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Impact pronostic et thérapeutique des troubles du sommeil chez des patients à risque cardiovasculaire élevé

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RESUME

Les troubles du sommeil sont fréquents dans la population générale et leur prévalence est encore plus élevée chez les patients avec des comorbidités métaboliques ou cardiovasculaires, entrainant des répercussions sur la qualité de vie et le pronostic cardiovasculaire.

Parmi ces troubles, le syndrome d'apnées hypopnées obstructives du sommeil (SAHOS) est considéré comme un facteur de risque cardiovasculaire indépendant. Le traitement de référence du SAHOS est la pression positive continue (PPC) qui permet d'améliorer la symptomatologie nocturne et diurne liée au SAHOS, et notamment la somnolence diurne, mais dont l'efficacité sur la prévention des événements cardiovasculaires reste débattue.

Les objectifs ce cette thèse étaient d'une part d'améliorer la compréhension des liens physiopathologiques et cliniques entre les troubles du sommeil, dont le SAHOS, et les maladies cardiovasculaires et d'autre part de préciser les impacts cliniques et physiopathologiques de différents traitements du SAHOS.

Nous avons apporté des éléments de réponse au premier objectif en démontrant que 1/la présence d'un SAHOS n'était pas associée au remodelage ventriculaire chez des patients ayant présenté un infarctus du myocarde et que 2/des paramètres témoignant d'un mauvais sommeil, et notamment une diminution du temps de sommeil total et la prise de médicaments agissant sur le système nerveux central, étaient associés à la survenue d'évènements cardiovasculaires majeurs chez des patients avec une insuffisance cardiaque. Concernant le deuxième objectif, nous avons démontré qu'un réentrainement à l'effort individualisé de 8 semaines améliorait la somnolence diurne évaluée objectivement et l'index d'apnées hypopnées en sommeil paradoxal, ces deux paramètres étant des marqueurs de sévérité du SAHOS et étant associés au risque cardiovasculaire.

Ces travaux s'inscrivent dans un projet de plus long terme qui doit permettre d'apporter des éléments de réponse pour évoluer pour une médecine de précision dans la définition et la prise en charge des troubles respiratoires du sommeil.

Mots clés : troubles du sommeil, syndrome d'apnées hypopnées obstructives du sommeil, obésité, cardiopathie ischémique, insuffisance cardiaque, risque cardiovasculaire, stress oxydant, inflammation, réentrainement à l'effort, réhabilitation, télémédecine.

ABSTRACT

Sleep disorders are frequent in the general population and their prevalence is higher in patients with metabolic or cardiovascular disorders, leading to repercucpapssions on quality of life and cardiovascular prognosis.

Among these disorders, obstructive sleep apnea syndrome (OSA) is considered as an independent cardiovascular risk factor. The first line treatment for OSA is continuous positive airway pressure (CPAP), which improves the symptoms associated with OSA, in particular daytime sleepiness, but with effectiveness in preventing cardiovascular events remaining debated.

The objectives of this thesis were on the one hand to improve the understanding of the physiopathological and clinical links between sleep disorders, including OSA, and cardiovascular diseases and on the other hand to specify the clinical and physiopathological impacts of different treatments of OSA.

We provided some answers to the first objective by demonstrating that 1 / the presence of OSA was not associated with ventricular remodeling in patients with an acute myocardial infarction and that 2 / parameters indicating poor sleep, and in particular a decrease in total sleep time and the intake of drugs acting on the central nervous system, were associated with the occurrence of major cardiovascular events in patients with heart failure. Regarding the second objective, we demonstrated that an individualized 8-week exercise training program improved objectively assessed daytime sleepiness and the apnea hypopnea index in REM sleep, these two parameters being markers of the severity of OSA and being associated with cardiovascular risk.

This work is part of a longer-term project that should provide some answers in order to move towards precision medicine in the definition and management of sleep-disordered breathing.

Keywords: sleep disorders, obstructive sleep apnea syndrome, obesity, ischemic heart disease, heart failure, cardiovascular risk, oxidative stress, inflammation, exercise training, rehabilitation, telemedicine.

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LISTE DES ABREVIATIONS

AP	Activité physique adaptée
CRP	C-reactive protein
ECM	Evènement cardiovasculaire majeur
EOR	Espèces oxygénées réactives
FE	Fraction d'éjection
FEVG	Fraction d'éjection du ventricule gauche
HI	Hypoxie intermittente
IAH	Index d'apnées hypopnées
ERO	Espèces réactives de l'oxygène
IC	Insuffisance cardiaque
IL	Interleukine
IMC	Indice de masse corporelle
ISI	Index de sévérité de l'insomnie
IRM	Imagerie par résonance magnétique
OAM	Orthèse d'avancée mandibulaire
PA	Pression artérielle
PPC	Pression positive continue
PSG	Polysomnographie
PSQI	Pittsburgh sleep quality index
PV	Polygraphie ventilatoire
RE	Réentrainement à l'effort
SAHOS	Syndrome d'apnées hypopnées obstructives du sommeil
SASC	Syndrome d'apnées du sommeil central
SCA	Syndrome coronaire aigu
SDE	Somnolence diurne excessive
SNC	Système nerveux central
SJSR	Syndrome des jambes sans repos

SP	Sommeil paradoxal
TA	Tension artérielle
TILE	Tests itératifs de latence d'endormissement
TNF-α	Tumor necrosis factor- α
TR	Téléréhabilitation
TRCVS	Troubles du rythme circadien veille-sommeil
TST	Temps de sommeil total
VAA	Ventilation auto-asservie
VAS	Voies aériennes supérieures

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PARTIE 1 : CONTEXTE THEORIQUE

I.Syndrome d'apnées hypopnées obstructives du sommeil : Généralités

(a) Définition et épidémiologie du SAHOS

Définition du SAHOS

Le syndrome d'apnées hypopnées obstructives du sommeil (SAHOS) est une pathologie respiratoire du sommeil caractérisée par la répétition de collapsus complets (apnées) ou incomplets (hypopnées) des voies aériennes supérieures, d'une durée minimale de dix secondes, avec la persistance d'efforts respiratoires (Douglas et Polo 1994).

Le diagnostic du SAHOS repose sur un enregistrement du sommeil, que ce soit une polysomnographie (PSG) ou une polygraphie ventilatoire (PV), et sur la présence de symptômes nocturnes/et ou diurnes. Il existe plusieurs critères diagnostiques pour définir le SAHOS. Les critères de la classification internationale des troubles du sommeil (ICSD-3) sont les suivants(Sateia 2014) :

- Présence de signes/symptômes (somnolence, fatigue, insomnie, ronflements, arrêts respiratoires objectivés,) ou de comorbidité (hypertension artérielle, maladie coronarienne, accident vasculaire cérébral, insuffisance cardiaque congestive, fibrillation auriculaire, diabète de type 2, troubles de l'humeur, troubles cognitifs) ET index d'évènements respiratoires principalement obstructifs ≥5/heure.

OU

- Index d'évènements respiratoires principalement obstructifs ≥ 15/heure

L'index d'apnées hypopnées (IAH) correspond au nombre d'évènements respiratoires recensés par heure de sommeil (ou d'enregistrement) et est couramment utilisé pour caractériser la sévérité du SAHOS (léger entre 5 et 15 par heure, modéré entre 15 et 30 par heure et sévère lorsque l'IAH est supérieur à 30 par heure).

Epidémiologie du SAHOS

Le SAHOS est la pathologie respiratoire du sommeil la plus fréquente. La prévalence du SAHOS dépend des critères diagnostiques retenus et varie en fonction de l'âge, du sexe, de l'indice de masse corporelle (IMC) et de l'ethnie.

Les premières études retrouvaient un SAHOS symptomatique chez 2% des femmes et 4% des hommes d'âge moyen(T. Young et al. 1993). Certaines études plus récentes montrent une prévalence encore bien plus élevée, probablement en raison de l'augmentation de la prévalence du surpoids et de l'obésité, avec un IAH≥15/heure chez 3 à 9% des femmes et 10 à 17% des hommes(Peppard et al. 2013). Les résultats de la cohorte européenne Hypnolaus confirment cette prévalence élevée chez des adultes de plus de 40 ans, dépendante des critères diagnostiques retenus(Heinzer et al. 2015) :

- 49.7% chez les hommes et 23.4% chez les femmes pour un IAH ≥ 15/heure selon les critères de l'American Academy of Sleep Medicine (AASM) 2012 (Berry et al. 2012).
- 12.5% chez les hommes et 5.9% chez les femmes pour un IAH ≥ 5/heure associé à une somnolence diurne excessive (Epworth>10/24).
- 74.7% chez les hommes et 52.1% chez les femmes lorsque les critères ICSD-3 sont utilisés.

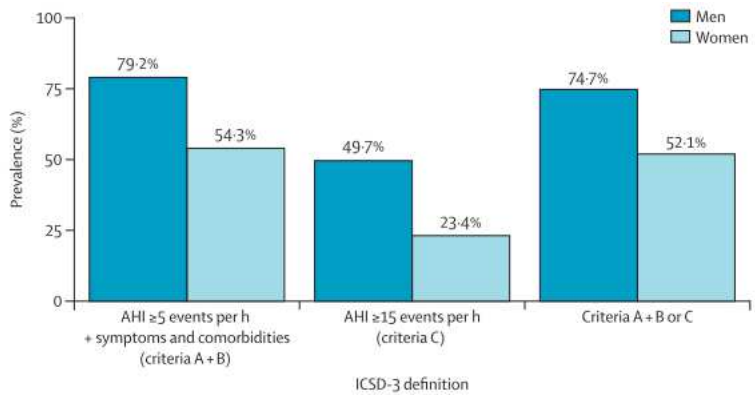

Figure 1. Prévalence du SAHOS en population générale en fonction des critères diagnostiques de l'ICSD-3 (Heinzer, , Lancet Respir Med, 2016).

La prévalence du SAHOS est encore plus élevée en cas de comorbidités cardiovasculaires(Javaheri et al. 2017) ou métaboliques telles que le diabète de type 2(Pamidi, Aronsohn, et Tasali 2010).

(b) Mécanismes du SAHOS

Les évènements respiratoires obstructifs (apnées, hypopnées et limitation de débit) correspondent à un rétrécissement de calibre des voies aériennes supérieures (VAS).

La physiopathologie est multifactorielle et est liée notamment à l'équilibre entre la tendance naturelle des VAS à se fermer (collapsibilité) et l'efficacité des muscles dilatateurs qui permettent de maintenir le pharynx ouvert(Lévy et al. 2015). Plusieurs mécanismes, dont la part respective est variable d'un individu à l'autre, peuvent tendre à rompre cet équilibre et aboutir à la réduction de calibre des VAS.

Facteurs anatomiques

La diminution de calibre des VAS est favorisée par l'**obésité** qui est le principal facteur de risque de SAHOS(Terry Young, Peppard, et Gottlieb 2002). Plus de la moitié des patients avec SAHOS sont obèses et la prévalence du SAHOS est proportionnelle à l'indice de masse corporelle. Les mécanismes impliqués sont le dépôt de tissu graisseux dans les parois pharyngées, la diminution des volumes pulmonaires ou encore la diminution de la commande ventilatoire(Luciano F. Drager et al. 2013).

Des **anomalies morphologiques** sont fréquemment retrouvées chez les patients avec SAHOS, au niveau osseux (malformation maxillo-mandibulaire, rétrognathie, abaissement de l'os hyoïde,) ou au niveau des tissus mous comme par exemple une hypertrophie de la luette, de la base de langue, des amygdales ou du voile du palais.

