nasal thermistor signals. Respiratory effort will be monitored using abdominal and thoracic bands. Oxygen saturation will be measured using a pulse oximeter. Respiratory events will be classified according to the American Academy of Sleep Medicine's guidelines (54). An apnea is defined as the complete cessation of airflow for at least 10 seconds and hypopnea as a reduction of at least 30% in the nasal pressure signal associated with either oxygen desaturation of ≥3% or an EEG arousal from sleep, both lasting for at least 10 seconds. Apneas will be classified as obstructive, central or mixed according to the presence or absence of respiratory effort. The classification of hypopneas as obstructive or central will be based on the thoraco-abdominal band signal and the shape of the nasal respiratory pressure curve (flow limited aspect or not). The AHI is defined as the number of apneas and hypopneas per hour of sleep. Sleep will be scored manually according to AASM criteria (54).

Procedures

At the baseline visit, MSNA, ABPM, calf blood flow, HRV and catecholamines will be measured. Then, during a one week titration phase optimal CPAP pressure will be obtained over eight nights at home using an auto CPAP device (RESMED^{TM}) to obtain a fixed CPAP pressure value. The optimal pressure (95th percentile) will be determined by one expert researcher, based on visual evaluation of the raw data recordings from nights with no significant leaks. The pressure determined during the titration nights will be used as the therapeutic pressure in the fixed CPAP mode, whereas in APAP the pressure level will be adjusted between a minimal pressure of 6 cmH_2O and a maximum of 16 cmH_2O. After the titration phase, participants with a minimum usage of 4 hours per night will be randomized to treatment with either APAP or fixed CPAP. During treatment, the healthcare provider of the device (Agiradom) will be responsible for solving potential problems with usage (e.g. mask leaks, side effects). The healthcare provider employees are trained in research good clinical practice, and how to maintain the blindness of allocation to patients and researchers during randomized trials. Finally, following one month of treatment, MSNA, ABPM, calf blood flow, HRV and catecholamines will be measured for comparison with baseline. Figure 2 shows the study schema.

Statistical considerations

Sample size

We powered the study based on the MSNA outcome. To date no previous study has compared these two PAP modalities using MSNA as primary outcome. Since there are no reliable MSNA data available, we hypothesized the impact of CPAP to be 8±5 bursts/min in one arm and 5±5 bursts/min in the other arm with no *a priori* assumption . Assuming an alpha error of 5%, a statistical power of 80%, in bilateral situation, 34 patients per arm will need to be enrolled in the study. In the sample size, we anticipate that 10 % will not meet the criteria of compliance to pressure support after 1 week, and 10% more will drop out before termination of the study.

Because it is a pilot study, we will perform a group sequential design, firstly an interim analysis will be performed on data from the first 24 patients (12 per arm) with a

nominal p value of 0.0081 required to demonstrate a significant difference between groups. If at the interim analysis, the observed p value for the primary outcome is greater than the nominal p value inclusions will continue until the final sample of 68 patients is reached. Conversely, if significance is observed, the patient inclusion would stop and no further inclusions will be needed. This interim analysis will be performed by a blinded statistical which have no regard on the randomization list neither contacts with the investigator nor involvement in the study.

Randomization

After titration of fixed CPAP (lasting 8 nights), participants with a minimum usage of 4 hours per night will be randomized to either fixed CPAP or APAP treatment. Randomization will be conducted by a statistician independent of the study using a computer-generated random numbers list (6 patients per block). Randomization list was provided by the clinical research department of Grenoble Alpes university hospital and the randomization list is held and followed by two independent persons from the study. These persons provide allocation directly to the healthcare provider maintaining blindness of the patient and the investigators.

Statistical methodology and analyses

The analysis will be done following the Intention to treat method. Continuous variables will be expressed as median (25th/75th percentiles) or mean (SD), while categorical variables will be reported as absolute numbers and percentages for both groups. Baseline comparisons between groups will be made using a Student test or Mann-Whitney test, depending on validation of normal distribution. For discrete variables, a Chi-square test will be used. Normality will be assessed using the Shapiro-Wilk test. If significant differences are observed between arms, a multivariable regression will be performed. In case of missing data, an imputation strategy will be applied according to the percentage of missing values. If less than 5% of missing value are observed, simple imputation will be performed, based on the median for quantitative variables or on the most frequent values for qualitative variables. If the proportion of missing values is between 5 and 20%, multiple imputations will be performed by using MCM chains for qualitative variables or full conditional specification for quantitative variables. Variables with more than 20% of missing values will not be taken

into account. The main outcome, difference between one-month and baseline values will be analyzed by using a Student t-test. In case of multivariable analysis, a linear mixed model will be performed by including a random effect for patient.