La **redistribution liquidienne** au niveau cervical lors du décubitus dorsal (fluid shift ou dynamique des fluides) peut également contribuer également à la diminution du calibre des VAS. On retrouve une prévalence plus élevée de SAHOS chez les patients présentant une rétention hydrosodée : insuffisants rénaux, insuffisants cardiaques ou encore hypertendus(Kasai 2016). Chez ces patients, le liquide accumulé au cours de la journée dans

les membres inférieurs est redistribué au niveau thoracique et au niveau cervical lors du passage en position allongée, favorisant le rétrécissement de calibre des VAS.

Contrôle neuro-musculaire

Les muscles dilatateurs du pharynx, dont le génioglosse, assurent la perméabilité des VAS. Le réflexe protecteur des VAS correspond à l'augmentation de l'activité de ces muscles en réponse à une augmentation de résistance pharyngée.

L'apparition des évènements obstructifs (hypopnées et apnées) pendant le sommeil est favorisée en cas d'altération de ce réflexe, retrouvée chez de nombreux patients apnéiques(Osman et al. 2020).

Contrôle ventilatoire

La ventilation est influencée par des boucles de rétrocontrôle dont les stimuli sont la pression artérielle en oxygène (PaO2) et la pression artérielle en dioxyde de carbone (PaCO2) qui transmettent l'information au système nerveux central via des chémorécepteurs périphériques et centraux.

Les micro-éveils succédant aux évènements respiratoires obstructifs sont caractérisés par une reprise ventilatoire. Certains patients apnéiques présentent une instabilité ventilatoire avec une réponse ventilatoire excessive (« loop gain » élevé) favorisant la survenue d'apnées(Deacon-Diaz et Malhotra 2018).

Seuil d'éveil

L'activation des muscles dilatateurs du pharynx et la restauration de la perméabilité des VAS après un évènement obstructif (apnée ou hypopnée) peut être secondaire ou non à un micro-éveil(Younes et al. 2012).

Certains patients apnéiques ont un seuil d'éveil abaissé. Cette situation entraine de nombreux micro-éveils dans le décours des évènements respiratoires obstructifs, favorisant une instabilité respiratoire (avec des séquences apnée, micro-éveil, hyperventilation-apnée).

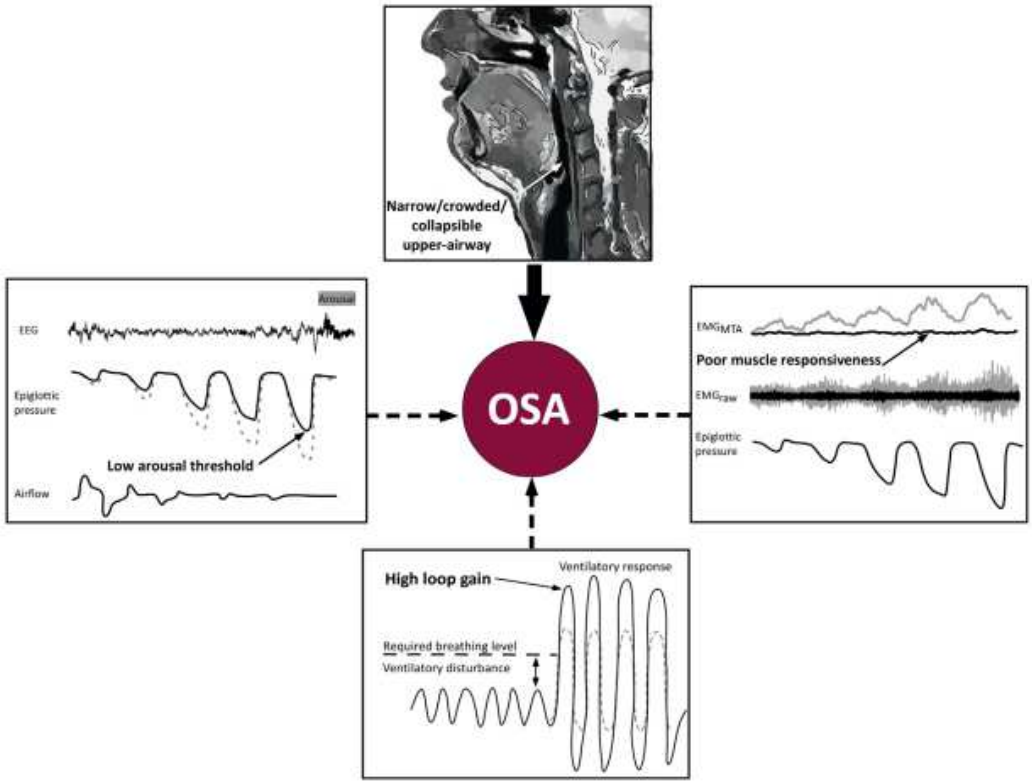

Figure 2. Mécanismes physiopathologiques du SAHOS. Carberry, Chest, 2018.

(c) Symptomatologie du SAHOS

Symptomatologie nocturne et diurne

Les ronflements sont retrouvés chez la grande majorité des patients et ont tendance à être intenses et déranger l'entourage. Les autres symptômes au cours de la nuit comprennent les arrêts respiratoires objectivés par l'entourage ou les réveils en suffocation, un sommeil agité, une transpiration importante ou encore la nycturie qui est définie par le fait d'uriner au minimum deux fois pendant la nuit. Les répercussions diurnes sont également nombreuses et comprennent la fatigue, les céphalées matinales, les troubles de la mémoire et de la concentration, les troubles de la libido ou encore l'altération de la qualité de vie.

Somnolence diurne

La somnolence diurne excessive (SDE) est un symptôme majeur du SAHOS et constitue le premier motif de consultation. Elle est définie par la tendance à s'endormir trop facilement pendant la journée et est un marqueur de sévérité du SAHOS.

La SDE est associée chez les patients apnéiques à une altération de la qualité de vie, aux accidents du travail, au risque accidentologique, à l'insulinorésistance ou encore à une augmentation de la prévalence de l'hypertension artérielle(Javaheri et al. 2019) et du risque cardiovasculaire(Blachier et al. 2012; Mazzotti et al. 2019). Dans la population générale, la SDE est associée à une augmentation du risque de mortalité cardiovasculaire(J. Li et al. 2021).

Il existe une importante variabilité du niveau de somnolence chez les patients apnéiques et la physiopathologie du lien entre SAHOS et SDE est multifactorielle. L'altération de l'architecture du sommeil, le temps de sommeil, le chronotype , les comorbidités, l'état émotionnel, le niveau d'activité physique ou encore les marqueurs inflammatoires sont associés à la SDE (Prasad et al. 2018; Vgontzas 2008).

La somnolence diurne peut être évaluée par mes méthodes subjectives et objectives. L'échelle d'Epworth et les tests itératifs de latence d'endormissement (TILE) sont les évaluations subjectives et objectives les plus utilisées chez les patients avec SAHOS. La corrélation entre le score d'Epworth et les TILE est inconsistante selon les études(Y. Li et al. 2014).

II.SAHOS et maladies cardiovasculaires

(a) SAHOS, facteur de risque cardiovasculaire et métabolique

Le SAHOS est reconnu depuis de nombreuses années comme un facteur de risque cardiovasculaire indépendant.

Le SAHOS est associé à l'altération du métabolisme glucidique(Pallayova, Banerjee, et Taheri 2014), lipidique(Kawano, Tamura, et Kadota 2012) et hépatique(Minville et al. 2014) ainsi qu'à l'athérosclérose(Luciano F. Drager 2011).

Des études de cohorte en population générale ont mis en évidence une association entre le SAHOS non traité et l'augmentation de l'incidence de l' hypertension artérielle (José M. Marin et al. 2012), des maladies coronariennes et cérébro-vasculaires(Jose M. Marin et al. 2005) ou encore des cardiopathies rythmiques(Laczay et Faulx 2021).

(b) Physiopathologie des complications cardiovasculaires du SAHOS

Le sommeil normal est associé à une diminution du stress physiologique pour le système cardiovasculaire, notamment lors du sommeil lent lors duquel l'activité sympathique est diminuée.

Le SAHOS altère la qualité du sommeil et a de nombreuses répercussions sur l'organisme en raison des conséquences liées aux collapsus répété des VAS. Les évènements obstructifs du sommeil entraînent une hypoxie et une hypercapnie intermittentes, des micro-éveils avec une fragmentation du sommeil, une variation de la pression intra thoracique et une augmentation du tonus sympathique. D'autres mécanismes tels que l'augmentation des médiateurs inflammatoires, le stress oxydant, la dysfonction endothéliale ou l'hypercoagulabilité sont également impliqués dans la genèse des complications liées au SAHOS(Javaheri et al. 2017) (Figure 3).

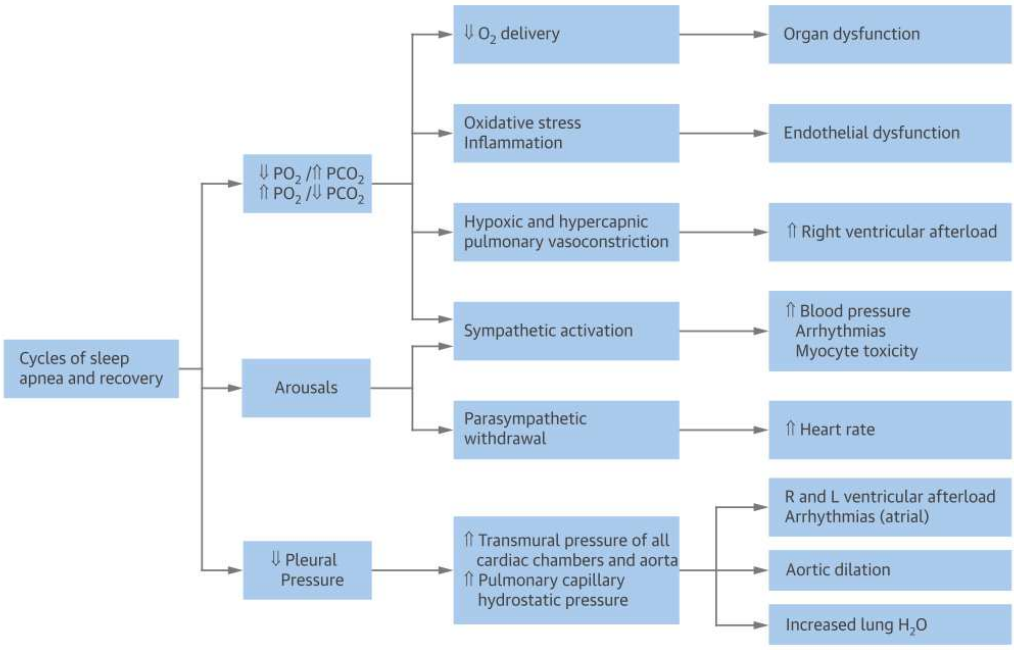

Figure 3. Conséquences physiopathologiques des apnées et hypopnées. Javaheri, JACC, 2017.

Hypoxie intermittente

L'hypoxie intermittente (HI) correspond à la succession de cycles de désaturation-réoxygénation suivant les évènements respiratoires nocturnes. L'HI chronique favorise le stress oxydant et l'inflammation, augmente la sensibilité des chémoréflexes, et par conséquent l'activité sympathique, et favorise la vasoconstriction(Dewan, Nieto, et Somers 2015).

L'HI est un des mécanismes principaux contribuant à la pathogenèse des complications du SAHOS(André et al. 2020).

La charge hypoxique (hypoxic burden) est une mesure de la désaturation liée aux évènements respiratoires (correspondant à l'aire sous la courbe de désaturation) et est associée à la mortalité cardiovasculaire(Azarbarzin et al. 2019).

Fragmentation du sommeil

Les évènements respiratoires obstructifs du sommeil peuvent entrainer d'incessants micro-éveils et donc une altération de l'architecture du sommeil(Korkalainen et al. 2021). Les micro-

éveils entraînent une hyperactivité sympathique et la fragmentation du sommeil favorise les complications du SAHOS et notamment la somnolence diurne excessive(Colt, Haas, et Rich 1991).

Variations de pression intra thoracique

Les efforts respiratoires consécutifs aux évènements respiratoires obstructifs entrainent une augmentation des pressions négatives intrathoraciques. Ces variations de pression augmentent la pression transmurale du ventricule gauche (et donc sa postcharge), et augmentent le retour veineux (et la précharge du ventricule droit)(Kasai et Bradley 2011).

Activation sympathique

Le SAHOS entraine une altération de la balance autonomique avec une augmentation du tonus sympathique et une diminution de l'activité parasympathique. Cette augmentation du tonus sympathique est secondaire notamment à la stimulation des chémorécepteurs par l'HI et aux micro-éveils(Imadojemu et al. 2007).

Des études récentes ont mis en évidence une association entre des marqueurs de l'hyperactivité sympathique et une augmentation de la morbidité et de la mortalité cardiovasculaire(Sankari et al. 2019; Azarbarzin et al. 2021).

Il existe de nombreuses méthodes afin d'évaluer la balance sympatho-vagale : dosage des catécholamines urinaires, intervalle R-R sur l'électrocardiogramme, microneurographie, ou encore scintigraphie MIBG.

Inflammation

Le SAHOS est caractérisé par un état inflammatoire systémique. Plusieurs études ont mis en évidence une augmentation des biomarqueurs inflammatoires chez les patients avec un SAHOS et notamment l'interleukine (IL)-6, le tumor necrosis factor (TNF)-α, la C-reactive protéine (CRP) et la CRP ultrasensible(Imani et al. 2021).

Cette composante inflammatoire intervient dans la physiopathologie des complications cardiovasculaires du SAHOS. Les taux d'IL-6, TNF-α et de CRP sont ainsi associés à l'épaisseur

intima-média, marqueur de l'athérosclérose(Ciccone et al. 2014), alors que la CRP ultrasensible est un marqueur biologique du risque cardiovasculaire(Ridker 2007).

Stress oxydant

Le stress oxydant est favorisé par l'HI et correspond à un déséquilibre entre la production des espèces réactives de l'oxygène (ERO) et les défenses antioxydantes. Plusieurs études ont mis en évidence un déséquilibre de cette balance entre espèces pro- et anti- oxydantes chez les patients avec un SAHOS(Maniaci et al. 2021).

Le stress oxydant est associé avec la dysfonction endothéliale, l'athérosclérose et l'hypertension artérielle et est donc considéré comme un des mécanismes majeurs expliquant les conséquences cardiovasculaires du SAHOS(Eisele, Markart, et Schulz 2015).

Dysfonction endothéliale

La dysfonction endothéliale (DE) est un marqueur infraclinique prédictif du risque cardiovasculaire. Une méta-analyse récente a montré une association entre le SAHOS sévère et la DE évaluée par pléthysmographie digitale(Bironneau et al. 2020). La DE dans le SAHOS est favorisée par différents mécanismes et notamment l'HI et le stress oxydant. Elle est médiée par des microvésicules qui contribuent aux dommages vasculaires(Trzepizur et al. 2014).

(c) Cardiopathie ischémique et SAHOS

L'association entre SAHOS et maladies coronariennes est bien établie et différentes études retrouvent une prévalence élevée, 30 % à 65%, de SAHOS chez les patients coronariens(Schäfer et al. 1999; Javaheri et al. 2019).

La prévalence est encore plus élevée chez les patients ayant présenté un syndrome coronaire aigu (SCA) (Morra et al. 2017). Une méta-analyse confirme la prévalence élevée dans cette population avec 69% des patients avec un IAH >5/heure, 43% avec un IAH >15/heure et 25% avec un IAH >30/heure(Huang et al. 2017).

L'impact pronostic et thérapeutique de la présence d'un SAHOS chez les patients avec une cardiopathie ischémique n'est pas encore totalement élucidé. D'un côté, le SAHOS est associé

à la sévérité du SCA à court terme(Barbé et al. 2015) et à une augmentation des évènements cardiovasculaires majeurs chez les patients ayant bénéficié d'une intervention coronarienne percutanée(C.-H. Lee et al. 2016). D'un autre côté, une étude observationnelle chez des patients avec un infarctus du myocarde a mis en évidence une atteinte cardiaque moins sévère en cas de SAHOS(N. Shah et al. 2013) et l'efficacité de la PPC en prévention secondaire des maladies cardiovasculaires n'a pas été démontrée. Ce point sera détaillé par la suite.

(d) Insuffisance cardiaque et SAHOS

La prévalence du SAHOS est élevée (20-66%) chez les patients avec une insuffisance cardiaque (IC) que ce soit à fraction d'éjection (FE) réduite ou préservée(Javaheri et al. 2017).

Les liens physiopathologiques entre SAHOS et IC sont bidirectionnels. D'une part, la présence d'un SAHOS sévère est associée à une augmentation de l'incidence d'IC(Gottlieb et al. 2010) par l'intermédiaire de différents mécanismes : variations des pressions intra thoraciques, élévation de la pression artérielle nocturne et hyperactivité sympathique. D'autre part, l'IC favorise les évènements obstructifs en raison de l'œdème pharyngé dû au déplacement du liquide rostral pendant le sommeil(Yumino et al. 2010).

Plusieurs études observationnelles ont mis en évidence une détérioration du pronostic avec notamment une augmentation de la mortalité chez des patients IC avec un SAHOS non traité(Wang et al. 2007; Damy et al. 2012).

Les patients avec IC présentent une grande variabilité du type d'évènements respiratoires d'une nuit à l'autre,(Vazir et al. 2008) et ont également une prévalence élevée (45-55%) de syndrome d'apnées du sommeil central (SASC), lié notamment à une instabilité de la commande ventilatoire.

III. Traitement du SAHOS par pression positive continue

(a) Généralités et efficacité

La pression positive continue (PPC) est le traitement de référence du SAHOS. La PPC agit comme une « attelle pneumatique » en propulsant de l'air pendant l'inspiration et l'expiration dans les VAS du patient par l'intermédiaire d'un masque nasal ou facial. La PPC permet une

normalisation de l'IAH, une amélioration de la qualité du sommeil, de la somnolence diurne ou encore de la qualité de vie(Patil et al. 2019).

La pression positive peut être délivrée selon un mode fixe ou un mode autopiloté. En mode fixe, la pression est identique tout au long de la nuit alors qu'en mode autopiloté, la pression varie au cours de la nuit en s'adaptant aux évènements respiratoires (limitations de débit, hypopnées et apnées notamment) selon les algorithmes de l'appareil. Si l'efficacité des deux modes est équivalente sur la réduction de l'IAH et de la somnolence(Smith et Lasserson 2009), une étude a mis en évidence une amélioration plus importante de la pression artérielle diastolique sur 24 heures en mode fixe par rapport au mode autopiloté(J. L. Pépin et al. 2016).

Les effets de la PPC sur les marqueurs cardiométaboliques sont non totalement élucidés. Si certaines études montre une efficacité de la a PPC sur la dysfonction endothéliale, l'insulinorésistance, l'inflammation ou le stress oxydant (Msaad et al. 2020; Xu et al. 2015), ces effets bénéfiques ne sont pas systématiquement retrouvés(Jullian-Desayes et al. 2015).

L'effet de la PPC sur la pression artérielle (PA) est limité avec une diminution de 2 mmHg en moyenne de la PA systolique moyenne et une efficacité qui peut être supérieure sur les mesures de PA nocturne(Posadas et al. 2020). Concernant l'efficacité de la PPC en prévention primaire des maladies cardiovasculaires, si des études observationnelles ont mis en évidence une diminution de la morbidité et de la mortalité cardiovasculaire en cas de SAHOS traité par PPC(Jose M. Marin et al. 2005; Campos-Rodriguez et al. 2014), aucune étude randomisée contrôlée n'a confirmé ce point.

(b) Impact de la PPC en prévention secondaire des maladies cardiovasculaires

Alors que des études observationnelles avaient mis en évidence un effet bénéfique de la PPC en prévention secondaire des maladies cardiovasculaires(Milleron et al. 2004), cette efficacité n'a pas été confirmée dans plusieurs études randomisées contrôlées.

Les études SAVE et RICCADSA n'ont pas mis en évidence de bénéfice de la PPC sur la réduction des évènements cardiovasculaires ou de la mortalité chez des patients avec un antécédent de maladie coronarienne ou cérébrovasculaires (McEvoy et al. 2016; Peker et al. 2016). Plus récemment, l'étude ISAAC est arrivée à la même conclusion en démontrant l'absence de

diminution des évènements cardiovasculaires après un syndrome coronaire aigu chez les patients avec un SAHOS, non somnolents, bénéficiant d'un traitement par PPC.(Sánchez-de-la-Torre et al. 2019) (Figure4).

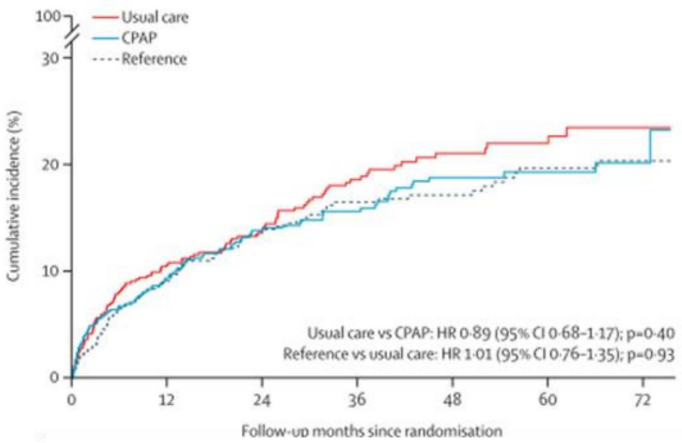

Figure 4. Incidence cumulée des évènements cardiovasculaires après syndrome coronaire aigu. Sanchez-de-la-Torre, Lancet Respir Med, 2019.

(c) PPC et insuffisance cardiaque

En raison de l'augmentation de la pression intrathoracique et de la variation des volumes pulmonaires, le traitement par PPC peut entraîner des répercussions hémodynamiques notamment en diminuant le retour veineux et en modifiant des résistances vasculaires pulmonaires(Kato, Suda, et Kasai 2014).

Quelques études de faible effectif ont mis en évidence des effets bénéfiques de la PPC chez les patients avec IC et SAHOS. La PPC améliore la FEVG, diminue la fréquence cardiaque de repos, la pression artérielle ou encore la qualité de vie(Vazir et Sundaram 2018). Aucune étude randomisée contrôlée n'a démontré une diminution à long terme du risque cardiovasculaire dans cette population avec la PPC.

Les effets de la PPC ont aussi été étudiés chez les patients avec IC et SACS. Alors que l'étude CANPAP n'a pas mis en évidence d'amélioration de la survie chez les patients traités par PPC(Bradley et al. 2005), une analyse à posteriori a démontré un effet bénéfique de la PPC sur

la survie chez les patients ayant un IAH résiduel inférieur à 15/heure après trois mois de traitement(Arzt et al. 2007).

Après optimisation du traitement à visée cardiologique, la PPC reste le traitement de première intention du syndrome d'apnées du sommeil obstructif et central chez les patients avec une IC(Randerath et al. 2017).

(d) Observance de la PPC

L'efficacité de la PPC est dépendante de l'observance au traitement notamment concernant l'amélioration de la qualité de vie ou la diminution de la somnolence(Sawyer et al. 2011). De plus, la diminution de la pression artérielle est corrélée à la durée d'utilisation de la PPC chez des patients apnéiques avec une HTA résistante(Martínez-García et al. 2013).

Les données concernant l'importance de l'observance pour l'efficacité de la PPC en prévention secondaire du risque cardiovasculaire sont contradictoires. En effet, alors que les analyses post-hoc de l'étude RICCADSA(Peker et al. 2016) ont mis en évidence une diminution des évènements cardiovasculaires chez les patients utilisant la PPC plus de 04 heures par nuit, cet effet bénéfique de la PPC chez les patients observants n'a pas été retrouvé dans l'étude SAVE(McEvoy et al. 2016).