Data management and statistical analyses will be performed using SAS® (version 9.4, SAS Institute, Cary, NC, USA).

Ethics

The current study will be conducted in accordance with the Declaration of Helsinki and the recommendations for Good Clinical Practice. The protocol was approved by The French Regional Ethics Committee (*Comite de Protection des Personnes Sud Est* V N^{o} IRB: 0006705 on 19 February 2018). Written informed consent (supplemental file) will be signed by all study participants before enrollment in the study. Patients have the right to withdraw from the study without incurring any prejudice at any time. The protocol is registered on the ClinicalTrials.gov website (NCT03428516). The study started in March 2018 with primary completion expected in March 2019.

Patient and Public Involvement

Patients, collaborators and sponsors were not directly involved in the design, recruitment and conduction of the study. Dissemination plans of the results include presentations at conferences and publication in peer-reviewed journals. Updates of the randomized trial will be available at ClinicalTrials.com. All patients will be informed that the dissemination of results will be accessible on request.

Sponsor and funding

The sponsor of the study is Grenoble Alpes University Hospital, France. The principal investigator is Renaud Tamisier. Erika Treptow is supported by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES) – Brazil. ResMed,"*Agir pour les maladies chroniques"* and the French National Research Agency in the framework of the "Investissements d'avenir" program (ANR-15-IDEX-02) will provide unrestricted funding. The

collaborators and sponsors were not involved in the design of the study and will not influence the execution, analysis and publication of results.

Discussion

CPAP remains the first-line therapy for OSA patients. In order to determine the optimal pressure that will maintain airway patency during sleep, a titration made during full night polysomnography is required. However, this is costly, demands technical expertise and may result in a delay in the initiation of treatment. Furthermore, night-time AHI can be variable, depending on position, sleep architecture, overnight rostral fluid shifts and alcohol intake, which may influence the determination of the optimal effective pressure if performed during only one night(55, 56). Therefore, over the last few years there has been an exponential increase of the use of APAP for automatic titration prior to long-term treatment at home. This simplified procedure is associated with comparable outcomes (57) and a significant cost reduction (58).

Currently, in many countries especially in Europe, APAP is by far the most commonly used device for OSA treatment and gives a slight increase in PAP adherence (59). However, the increase in APAP use is accompanied by unresolved scientific questions: is APAP as effective as fixed CPAP in reducing cardiovascular risk? Is it safe to use APAP in patients with comorbidities? Do APAP and CPAP have the same efficacy in normalizing sleep in patients with OSA? The proposed study will focus on the cardiovascular response to these different PAP modalities. To achieve this, we shall use complementary reference tools to evaluate sympathetic activity in patients using fixed CPAP or APAP. Vascular and cardiac sympathetic activity will be explored in addition to circulating catecholamine levels.

Since its first description in 1967 (60) vascular sympathetic activity measured by microneurography has provided insights into our understanding of the pathophysiology of hypertension, cardiac failure and sleep apnea (16, 18, 61). This method allows the recording of impulses in peripheral nerves and is the gold standard for measurement of vascular sympathetic activity. When applied by experienced professionals, MSNA is reproducible and allows evaluation between subjects before and after an intervention, with minor risks and side effects (51, 62). It has been demonstrated that intermittent hypoxia is a major contributor to inducing sympathetic activation in healthy humans and patients with OSA (13, 17, 63) and that treatment with CPAP lowers MSNA (23). One of the strengths of the present

study is that, in addition to MSNA, we will measure heart rate variability and urinary catecholamines to assess cardiac and whole body sympathetic activity respectively.

Moreover, we will provide a better understanding of BP responses under the two PAP therapies and possibly identify the type of patients who would benefit the most from APAP.

The sympathetic APAP-CPAP protocol is key randomized controlled trial that will assess, for the first time, different PAP modalities that might differ in terms of the decrease in sympathetic activity they induce in patients with OSA. The results of the APAP-CPAP study should provide further clarification as to the cardiovascular benefits of an effective treatment for patients with OSA. In addition, the findings might have important implications for individualized therapeutic strategies by identifying the best phenotypes to be treated by a given PAP therapy.