L'amélioration de l'observance de la PPC reste un défi. En effet, plusieurs études montrent qu'à moyen et long terme, une utilisation moyenne supérieure ou égale à 04 heures par nuit n'est est obtenue que chez 59 à 64% des patients(Gagnadoux et al. 2011; Campos-Rodriguez et al. 2016). Une étude utilisant les données massives (big data) a retrouvé une observance supérieure à 04 heures sur plus de 70% des nuits chez 75% des patients(Cistulli et al. 2019).

Les facteurs liés à une mauvaise observance sont multiples et variés et comprennent les caractéristiques sociales, démographiques et économiques du patient, son profil psychologique mais aussi la sévérité de la maladie et les effets secondaires du traitement(Mehrtash, Bakker, et Ayas 2019; Rotty et al. 2021). Une étude récente a n'a pas mis en évidence de relation entre l'IAH résiduel et le niveau de fuite importante rapportés par les PPC et l'observance au traitement(Rotty et al. 2019).

IV. Autres traitements du SAHOS et impacts cardiovasculaires et métaboliques

(a) Orthèse d'avancée mandibulaire

Le traitement par orthèse d'avancée mandibulaire (OAM) représente une alternative à la PPC en cas de SAHOS modéré ou en cas d'intolérance ou de refus de la PPC(Ramar et al. 2015).

L'OAM est efficace pour diminuer l'IAH bien qu'à des degrés différents selon les patients et améliore la somnolence diurne et la qualité de vie(Marklund, Braem, et Verbraecken 2019). L'efficacité sur la tension artérielle est similaire à la PPC(Bratton et al. 2015).

Son efficacité n'est cependant pas démontrée pour la prévention du risque cardiovasculaire chez les patients apnéiques. Des études ont en effet démontré l'absence d'amélioration de la fonction endothéliale et la tension artérielle(Gagnadoux et al. 2017) ou son efficacité sur l'amélioration des biomarqueurs métaboliques et cardiovasculaires n'est pas établie(Recoquillon et al. 2019; Mecenas et al. 2021).

(b) Ventilation auto-asservie

La ventilation autoasservie (VAA) est un mode ventilatoire associant une aide inspiratoire variable à une pression expiratoire qui peut être fixe ou autopilotée et permettant de traiter les évènements respiratoires (apnées et hypopnées) obstructifs et centraux ainsi que la respiration périodique de Cheyne-Stokes.

Elle est contre-indiquée chez les patients insuffisants cardiaques avec une FEVG ≤ 45% et un SASC suite aux résultats de l'étude SERVE-HF qui a démontré un excès de mortalité chez les patients traités par VAA(Cowie et al. 2015).

La VAA permet une meilleure correction des évènements respiratoires que la PPC chez les patients présentant un SAS émergent (apparition d'apnées centrales sous PPC)(Morgenthaler et al. 2014) avec une amélioration de l'observance au traitement(J.-L. D. Pépin et al. 2018). Des études observationnelles ont objectivé que la VAA est utilisée essentiellement chez des patients avec un SAS émergent ou un SACS dont les comorbidités les plus fréquentes sont cardiologiques, neurologiques et rénales ainsi que chez les patients prenant des opioïdes(Jaffuel et al. 2019; Cantero et al. 2020). Des études randomisées contrôlées sont

nécessaires afin de préciser l'efficacité de la VAA notamment sur l'amélioration du pronostic cardiovasculaire et de la survie.

(c) Règles hygiéno diététiques

Les patients avec un SAHOS ont une diminution de leur niveau d'activité physique(Vivodtzev et al. 2017) et de leur aptitude à l'effort (Mendelson, Marillier, et al. 2018). De plus, le traitement par PPC peut entrainer une augmentation du poids et de l'IMC(L. F. Drager et al. 2015).

Les modifications du mode de vie sont recommandées dans la prise en charge du SAHOS afin de diminuer sa sévérité et ses complications (Epstein et al. 2009; Hudgel et al. 2018).

Le réentrainement à l'effort permet de diminuer la sévérité du SAHOS, la somnolence diurne et d'améliorer l'aptitude physique aérobie indépendamment de la perte de poids(Mendelson, Bailly, et al. 2018).

Chez des patients obèses avec un SAHOS, une intervention combinant restriction calorique, réentrainement à l'effort et stratégies cognitivo-comportementales a permis, contrairement à la PPC, une amélioration de la CRP, de l'insulinorésistance et des taux de triglycérides, résultat non retrouvé lors du traitement par PPC. La combinaison de cette intervention avec une PPC a permis une amélioration significative de la TA chez les patients observant mais n'a pas démontré de réduction significative de la CRP par rapport à la PPC seule(Chirinos et al.

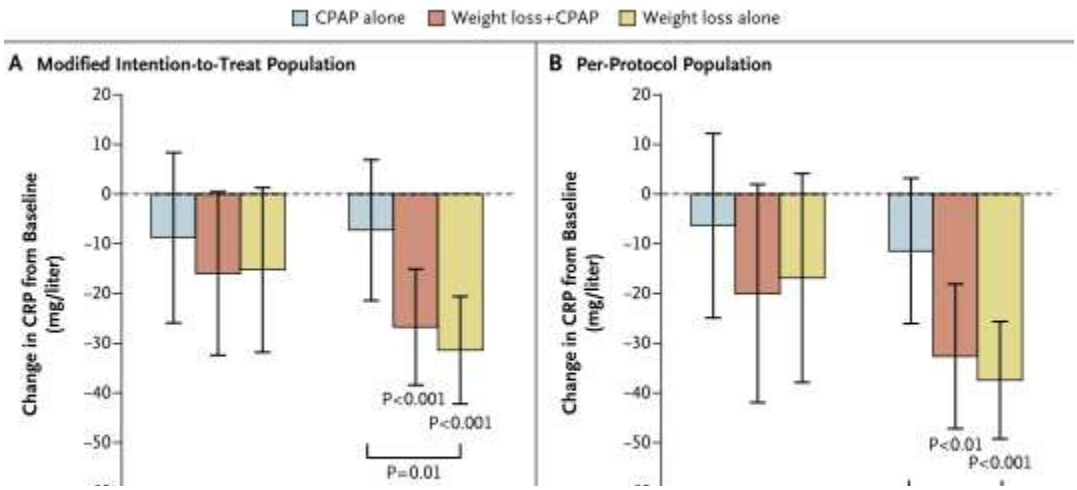

Figure 5. Evolution de CRP par rapport à l'inclusion entre les groupes PPC, intervention visant à la perte de poids et intervention combinée. Chirinos, NEJM, 2014.

2014) (Figure 5). Plus récemment, une étude a mis en évidence une efficacité du régime méditerranéen et d'une intervention visant à modifier le style de vie sur certains marqueurs de l'inflammation et du stress oxydant(Georgoulis et al. 2021).

La réhabilitation, intervention globale et individualisé incluant le réentraînement à l'effort, l'éducation thérapeutique et les changements de comportement(Spruit et al. 2013), a un effet bénéfique sur la sévérité du SAHOS et les composantes du syndrome métabolique qui y sont associés(Desplan et al. 2014; Dobrosielski et al. 2017).

(d) Traitement médicamenteux

Aucun traitement médicamenteux n'est recommandé pour traiter le SAHOS(Mason, Welsh, et Smith 2013). Cependant, deux études ont récemment mis en évidence une efficacité d'une association de deux médicaments ayant des effets noradrénergiques et anti muscariniques (ATOMOXETINE ou REBOXETINE et OXYBUTININE) sur la diminution de l'IAH (Taranto-Montemurro et al. 2018; Perger et al. 2021). Ces études sont de très courte durée (une nuit et une semaine) et ne permettent évidemment pas de juger d'un un éventuel bénéfice cardiovasculaire.

Par ailleurs, la prise en charge médicamenteuse de la somnolence résiduelle sous PPC a connu des avancées majeures ces dernières années. D'une part, le SOLRIAMFETOL, un inhibiteur sélectif de la recapture de la noradrénaline et de la dopamine, améliore l'éveil et réduit la somnolence diurne excessive chez des patients apnéiques traités après douze semaines de traitement (Schweitzer et al. 2019) avec des effets qui se maintiennent après douze mois de traitement(Malhotra et al. 2020). Le profil de tolérance est marqué par un risque psychiatrique (anxiété, insomnie irritabilité,…) et cardiovasculaire notamment en raison d'une possible augmentation de la fréquence cardiaque et de la pression artérielle(Abad 2021). D'autre part, le PITOLISANT, un agoniste inverse sélectif des récepteurs H3 (histamine) diminue significativement la somnolence diurne excessive chez des patients avec un SAHOS modéré à sévère observant ou non à la PPC avec un bon profil de sécurité cardiovasculaire.(J.-L. Pépin et al. 2021; Dauvilliers et al. 2020).

(e) Autres traitements du SAHOS

Les patients avec un SAHOS peuvent également bénéficier d'autres traitements que ceux mentionnées ci-dessus.

La neurostimulation du nerf hypoglosse permet une diminution significative de l'IAH et de la somnolence diurne après douze mois de traitement(Strollo et al. 2014) avec des effets qui se maintiennent dans le temps(Woodson et al. 2018). Un IMC inférieur à 32kg/m² et un collapsus antéro-postérieur des VAS sont des facteurs de succès de ce traitement. En raison des limites méthodologiques des études, et notamment de l'absence de bras contrôle, ce traitement ne bénéficie pas d'une prise en charge en France.

Le traitement positionnel, dont le but est d'empêcher le décubitus dorsal, permet une diminution de l'IAH chez des patients qui présentent un SAHOS positionnel défini par un IAH ≥ 15/h et au moins deux fois plus d'évènements respiratoires obstructifs (apnées et hypopnées) en décubitus dorsal avec un IAH < 10/heure en décubitus non dorsal(Berry et al. 2019).

La thérapie myofonctionnelle oro-faciale, intervention combinant différents exercices oro-pharyngés(Camacho et al. 2015), permet également une diminution de l'IAH et de la somnolence diurne mais des études randomisées contrôlées à plus large échelle sont nécessaires afin de mieux préciser la place de cette prise en charge du SAHOS.(Rueda et al. 2019).

La chirurgie ORL et notamment l'uvulopalatopharyngoplastie permet de diminuer l'IAH mais son efficacité est limitée et l'intervention comprend des risques, notamment hémorragiques, d'autant plus qu'elle est élargie(Hsu et al. 2019). Enfin, la chirurgie bariatrique permet également une diminution significative de l'IAH chez des patients avec une obésité morbide(Ming, Yang, et Chen 2021).

Ces différents traitements du SAHOS permettent donc une amélioration des marqueurs de sévérité du SAHOS mais leur efficacité est limitée à certains phénotypes de patients et il existe peu de données sur leur efficacité à long terme. Par ailleurs, aucun de ces traitements n'a montré une efficacité sur la diminution du risque cardiovasculaire.

V. Association entre la qualité du sommeil, les troubles du sommeil non respiratoires et les maladies métaboliques et cardiovasculaires

Ce paragraphe aborde le lien entre la qualité du sommeil, la durée du sommeil et les troubles du sommeil, non respiratoires, avec les maladies cardiovasculaires et métaboliques.
Ces différents termes seront d'abord définis avant de détailler leur association avec les désordres cardiométaboliques

(a) Généralités

Qualité de sommeil

La qualité du sommeil est un paramètre prédictif important de la santé mentale et physique. Elle est fréquemment évaluée subjectivement, notamment par l'intermédiaire de l'échelle de qualité du sommeil de Pittsburgh-PSQI(Buysse et al. 1989). Le score global est de 21 points et plus le score est élevé, plus le sommeil est de mauvaise qualité. Un score PSQI global supérieur à 5 définit un mauvais dormeur.

La qualité du sommeil peut également être définie par l'intermédiaire de différents critères objectifs(Ohayon et al. 2017). Une latence d'endormissement ≤ 30 minutes, un temps d'éveil intra-sommeil ≤ 20 minutes, une efficacité du sommeil ≥85% et un nombre de réveils nocturnes ≤ 2 par nuit sont considérés comme des marqueurs de sommeil de bonne qualité.

Durée de sommeil

La durée de sommeil est variable d'un individu à l'autre et dépend de facteurs génétiques, environnementaux et comportementaux.

Pour les adultes en bonne santé, la durée minimale de sommeil recommandée est de sept à neuf heures par nuit(Watson et al. 2015). L'insuffisance de sommeil est devenue une véritable épidémie avec aux USA avec 35% des adultes dormant moins de 7 heures et 30% moins de six heures.

Troubles, non respiratoires, du sommeil

Les troubles du sommeil affectent plusieurs centaines de millions de personnes à travers le monde, constituant un véritable problème de santé publique avec des conséquences sévères telles qu'une augmentation des maladies psychiatrique, neurodégénératives ou encore cardiovasculaires. Les troubles du sommeil sont définis dans la classification internationale des troubles du sommeil-ICSD3(Sateia 2014). Les parasomnies et les hypersomnolences d'origine centrale ne sont pas détaillés dans ce travail. Parmi les mouvements anormaux liés au sommeil, seul le syndrome des jambes (SJSR) sans repos est abordé.

Le désordre avec la prévalence la plus élevée est l'**insomnie** qui touche environ 20% de la population générale. L'insomnie est une plainte subjective de mauvais sommeil, survenant malgré des circonstances adéquates, et entrainant des répercussions diurnes. On parle d'insomnie chronique lors que les troubles du sommeil et les symptômes diurnes surviennent au minimum trois fois par semaine pour une durée supérieure à trois mois. L'index de sévérité de l'insomnie (ISI) permet d'estimer la sévérité des difficultés de sommeil au cours du dernier mois. Il comprend sept items notés entre 0 et 4 avec un score total entre 0 et 28. La sévérité de l'insomnie est fonction du score total : non cliniquement signifiante entre 0 et 7, légère entre 8 et 14, modérée entre 15 et 21 et sévère entre 22 et 28(Bastien, Vallières, et Morin 2001).

Le syndrome des jambes sans repos (SJSR) est un trouble sensorimoteur également appelé syndrome de Willis-Ekbom. On le retrouve deux fois plus fréquemment chez les femmes que chez les hommes et la prévalence est de 5 à 10% dans la population générale. La symptomatologie doit débuter ou s'aggraver lors des périodes de repos ou d'inaction (souvent en position assise ou allongée), être soulagée par le mouvement (la marche par exemple) et survient principalement ou exclusivement le soir ou la nuit(Allen et al. 2014). Le SJSR est considéré comme chronique lorsque les plaintes surviennent plus de deux fois par semaine pendant plus d'un an et sa sévérité est évaluée par un questionnaire dont un score supérieur à 21/40 témoigne d'un SJSR sévère ou très sévère(Walters et al. 2003). La principale complication du SJRS est une plainte de mauvais sommeil avec une insomnie, les patients présentant fréquemment des difficultés d'endormissement et des réveils nocturnes. Le SJSR

entraine également des répercussions diurnes tels qu'une fatigue, une somnolence ou des troubles de l'humeur et de la concentration avec une altération de la qualité de vie.

Les **troubles du rythme circadien veille-sommeil** surviennent en l'absence de synchronisation entre le rythme veille-sommeil (horloge biologique interne) et le rythme jour-nuit (lumière-obscurité). La symptomatologie est marquée par une insomnie et/ou une somnolence diurne excessive ainsi que par des répercussions diverses notamment sur les fonctions cognitives et l'humeur.

(b) Liens entre qualité du sommeil, durée de sommeil et troubles non respiratoires du sommeil avec les maladies cardiométaboliques

<u>En population générale</u>

Une méta-analyse récente a mis en évidence une association entre une mauvaise qualité de sommeil et les maladies coronariennes mais sans lien avec la mortalité(Kwok et al. 2018).

Un sommeil de courte durée est également associé à une augmentation de l'obésité, du diabète de type 2, de l'hypertension artérielle et des maladies cardiovasculaires(Chaput, Dutil, et Sampasa-Kanyinga 2018). Une durée de sommeil supérieure à 09 heures par nuit est associée à une augmentation de la mortalité cardiovasculaire alors que les données concernant le lien entre sommeil de courte durée et mortalité sont discordantes(Krittanawong et al. 2019; Kwok et al. 2018).

L'association entre les troubles du sommeil et les désordres cardiométaboliques est complexe et pas encore totalement élucidée. Les patients avec une insomnie et un sommeil de mauvaise qualité ont une augmentation de l'incidence des maladies cardiovasculaires(Bertisch et al. 2018) alors que les liens entre l'insomnie et l'obésité(Chan, Levsen, et McCrae 2018), l'hypertension artérielle ou les maladies cardiovasculaires ne sont pas établis(Jarrin et al. 2018).

Enfin, les troubles du rythme circadien veille-sommeil sont associés à une augmentation du risque de cancer et désordres métabolique et cardiovasculaires(Pavlova 2017) alors que le syndrome des jambes sans repos est associé avec des anomalies de la TA(Chenini et al. 2019) et une augmentation du risque cardiovasculaire(Gao et al. 2021).

Chez les patients avec une comorbidité cardiovasculaire

La présence d'une ou de plusieurs maladies chroniques est fréquemment associée à un sommeil de moins bonne qualité(Foley et al. 2004).

Un sommeil de mauvaise qualité a été associée à un moins pronostic chez des patientes avec une maladie coronarienne(Leineweber et al. 2003) alors qu'après un infarctus du myocarde, un pronostic plus sombre a été objectivé chez les femmes se plaignant d'un sommeil perturbé et chez les hommes mentionnant des troubles de l'éveil(Clark et al. 2014).

Les patients avec insuffisance cardiaque (IC) présentent également fréquemment une mauvaise qualité du sommeil qui est associée à une détérioration de la qualité de vie, de la vigilance et de l'humeur ainsi qu'à une altération du pronostic vital(K. S. Lee et al. 2016).

OBJECTIFS DU TRAVAIL

Cette thèse s'inscrit dans un travail de plus long terme comprenant deux objectifs :

1. **Améliorer la compréhension des liens physiopathologiques et cliniques entre les troubles du sommeil, et notamment le SAHOS, et les maladies cardiovasculaires.**
2. **Préciser les impacts cliniques et physiopathologiques de différents traitements du SAHOS.**

Les travaux réalisés au cours de cette thèse doivent permettre d'apporter des réponses aux questions soulevées par ces objectifs. La partie 2 du manuscrit comprend les articles publiés et soumis alors que la partie 3 décrit les travaux en cours et les perspectives.

La répartition des travaux en fonction des objectifs de la thèse est la suivante :

1/Améliorer la compréhension des liens physiopathologiques et cliniques entre les troubles du sommeil, et notamment le SAHOS, et les maladies cardiovasculaires

- Etude SAS IDM (Partie2, Etude 2). Impact du syndrome d'apnées du sommeil sur le remodelage ventriculaire de patients avec infarctus du myocarde
- Etude PROTISC (Partie 2, Etude 3). Impact pronostic des troubles du sommeil chez des patients avec insuffisance cardiaque
- Etude CardioXSAS (Partie 3, Etude 5). Evaluation des biomarqueurs métaboliques et cardiovasculaires chez des patients coronariens avec un SAHOS

2/ Préciser les impacts cliniques et physiopathologiques de différents traitements du SAHOS

- Etude REEVASAS : (Partie 2, Etude 1). Effet d'un programme individualisé de réentrainement à l'effort sur les marqueurs de sévérité du syndrome d'apnées hypopnées obstructives du sommeil
- Etude m-Rehab OSA : (Partie 3, Etude 4). Effet d'une solution de téléréhabilitation associée à la PPC sur les marqueurs de sévérité du SAHOS chez des patients obèses
- Etude CardioXSAS (Partie 3, Etude 5). Effet de la PPC sur les marqueurs de stress oxydant de patients coronariens avec SAHOS modéré.

PARTIE 2 : PRESENTATION DES TRAVAUX

Etude 1 : Effet d'un programme de réentrainement à l'effort individualisé sur les marqueurs de sévérité du syndrome d'apnées hypopnées obstructives du sommeil. Etude REEVASAS.

Prérequis

Le SAHOS est un trouble respiratoire du sommeil fréquent dont la prévalence augmente avec l'âge et en lien avec l'obésité(Heinzer et al. 2015). Les patients avec un SAHOS ont un niveau d'activité physique abaissé(Vivodtzev et al. 2017) et une aptitude physique à l'effort réduite(Mendelson, Marillier, et al. 2018). Le SAHOS est constitue un enjeu de santé publique et un enjeu économique en raison des nombreuses conséquences qui y sont associées et notamment la somnolence diurne excessive (SDE), l'altération de la qualité de vie, l'altération des capacités cognitives et les accidents de la voie publique(Gottlieb et Punjabi 2020). Le SAHOS est également associée avec une augmentation de l'incidence de l'hypertension artérielle et des maladies cardiovasculaires(José M. Marin et al. 2012; Javaheri et al. 2017).

La PPC est le traitement de référence du SAHOS en améliorant notamment l'IAH , la SDE et la qualité de vie(Patil et al. 2019) mais son efficacité sur les biomarqueurs cardiométaboliques(Jullian-Desayes et al. 2015) et sur la prévention primaire et secondaire des maladies cardiovasculaires reste débattue(McEvoy et al. 2016; Sánchez-de-la-Torre et al. 2019). Par ailleurs, la PPC peut entrainer une prise de poids(L. F. Drager et al. 2015).

Des **thérapeutiques alternatives** et/ou complémentaires à la PPC sont donc essentielles afin d'optimiser la prise en charge des patients avec un SAHOS. La prise en charge des troubles métaboliques est primordiale en cas de SAHOS. Une perte de poids est recommandée pour les patients apnéiques avec IMC élevé(Epstein et al. 2009) en privilégiant les modifications du mode de vie et les thérapies cognitivo- comportementales afin de réduire l'IAH. Une perte de poids de 10% est associée avec une réduction de l'IAH de 26%(Peppard et al. 2000) et la perte pondérale secondaire à des modifications nutritionnelles et un réentrainement à l'effort permet également de diminuer l'insulinorésistance, l'hypertriglycéridémie et l'inflammation(Chirinos et al. 2014). La majorité des études sur les effets de la perte de poids

ont employé des régimes restrictifs avec un suivi diététique rapproché. **Le réentrainement à l'effort** (RE) par lui-même peut aussi avoir un effet bénéfique sur le SAHOS avec une diminution de la sévérité du SAHOS , une amélioration de l'aptitude physique aérobie et de la somnolence diurne évaluée subjectivement, indépendamment de la perte de poids(Mendelson, Bailly, et al. 2018). Un programme de réentrainement à l'effort ou de réhabilitation permet également une diminution de la sévérité du SAHOS chez des patients coronariens(Mendelson et al. 2016; Loboda et al. 2021). Enfin, la pratique d'une activité physique permet d'améliorer différents paramètres du sommeil tels que le temps de sommeil, l'efficacité du sommeil, la latence d'endormissement ou encore la qualité du sommeil(Kline et al. 2021). Aucune étude n'a étudié l'impact d'un programme de RE sur la somnolence diurne chez les patients avec un SAHOS.