Author contributions

ET participated in the design of the study, wrote the article based on the study protocol, will include patients, collect and analyze data into the protocol.

JLP and PL designed the study, wrote the study protocol, critically revised the manuscript and will include patients into the protocol.

SB participated in the design of the protocol, established the statistical analysis plan, and calculated the sample size.

CB revised the manuscript and will include patients into the protocol.

MD revised the manuscript and will include patients into the protocol.

HW participated in the design of the study and critically revised the manuscript.

RT designed the study, wrote the study protocol and article, critically revised the manuscript and will include patients, and collect and analyze data.

The submitted manuscript has been approved by all authors.

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Competing interests

RTamisier reports travel grants from Agiradom (a Home Healthcare provider) and research grants from Resmed.

Ethics approval

The protocol was approved by the French Regional Ethics Committee (*Comite de Protection des Personnes SudEst V*) on 19 February 2018 and is registered on ClinicalTrials.gov (NCT03428516).

Patient consent

Written informed consent will be signed by all study participants before enrollment in the study (see supplement materials).

Tables

Table 1. Literature on the impact of CPAP versus APAP on BP

Author (ref.)	Year	Sample Size	Study design	Duration	Intervention	Findings
Bloch KE (44)	2017	208	Randomized, parallel	2 years	APAP (5-15 cmH_2O) vs CPAP (90^{th} percentile during titration)	Reduction in MBP, SBP and DBP by 3-4 mmHg (ITT) and 4-6 mmHg (PPT), similar in APAP x CPAP *
Pépin JL (43)	2016	322	Randomized, parallel	4 months	APAP (minimal interval of 5 cmH_2O) vsCPAP (95^{th} percentile during titration)	CPAP was more effective in reducing 24h DBP than APAP * †
Marrone O (45)	2011	17	Randomized, parallel	2 months	APAP (5-18 cmH_2O) vs CPAP (fixed pressure determined during titration)	Treatment reduced SBP during sleep and DBP during both sleep and wakefulness. Similar reductions in BP were demonstrated in both groups *
Patruno V (42)	2007	31	Randomized, parallel	3 months	APAP (4-15 cmH_2O) vs CPAP (fixed pressure determined during titration)	Significant reduction in SBP (from 144 ± 10 to 132 ± 8 mm Hg; $p < 0.001$) and DBP (from 88 ± 4 to 79± 6 mmHg; $p < 0.001$) in the CPAP group but not in the APAP group (SBP, 142 ± 12 to 136 ± 6 mm Hg;DBP, 87.5 ± 4 to 86 ± 4 mm Hg) †
West SD (46)	2006	98	Randomized, parallel	6 months	APAPvs APAP for 1 week and then CPAP (95^{th} percentile during titration)or CPAP (determined by an algorithm)	No difference between groups in MBP *

CPAP, continuous positive pressure; APAP, auto-adjusting continuous positive pressure; BP, blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ITT, intention-to-treat analysis; PPT, per protocol analysis.
*Ambulatory Blood Pressure Monitoring (24h) † Office blood pressure measurements.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients aged 18 to 80 years	Pregnancy
OSA (AHI ≥ 20 events/ h)	Person deprived of liberty or subject to a legal protection measure.
Daytime sleepiness	Patient with heart failure
Naive of any pressure treatment for OSA	Patient with central sleep apnea index above 20% of AHI
Able to provide written informed consent	Patient with unstable comorbidities that could influence the results
Not a vulnerable person or legally protected adult	

OSA, obstructive sleep apnea; AHI, apnea hypopnea index

Figure legend

Figure 1. Settings, acquisition, recording and reporting of muscle sympathetic nerve activity (MSNA)**.** Measurement of MSNA is obtained by placement of an un-insulated tungsten register electrode in the peroneal nerve in the popliteal fossae or close to the fibula head. The objective is to reach post ganglionic efferent sympathetic neurons. Potential voltage signal is recorded between the nerve electrode and a reference electrode placed on the external side of the knee. The acquired electrical signal is then amplified, band-filtered (700 to 2000 Hz), rectified and integrated. Sympathetic burst, which correspond to nerve firing, are detected and scored using an automatic software in order to minimize subjective interpretation of the signal MSNA results may be expressed in number of bursts per min or per 100 heart beats, Burst/min and bursts/100 heart beats respectively or using the sum of areas under the curve of all burst in arbitrary integration units per minute or per 100 heart beats, AUI/min and AUI/100 heart beats respectively.