Les mécanismes impliqués dans les bénéfices du RE chez les patients avec SAHOS sont multifactoriels et pas encore totalement élucidés : réduction du tissu adipeux et du déplacement des fluides dans la zone des voies respiratoires supérieures, augmentation de la force musculaire oropharyngée, modification des médiateurs de l'inflammation, modification de l'architecture du sommeil lent profond(Mendelson, Bailly, et al. 2018; Torres-Castro et al. 2021). Les bénéfices du RE peuvent également s'expliquer par l'intermédiaire de son action sur la diminution de la sévérité des comorbidités associées au SAHOS telles que le diabète, l'hypertension artérielle ou les maladies cardiovasculaires(Adams et Linke 2019). (Figure 6)

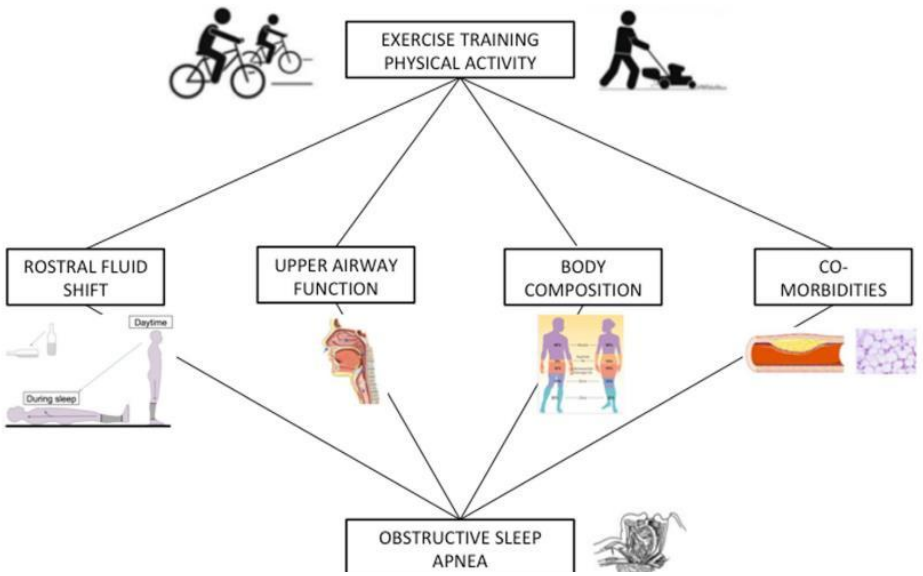

Figure 6. Mécanismes physiopathologiques entre le réentrainement à l'effort et le SAHOS. Mendelson, Frontiers in Neurology, 2018.

Article

Effects of an individualized exercise training program on severity markers of obstructive sleep apnea syndrome: a randomized controlled trial.

Bughin F, Desplan M, Mestejanot C, Picot MC, Roubille F, Jaffuel D, Mercier J, Jaussent I, Dauvilliers Y

Sleep Med 2020 Feb 18;70:33–42. PMID:32193052

Objectifs

Evaluer l'efficacité d'un programme de réentrainement à l'effort (RE) individualisé de 8 semaines sur les marqueurs de sévérité du SAHOS.

Méthodes

Etude randomisée contrôlée avec un groupe intervention association RE et sessions éducatives et un groupe contrôle contenant seulement des sessions éducatives. Les critères d'inclusion étaient la présence SAHOS modéré ou sévère (IAH 15-45/heure) et un faible niveau d'activité physique (Voorrips<9). Tous les patients ont réalisé à l'inclusion et en fin d'étude une polysomnographie, des tests itératifs de latence d'endormissement (TILE), une épreuve d'effort sur cycloergomètre et un bilan sanguin et ont rempli des auto-questionnaires. Le critère d'évaluation principal était la variation de l'IAH entre l'inclusion et la fin de l'étude entre les deux groupes.

Résultats

64 patients ont été inclus et 54 patients ont fini l'étude. Aucune différence significative entre les groupes n'a été mise en évidence pour les variations de l'IAH. Une réduction de l'IAH a été trouvée dans le groupe intervention (p=0,005) avec une chute de l'IAH de 21.5% entre l'inclusion et la fin de l'étude.

Par rapport au groupe contrôle, le RE a entrainé une diminution plus importante de l'IAH pendant le sommeil paradoxal (p=0,0004), et une augmentation significative de la latence moyenne d'endormissement aux TILE (p=0,02).

Le RE a également permis une amélioration de la tolérance à l'effort, une diminution du poids, de la sévérité de la fatigue ainsi que des scores d'insomnie et de dépression.

Des analyses en sous-groupes ont mis en évidence une réduction de l'IAH entre les deux groupes uniquement chez les femmes. Dans le groupe RE, une diminution de l'IAH a été observée chez les hommes, les patients obèses, les patients âgés de plus de 55 ans et ceux avec un IAH initial supérieur à 30/heure.

Conclusion et discussion

Un programme de RE individualisé de 8 semaines n'a pas diminué significativement l'IAH par rapport au groupe contrôle chez des patients avec SAHOS modéré à sévère. Le RE a permis une amélioration de plusieurs marqueurs de sévérité du SAHOS et notamment l'IAH en sommeil paradoxal et la somnolence diurne évaluée de manière objective.

L'efficacité du RE sur la diminution de la **somnolence diurne**, évaluée de manière objective par des tests itératifs de latence d'endormissement, a un intérêt certain dans la prise en charge des patients avec un SAHOS. La somnolence diurne est en effet la plainte principale des patients avec un SAHOS(Gottlieb et Punjabi 2020) et est associée avec une altération de la qualité de vie, les accidents de la voie publique, l'insulinorésistance ou encore avec une incidence accrue de maladies cardiovasculaires(Mazzotti et al. 2019).

Notre étude a mis en également évidence que le programme de RE permettait une diminution de **l'IAH en sommeil paradoxal (SP)**, ce qui peut avoir un intérêt dans le cadre de la prévention des troubles cardiométaboliques associés au SAHOS. Le SP représente environ 20 à 25% du temps de sommeil total et survient principalement en deuxième partie de nuit. La physiopathologie des évènements respiratoires obstructifs est différente pendant le SP notamment en raison de l'atonie musculaire du muscle génioglosse, dont la contraction participe à assurer la perméabilité des voies aériennes supérieures(Arrigoni, Chen, et Fuller 2016). Le SP est également marqué par une diminution de la chémosensibilité avec une

diminution de la commande ventilatoire. Ces phénomènes entrainent des évènements respiratoires plug longs et plus désaturant ainsi qu'une augmentation de l'activité sympathique(Varga et Mokhlesi 2019) (Figure 7). Le SAHOS en SP a différentes définitions et la condition constante est la présence d'un IAH en sommeil SP au moins deux fois supérieur à l'IAH en sommeil lent(Alzoubaidi et Mokhlesi 2016). La présence d'un SAHOS en SP est associée à une augmentation de la prévalence et l'incidence de l'HTA(Appleton et al. 2016) ainsi qu'au diabète de type 2 et au syndrome métabolique(Acosta-Castro et al. 2018). Par ailleurs, le SAHOS en SP est associé à une moins bonne observance de la PPC(Hoshino et al. 2018). La diminution de l'IAH en SP peut donc être une cible thérapeutique intéressante dans l'optique de diminuer les complications cardiométaboliques liées au SAHOS(Rishi et Rishi 2021).

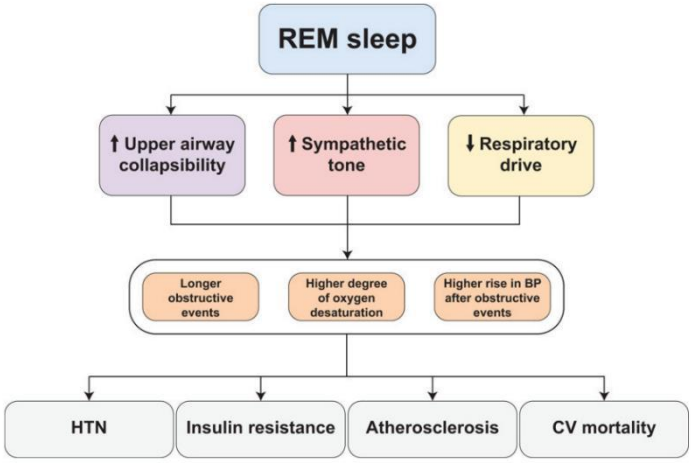

Figure 7. Liens entre SAHOS en Sommeil Paradoxal et complications cardiométaboliques. Varga et Mokhlesi, Sleep Breath, 2019.

Cette étude confirme donc les bénéfices d'un programme de RE sur les marqueurs de sévérité du SAHOS chez des patients inactifs et avec une composante métabolique. La prescription d'un programme de RE pourrait compenser les limites du traitement par PPC sur la prévention des complications cardiométaboliques du SAHOS. Des études complémentaires sont cependant nécessaires afin de mieux préciser les mécanismes liant le RE au SAHOS et à ses complications.

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Original Article

Effects of an individualized exercise training program on severity markers of obstructive sleep apnea syndrome: a randomised controlled trial

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) is a high prevalent disorder with severe consequences including sleepiness, metabolic, and cardiovascular disorders. The aim of this study was to assess the effect of an individualized exercise-training (IET) program with educational sessions vs educational sessions alone on severity markers of OSA over an eight-week duration.

Methods: This was a randomised, controlled, parallel-design study. In sum, 64 patients with moderate-to-severe OSA (apnea-hypopnea index AHI 15–45/hour), low physical activity level (Voorrips<9), body-mass index (BMI) <40 kg/m^2 were included in intervention group (IG) or control group (CG), and 54 patients finished the study. All underwent polysomnography (PSG), multiple sleep latency test (MSLT), constant workload exercise test, blood samples and fulfilled questionnaires twice. The primary endpoint was the change in apnea-hypopnea (AHI) at eight weeks from baseline. Main secondary endpoints were daytime sleepiness assessed by questionnaire and objective tests.

Results: No significant between-group differences were found for changes in AHI. A reduction in AHI was found in IG only ($p = 0.005$). Compared to CG, exercise training leads to a greater decrease in AHI during REM sleep ($p = 0.0004$), with a significant increase in mean daytime sleep latency ($p = 0.02$). Between-group differences were significant for weight reduction, severity of fatigue, insomnia and depressive symptoms with trend for sleepiness symptoms.

Conclusions: In adult patients with moderate-to-severe OSA, IET did not decrease AHI compared to the control group but improved markers of severity of OSA, in particular AHI in rapid eye movement (REM) sleep and objective daytime sleepiness. Adding personalized exercise training to the management of patients with OSA should be considered.

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1. Introduction

Obstructive sleep apnea (OSA) is a common sleep breathing disorder characterized by recurrent episodes of upper airway obstruction leading to intermittent hypoxia, arousals, increasing of sympathetic activity, oxidative stress, systemic inflammation and changes in intrathoracic pressure [1]. Excessive daytime sleepiness

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(EDS) is a cardinal symptom of OSA and is also associated with impaired quality of life, increased risk for accidents and metabolic and cardiovascular diseases [2–5].

Continuous positive airway pressure (CPAP) is the first-line treatment of OSA resulting in decrease of apnea-hypopnea index (AHI), EDS, and improvement of sleep quality. However, long-term CPAP effectiveness remains limited by low adherence [6] and no randomized controlled trial has demonstrated a key protective effect in prevention of cardiovascular diseases [7]. CPAP therapy showed no effect on weight loss, energy expenditure, and no clinical significant impact on metabolic disorders or biomarkers associated with OSA [8]. Other treatments such as oral appliances or upper airway surgery only partially correct OSA, may have side effects, and their efficacy on the metabolic and cardiovascular consequences of OSA are poorly studied [9].

OSA is closely related to being overweight/obese, with a bidirectional link. Obesity is the most important risk factor for OSA [10] and OSA by itself can contribute to weight gain [11]. Moreover, patients with OSA present a decreased level of physical activity [12]. Lifestyle modification including diet and exercise training may be effective in reducing weight and severity of OSA, and are therefore recommended for the management of OSA [13,14].

Currently, few studies addressed the impact of non-pharmacological strategies such as hypocaloric diets and exercise training on severity of OSA. Recent meta-analysis showed a significant decrease in AHI and subjective sleepiness after exercise training regardless of weight loss [15,16]. The mechanisms underlying such improvement remain unclear; however a reduction of adipose tissue and in fluid shift in the upper airway area, an increase in oropharyngeal muscle strength, a change in humoral mediators of inflammation and metabolism, and a modification of sleep architecture with increased slow wave sleep associated with an increased respiratory stability may attenuate the propensity towards airway collapse during sleep [15,16]. The benefits of exercise training may also reduce severity of comorbidities associated with OSA (eg, diabetes, hypertension or cardiovascular diseases) and increasing physical activity is recommended to prevent cardiovascular diseases [15]. We previously showed positive effects of exercise training on cardiometabolic parameters and subjective EDS assessed by the Epworth Sleepiness Scale (ESS) in OSA patients [17], but its impact on objective sleepiness had not been evaluated.

The aim of this randomized, parallel-design study was to evaluate the efficacy of an individualized exercise training (IET) program with educational sessions compared to educational sessions only in patients with low physical activity level and moderate-to-severe OSA over an eight-week duration on severity markers of OSA: (1) change in AHI at endpoint vs baseline, (2) changes in EDS assessed by questionnaire and objective tests, and (3) subgroups analyses of patients according to their age, gender, BMI, ESS and AHI levels.

2. Methods

2.1. Study design

The REEVASAS trial was a randomized, controlled, parallel-design study of the efficacy of an IET program with educational sessions vs educational sessions only over an eight-week duration in patients with moderate-to-severe OSA.

All participants were admitted to the Sleep Unit, Department of Neurology, University Hospital Center of Montpellier and gave their written informed consent. The study was conducted in accordance with the CONSORT ethical guidelines and was approved by the local ethics committee (CPP Sud-Méditerrannée IV) (ClinicalTrials.gov identifier NCT01256307).

2.2. Patients

Patients were adults aged between 30 and 65 years, with a diagnosis of moderate to severe OSA (AHI 15–45 events per hour), and low physical activity level (Physical activity score at the Voorrips questionnaire <9 [18]). Key exclusion criteria as follows: were current treatment for OSA (CPAP or mandibular advancement devices), a body-mass index (BMI)≥40 kg/m^2, contraindication for exercise training (like unstable cardiovascular disease), and taking drugs interfering with sleep architecture, continuity and daytime functioning.

A cardiopulmonary exercise test was performed at baseline using a cycle ergometer (Ergoline, GmBh) to determine the peak oxygen uptake (VO2peak) and the ventilatory threshold to further individualize the exercise training intensity.

2.3. Intervention and control groups

Patients who fulfilled selection criteria were randomized between intervention group (IG) or control group (CG). The randomization sequence was computer-generated using random blocks in an order unknown by the investigators. The list was established by a statistician and only accessible by personnel in charge of randomization.

In the IG, patients received an eight -week IET program that includes sessions 3 times per week. Each 120-min session included the following exercises: warming up muscles (15 min), endurance training (45 min), resistance training (30 min), stretching (15 min), and postural and balance exercises (15 min). A gradual increase in exercise dose was performed over the eight-week program to limit the risk of injury. The endurance training consisted of lower limb exercises on a cycle ergometer at moderate intensity determined via the heart rate at 60% V' O2 peak during the maximum exercise test. Heart rate was continuously measured with a heart rate monitor and load was adjusted every five minutes. Resistance training program included different exercises of upper and lower limbs with initial loads equivalent to 60% of the one repetition maximum. Resistance was increased when the patient could performed the current workload for 2 sets of 8 to 10 repetitions.

The sessions took place in the University Hospital of Montpellier and were supervised by a fitness trainer. The duration of IET was eight weeks and the composition of the sessions were based on the recommendations on respiratory rehabilitation [18–20].

Every week during 30–45 min, patients also benefited from group educational sessions aiming to better understand the role of sleep, OSA pathophysiology, disease management, diet balance, interest of physical activity practice and its impact on sleep. In the CG, patients received only educational sessions without exercise program. The health education program included similar educational activities and themes for both groups. No restrictive diet was prescribed in both groups but all patients were counseled on the nutritional balance.

2.4. Outcomes

The primary efficacy outcome was the change in AHI between baseline and eight-week follow-up in the IG group vs CG group.

Main secondary outcomes were changes from baseline in AHI in rapid eye movement (REM) and non-REM sleep, and in EDS using ESS and multiple sleep latency test (MSLT). Other outcomes were changes from baseline in others polysomnographic measures (total sleep time, sleep efficiency, micro arousal index, percentage of time spent at SpO2 below 90%, and oxygen desaturation index), and in self-reported questionnaires to assess fatigue (Chalder Fatigue [21]), anxiety and depressive (Hospital Anxiety and Depression Scale-

HADS [22]) and insomnia (Insomnia Severity Scale, ISI [23]) symptoms, and in weight, glycemia, and cholesterol levels.

All patients underwent in an in-lab polysomnography (PSG) followed the next day by a MSLT at baseline and at endpoint. PSG included EEG leads, electrooculogram, electromyography of chin and tibialis anterior muscle, electrocardiogram, nasal cannula/pressure transducer, mouth thermistor, chest and abdominal bands, and pulse oximeter. Obstructive apnea was defined as an airflow cessation (>90%) for more than 10 s associated with thoracoabdominal movements, and hypopnea as airflow reduction of more than 30% associated with a drop in SpO2 of more than 3% or a micro-arousal. Sleep stage, micro-arousals, periodic limb movements (PLM), and respiratory events were scored manually according to standard criteria [24]. Moderate OSA was defined by an AHI between 15 and 29.9 events per hour of sleep, and severe OSA by an AHI of more than 30 events per hour. Physicians who analysed the sleep data were blinded to the group allocation.

MSLT consisted of five naps scheduled at 2-h intervals between 9:00 AM and 5:00 PM. For each recording, the patients were allowed 20 min to fall asleep. If they did fall asleep, they were allowed to sleep an additional 15 min after which they were awakened. Sleep onset was determined by the first epoch of any stage of sleep. Mean sleep latency (MSL) from the five naps was computed for each subject. MSLT were scored by sleep experts blind to the experimental data and randomisation.

All patients were also administered standardised questionnaires and underwent clinical examinations, fasting blood intake to measure glycemia (mmol/L), and cholesterol total (g/L). Patients of both groups performed a constant-load exercise test on an electromagnetically braked cycle ergometer at a work rate equal to 80% of peak work capacity achieved during incremental cycle ergometry. Patients were asked to cycle for as long as possible and were told to stop when the pedalling rate of 60/min could not be kept up. All tests and evaluations of the study were assessed twice (at baseline and follow-up), at the same place for each group in the same conditions and with the same devices.

2.5. Power calculations

Statistical power was based on results comparing two groups of patients with moderate OSA with a change in AHI after intervention (four-months follow-up) equalled to −10.7 (SD = 7.7) in the trained group and −4.5 (SD = 6.9) in the control group [25]. Therefore, a total of 68 patients (34 per arm) provided a power of more than 90% for detecting a between-group difference for change in AHI of 6 at the endpoint using a 2-sided 2-sample t test with a significance level of 0.05.

2.6. Statistical analysis

Analyses of the primary outcome (AHI) were performed by intention-to-treat (ITT) principle. Missing data for the primary outcome were replaced using the Last Observation Carried Forward (LOCF) method. A sensitivity analysis was performed in a per-protocol population (PP) (excluding patients with major protocol violation with regard to inclusion or exclusion criteria (n = 4), with major protocol violation during the course of the treatment (n = 9) and premature discontinuation during the study (n = 1)). Secondary outcomes were analysed in PP population.

The characteristics of the study population were described using number and percentage for categorical variables and medians and interquartile ranges (IQR) for continuous variables because their distributions were mostly skewed according Shapiro–Wilk test. Nonparametric statistical tests were used due to the small sample size (less than 30 in each group in PP) and the distribution of continuous variables. Chi-square or Fisher's exact tests were used to compare categorical variables between the two groups, and Mann–Whitney U test for continuous variables. Changes in each outcome between baseline and two-month follow-up were compared between the groups using a Mann–Whitney U test. For the between-group differences, 95% Confidence Intervals (CI) were constructed. To compare differences between baseline and two-month follow-up within group, Wilcoxon signed-rank tests were used. Spearman's rank order correlations were used to determine associations between continuous variables. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with SAS version 9.4.

3. Results

3.1. Patients

Of the 68 patients who were randomized, 34 were in the IG and 34 in the CG (Fig. 1). Two patients randomized to IG and two patients randomized to CG were not eligible to continue the trial due to non-respect of selection criteria (due to a posteriori double blind rescoring of PSG to validate thresholds of baseline AHI). One death occurred in IG (unrelated to study). Of the 63 remaining patients, nine (four in IG and five in CG) discontinued the trial prior to endpoint without a post baseline assessment that include six patients due to withdrawal of consent and three with lost to follow-up. A total of 27 patients in IG and 27 in CG were included in per protocol analysis. Baseline characteristics were similar among the two groups (Table 1). Patients in IG who completed the eight-week intervention attended 77.9 ± 24.9% of their exercise sessions.

3.2. Main outcome

No significant between-group differences were found for changes in AHI from baseline to follow-up.

3.3. Secondary outcomes

In the IG, a significant decrease in AHI was found from baseline to endpoint ($p = 0.009$) with no effect in CG (Table 2). Compared to CG, IG resulted in greater decrease in AHI during REM sleep in PP analyses (Tables 2 and 3, Fig. 2). No effect of the IET was found on the postural AHI, with no between-group differences observed for supine and non-supine AHI at baseline and follow-up (Table 2). No other between-group differences were found on PSG measurements. A decrease in NREM 1–2 of sleep and an increase in NREM 3 were found in IG only.

A significant between-group increase in MSL on the MSLT ($p = 0.02$) was found (Table 3, Fig. 3). MSL was increased by 101.65 ± 206.05 s in IG ($p = 0.02$) with no change in CG. Among patients in IG, 12 patients had MSL below 900 s that corresponds to those with the greatest tendency to fall asleep during the day. These patients increased the MSL of 5 min or more after exercise training (median increase 300 s [288–480], $p = 0.001$) while no significant changes were found in patients from CG with baseline MSL below 900 s (n = 7; 24 s [-60-240], $p = 0.31$).

Between-group differences were significant for the weight ($p = 0.008$) that indicates a decrease in IG (Table 4) and no correlations were found between changes in AHI and weight ($r = -0.18$, $p = 0.38$). Moreover, no correlations were found between changes in weight and in AHI-REM or AHI-NREM in either IG or CG groups. Significant reduction were observed for fasting glycemia, with same tendency for cholesterolemia in IG group only, with no significant between-group differences.