Figure 2. Study protocol

MSNA, Muscle Sympathetic Nerve Activity; HRV, heart rate variability; CPAP, fixed continuous positive pressure; APAP, auto-adjusting continuous positive pressure.

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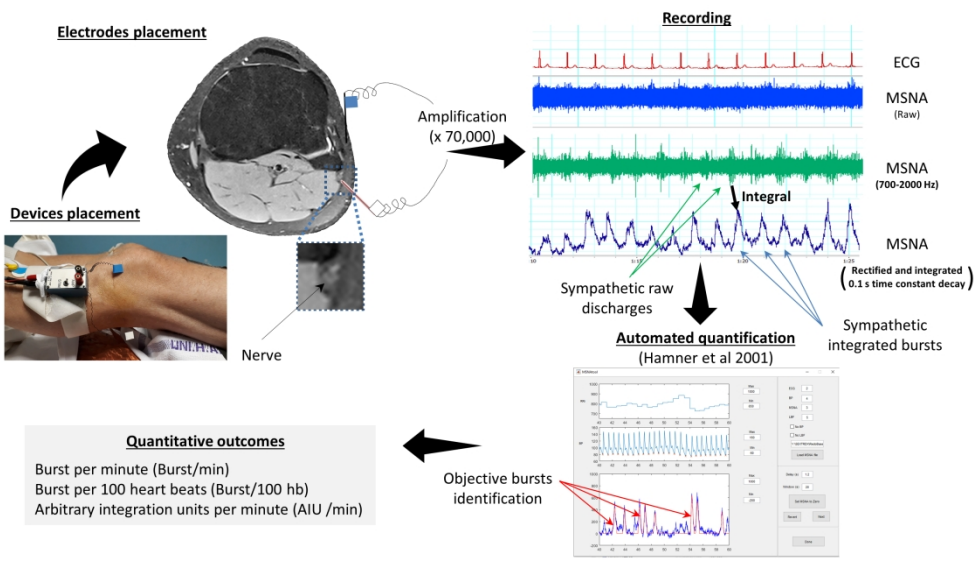

Figure 1. Settings, acquisition, recording and reporting of muscle sympathetic nerve activity (MSNA). Measurement of MSNA is obtained by placement of an un-insulated tungsten register electrode in the peroneal nerve in the popliteal fossae or close to the fibula head. The objective is to reach post ganglionic efferent sympathetic neurons. Potential voltage signal is recorded between the nerve electrode and a reference electrode placed on the external side of the knee. The acquired electrical signal is then amplified, band-filtered (700 to 2000 Hz), rectified and integrated. Sympathetic burst, which correspond to nerve firing, are detected and scored using an automatic software in order to minimize subjective interpretation of the signal MSNA results may be expressed in number of bursts per min or per 100 heart beats, Burst/min and bursts/100 heart beats respectively or using the sum of areas under the curve of all burst in arbitrary integration units per minute or per 100 heart beats, AUI/min and AUI/100 heart beats respectively.

254x142mm (300 x 300 DPI)

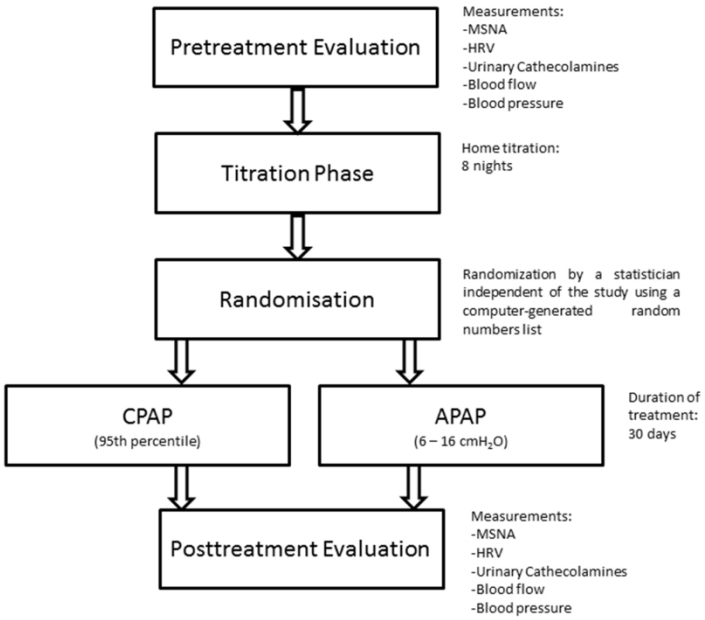

Figure 2. Study protocol. MSNA, Muscle Sympathetic Nerve Activity; HRV, heart rate variability; CPAP, fixed continuous positive pressure; APAP, auto-adjusting continuous positive pressure.

254x190mm (300 x 300 DPI)

Supplementary file

Patient consent forms: French and English versions.

Supplementary material – Consent form (original French version)

FORMULAIRE DE CONSENTEMENT ECLAIRÉ

Diminution du tonus sympathique chez les patients avec une apnée obstructive du sommeil: La CPP fixe est-elle plus efficace que la CPP auto ajusté?

Titre court : APAP CPAP

Promoteur de l'étude : CHU de Grenoble – DRCI (Direction de la Recherche Clinique et Innovation) : CHU de Grenoble, CS 10217, 38043 Grenoble Cedex 09 - Tel : 04 76 76 56 09 Fax : 04 76 76 52 21

Investigateur principaL : Pr. Renaud Tamisier

Investigateurs du CHU de Grenoble participant à cette étude :

Pr Jean-Louis Pépin, Pr Renaud Tamisier, Pr Patrick Levy, Dr Marie Destors, Dr Erika Treptow, Dr. Holger Whorle: Physiologie Sommeil et Exercice - Pôle Locomotion Rééducation et Physiologie; Dr Cecile Bosc : Centre Santé et Sommeil.

Le Dr ……..m'a proposé de participer à l'étude APAP CPAP. Il m'a expliqué en détail les objectifs et le déroulement de celle-ci, ainsi que les bénéfices, les risques et les contraintes.

Une notice d'information m'a été remise et j'ai eu suffisamment de temps pour la lire et prendre la décision d'accepter ou non de participer à l'étude. J'ai pu poser toutes les questions que je souhaitais et j'ai obtenu des réponses satisfaisantes. J'ai bien compris que ma participation à l'étude est volontaire et que je peux à tout moment retirer mon consentement, quelles que soient mes raisons, sans engager ma responsabilité et sans que cela modifie la qualité des soins qui me seront donnés, ni l'attention de mon médecin.

J'ai bien pris connaissance que cette recherche sera conduite en conformité avec le Code de la Santé Publique.

J'ai eu l'assurance que les décisions qui s'imposent pour ma santé seront prises à tout moment, conformément à l'état actuel des connaissances médicales.

J'ai compris que je ne dois pas participer à une autre recherche en même temps que celle-ci.

En cours d'étude, tout élément nouveau me concernant et pouvant modifier mon consentement me sera communiqué.

J'accepte que les données de mon dossier médical qui se rapportent à l'étude soient accessibles aux responsables de l'étude et aux représentants des autorités de santé. A l'exception de ces personnes, qui traiteront les informations dans le plus strict respect du secret médical, mon anonymat sera préservé.

J'ai pris connaissance que cette recherche a reçu l'avis favorable du Comité de Protection des Personnes et l'autorisation de l'ANSM le.

Le promoteur de la recherche (CHU de Grenoble) a souscrit une assurance de responsabilité civile en cas de préjudice auprès de la société.

J'accepte que les données enregistrées à l'occasion de cette étude fassent l'objet d'un traitement informatisé par le service de Physiologie Sommeil et Exercice du CHU de Grenoble, responsable de l'analyse statistique. Je peux accéder, directement ou par

l'intermédiaire d'un médecin de mon choix, à l'ensemble de mes données médicales. Mon droit d'accès, de rectification et d'opposition prévu par la loi " informatique et libertés " s'exerce à tout moment, auprès du médecin en charge de la recherche.

Mon acceptation de participer à l'étude ne dégage pas les médecins et les organisateurs de l'étude de leur responsabilité. Je conserve tous mes droits garantis par la loi.

J'ai reçu une copie du présent document et j'ai été informé qu'une copie serait également conservée par l'investigateur et le promoteur dans des conditions garantissant la confidentialité et j'y consens.

Je certifie avoir lu ce document ainsi que la notice d'information et accepte de participer, librement, à cette recherche, dans les conditions qui m'ont été précisées.

En cas d'événements indésirables ou de problèmes, ou si j'ai d'autres questions au cours de ma participation, je pourrai contacter le médecin en charge de la recherche au numéro de téléphone suivant : ……

Nom / Prénom du patient :	Nom du médecin :
……..	…….
……..	…….
Date : ……./……./…….	Date : ……./……./…….
Signature du patient :	Signature du médecin :

Supplementary material – Consent form (English version)

Reduction of Sympathetic tone in OSA patients:

Is CPAP more effective than APAP? – a randomized, parallel clinical trial protocol

Short title : APAP-CPAP

Study Sponsor: CHU de Grenoble – DRCI (Direction de la Recherche Clinique et Innovation) : CHU de Grenoble, CS 10217, 38043 Grenoble Cedex 09 - Tel : 04 76 76 56 09 Fax : 04 76 76 52 21

Principal investigator: Renaud Tamisier

Members of Grenoble Alpes University Hospital participating in this study :

Pr Jean-Louis Pépin, Pr Renaud Tamisier, Pr Patrick Levy, Dr Marie Destors, Dr Erika Treptow, Dr. Holger Whorle: Physiologie Sommeil et Exercice - Pôle Locomotion Rééducation et Physiologie (Physiology, Sleep and Exercise – Centre for locomotion, Reeducation and Physiology); Dr Cecile Bosc: Centre Santé et Sommeil (Health and SleepCenter).

Dr. .....has proposed that I participate in the study APAP-CPAP study. I have received detailed explanations about the objectives and procedures of the study, as well as its benefits, risks and constraints.

I have received an information sheet and I've had enough time to read it and to make the decision to participate, or not, in the study. I've had the opportunity to ask all my questions and I'vereceived satisfactory answers. I understood that my participation in the study is voluntary and that I can, at any time, withdraw my consent, whatever my reasons, without incurring any responsibility and without any modification in the treatment received.

I have been informed that this study will be conducted according to the French Code of Public Health, and have been assured that all study procedures will be made in

accordance with the current medical recommendations.

I have understood that I should not participate in any other biomedical research protocolduring the period of this study.

During the study, I will be informed of any event concerning my health that could influence my consent.

I accept that the data in my medical file(s) related to the study will be accessible to the study´s collaborators and to representatives of the health authorities. With the exception of these people, who will deal with my data in respect of professional secrecy, my anonymity will be preserved.

I have been informed that this research has been approved by the Regional Biomedical Ethics committee (*Comité de Protection de Personnes*) and authorized by the French National Agency for the Safety of Medicines and Health Products.

The sponsor of the study (Grenoble Alpes University Hospital) has contracted an additional insurance of civil responsibility in case of harms.

I accept that the data concerning me acquired during this study will be registered by the Department of Physiology, Sleep and Exercise of Grenoble Alpes University Hospital, which is responsible for the statistical analysis. I have the right to access, directly or through a physician of my choice, the set of information and medical data concerning me. At any time I will have the right of access and correction of computerized data according to the law on "*informatique et libertés*" through the physician responsible for the research.

My acceptance to participate inthe study does not discharge the organizers and investigators of the study from their responsibilities. I retain all my rights guaranteed by law.

I have received a copy of the current consent sheet and I was informed that one copy will be retained by the investigator and another by the sponsor under conditions guaranteeing confidentiality.

I certify that I have read this document as well as the patient information sheet and I freely accept to participate in the study according to the conditions specified.

In case of any undesirable events or problems, or if I have any other questions during

my participation of the study, I may contact the physician responsible for the research through the telephone number +33 (0)4 76765516.

Surname / First Name of participant :	Surname of investigating physician
in :	
……..	……..
……..	……..
Date : ……./……./…….	Date : ……./……./…….
Participant´s signature :	Physician´s signature :

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 16
	5b	Name and contact information for the trial sponsor	1 and 12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8 and Clincal Trials.gov (NCT03428516)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1 and page 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8 and 11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11 and figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11 and 12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	3, 4 and 12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8 and 11

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12 and 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	no DMC
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11 and 12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13 and 14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13 and 17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13 and 16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3 and 13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	none as yet
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Translations from French originals available as supplementary documentation _

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	7 and 10

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.