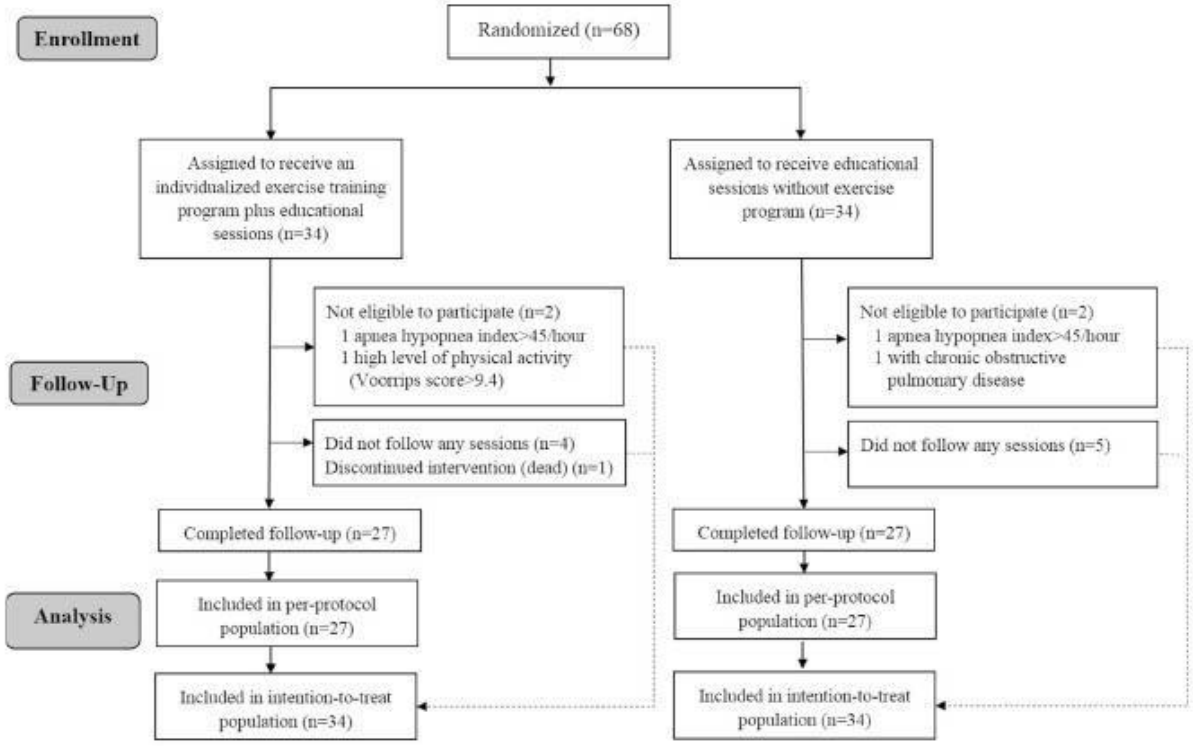

Fig. 1. Flow chart: REEVASAS study.

Significant between-group reductions were found for severity of fatigue, insomnia and depressive symptoms with similar trend for EDS using ESS ($p = 0.05$). Exercise training resulted in significant decrease of all these symptoms while no significant changes were found in CG. No correlation were found between changes in ESS and in MSL in the both groups ($r = -0.034$, $p = 0.86$ in CG; $r = 0.009$, $p = 0.97$ in IG) (Table 4).

Patients improved exercise tolerance and training adaptations at the end of the trial after IET with greater Voorrips scores and larger increased in cycle endurance time in the IG than in CG ($p < 0.02$, $p < 0.0001$ respectively) (Table 4).

3.4. Subgroup analyses

Additional analyses were performed by subgroups of patients according to their age, gender, BMI, ESS and AHI levels (Table 5). In intention-to-treat analyses, we found significant between-group differences for AHI only in female. In IG, AHI significantly decreased in male, patients obese and aged above 55 years and in those with initial AHI greater than 30 per hour. In contrast, between-group differences were found for AHI in REM sleep in patients obese, non-sleepy (ESS $\leq$ 10), aged above 55 years and with moderate OSA in intention-to-treat analyses (Table 5).

4. Discussion

In adult patients with moderate-to-severe OSA, IET did not decrease AHI compared to the control group, but a significant reduction in AHI was found from baseline to end of the study in the group with IET. Compared to CG, IET resulted in greater decrease in AHI during REM sleep and a significant increase in mean sleep latency on the MSLT. Besides, IET improve severity of fatigue, insomnia and depressive symptoms.

While the primary outcome was not reached, we found a reduction of 21.5% in AHI in IG in line with our previous study [17] and with a recent meta-analysis showing a mean reduction of 28% after exercise training interventions [15]. The lack of significant between-group difference may be partly explained by the improvement in CG patients with 33% decreasing their AHI by more than 20%. Such improvement in CG may be related to behavioral changes secondary to educational sessions on physical activity and diet balance, being finally not an optimal control group per se. We also found no effect of the IET on the postural AHI, with no between-group differences for changes in supine and non-supine AHI.

Our trial found a significant between-group improvement in weight. The loss of weight in our trial could be partly explained by changes in diet secondary to educational sessions, although no defined diet prescriptions were provided. We found no correlations between the changes in weight and in AHI, AHI in REM, and AHI in NREM that suggest an independent role of exercise in improving severity of OSA. The global effects of exercise training on OSA are really diverse, often moderate; thus the benefits reported of improving OSA severity were not directly related to weight reduction. Other mechanisms (eg, fat loss, fluid shifts, changes in mediators of inflammation and metabolism, changes in oropharyngeal muscle function, and increased slow-wave sleep) may be also involved and remain to be elucidated [14,15,26,27].

We reported that IET may improve objective measures of EDS. These results could be even better than those obtained with CPAP

Table 1
Characteristics of participants randomized to Intervention Group vs Control Group.

Variable	Control Group N = 34		Intervention Group N = 34		p
	n	%	n	%	
Demographic and clinical characteristics					
Sex, Female	4	11.76	9	26.47	0.12
Age, in years[a]	55.00 (10.27)		53.71 (9.86)		0.75
BMI, kg/m^2[a]	30.60 (3.40)		30.65 (6.20)		0.92
Diabetes mellitus, Yes	5	14.71	3	9.09	0.71
Hypertension/antihypertensive intake, Yes	12	35.29	9	27.27	0.85
Dyslipidemia, Yes	14	41.18	9	27.27	0.32
Current smoker, Yes	8	23.53	4	12.12	0.30
Family history of cardiovascular diseases, Yes	13	39.39	11	33.33	0.67
Polysomnographic measurements					
TST, minutes[a]	440.00 (97.00)		436.00 (92.00)		0.73
Sleep efficiency, %[a]	83.57 (19.93)		78.74 (15.01)		0.32
N1–N2, %[a]	62.57 (9.77)		66.81 (12.76)		0.32
N3, %[a]	15.04 (11.81)		14.24 (9.00)		0.60
REM, %[a]	20.22 (10.73)		20.38 (6.93)		0.48
PLMS index,/hour[a]	1.45 (5.02)		3.93 (6.45)		0.08
AHI,/hour[a]	26.10 (15.78)		28.15 (12.89)		0.65
Time spent with SaO2 < 90%, min[a]	1.10 (3.25)		1.07 (2.10)		0.94
Mean SaO2, %[a]	94.00 (2.00)		94.00 (2.00)		0.92
Arousal index events,/hour[a]	19.15 (10.81)		20.91 (11.22)		0.72
Oxygen desaturation Index,/hour[a]	18.23 (28.16)		22.29 (17.63)		0.22

BMI: body mass index; AHI: apnoea hypopnoea index; REM: rapid eye movement sleep.
[a] Continuous variables were expressed as median (interquartile range).

or mandibular advancement device [28]. EDS is one of the most common symptom in OSA patients and is associated with lower quality of life, work or traffic accidents, obesity, and diabetes [29,30]. The severity of EDS is often quantified by ESS with either weak or no correlation with severity of AHI, and never with AHI in REM sleep [31]. Moreover, no or only weak correlations were found between ESS and objective measurement of EDS in patients with OSA or with other sleep conditions [32]. Here, we found a between-group difference for mean sleep latency with improvement of more than 2 min, with greater results in patients with the highest objective sleepiness at baseline. In contrast to narcolepsy [33,34], there is a lack of normative MSLT data in OSA with a wide range of baseline MSL results [35]. We found here no correlation between baseline MSL and ESS, AHI, AHI-REM and sleep stages, and between changes in MSL along the study with ESS, AHI or AHI-REM and sleep stage modifications. These results are consistent with the literature and confirmed that the determinants of EDS are multiple (ie, depressive symptoms, obesity, short sleep duration, age, race, low-grade inflammation) and complex, as well as to in OSA [32]. Other symptoms were frequently reported by patients with OSA such as fatigue, insomnia and depressive symptoms [36] and all improved after our exercise training program.

We found a significant between-group difference of AHI during REM sleep, with a larger reduction of 37.5% in IG. A reduction of AHI in REM sleep was already reported following exercise training in patients with AHI >15/hour [37], but not in a smaller four-week study including patients with coronary artery disease associated with OSA or central sleep apnea [26]. In contrast, the latter study found that exercise induced a reduction in the non-REM AHI. The decrease of AHI in REM sleep is of major interest given that OSA during REM sleep have worse cardiometabolic consequences than OSA in NREM sleep. Apnea and hypopnea in REM sleep are longer and associated with greater desaturation than in non REM sleep [38]. Recent studies found that OSA in REM sleep is independently associated with prevalent and incident hypertension, non-dipping nocturnal blood pressure, increased insulin resistance and cardiovascular diseases [39–41]. Therefore, decreasing AHI specifically in REM sleep after IET may be a target to prevent from metabolic and cardiovascular disorders. Our study emphasized that IET associated with health education program including diet balance improved anthropometric and metabolic parameters, in decreasing weight, fasting glycemia, with same tendency for cholesterolemia in IG. These results are of interest given the limited effects of CPAP on the glycemic and lipid balance, and on OSA in REM sleep [8]. The 4-h of

Table 2
Changes in apnea hypopnea indexes between baseline and 8-week follow-up in intention to treat population.

Variable	Control Group (N = 34)				Intervention Group (n = 34)					
	Baseline	Follow-up	Within-Group Difference[a]		Baseline	Follow-up	Within-Group Difference[a]		Between-Group Difference[b]	
	Median (IQR)	Median (IQR)	Median (IQR)	p	Median (IQR)	Median (IQR)	Median (IQR)	p	Median [95%CI]	p
Primary outcome										
AHI,/hour	26.10 (15.78)	25.47 (18.00)	0.00 (12.86)	0.83	28.15 (12.89)	21.80 (17.29)	−4.23 (12.35)	0.009	3.47 [-1.60; 9.67]	0.22
AHI-REM,/hour	20.84 (30.44)	23.38 (40.68)	0.06 (22.27)	0.33	40.28 (20.19)	28.39 (25.81)	−10.00 (20.89)	<0.001	13.70 [5.22; 24.70]	0.001
AHI-NREM,/hour	26.82 (14.66)	24.51 (21.97)	−1.41 (15.98)	0.50	24.75 (13.73)	19.83 (18.26)	−1.33 (9.65)	0.09	0.05 [-5.23; 6.72]	0.85
AHI-supine/hour	30.95 (16.70)	31.16 (28.26)	0.00 (22.41)	0.67	30.60 (22.20)	22.90 (20.94)	0.00 (14.48)	0.41	2.47 [-4.73; 10.75]	0.54
AHI-non supine,/hour	10.35 (4.70)	11.35 (14.29)	0.00 (14.41)	0.74	11.90 (13.34)	8.34 (14.01)	−3.17 (11.93)	0.11	3.74 [-1.39; 9.31]	0.16

AHI: Apnea Hyponea Index; REM: Rapid Eye Movement.
[a] Indicates medians change between follow-up and baseline.
[b] Indicates medians change difference between the control group and the intervention group.

Table 3
Changes in polysomnographic and daytime sleepiness measurements between baseline and 8-week follow-up in per-protocol population.

Variable	Control Group (N = 27)				Intervention Group (n = 27)					
	Baseline	Follow-up	Within-Group Difference[a]		Baseline	Follow-up	Within-Group Difference[a]		Between-Group Difference[b]	
	Median (IQR)	Median (IQR)	Median (IQR)	p	Median (IQR)	Median (IQR)	Median (IQR)	p	Median [95%CI]	p
Primary outcome										
AHI,/hour	26.00 (12.70)	25.91 (22.03)	−1.60 (20.77)	0.94	26.50 (13.00)	16.80 (16.59)	−5.53 (12.63)	0.005	5.13 [-1.40; 13.64]	0.11
Secondary polysomnographic outcomes										
AHI-REM,/hour	20.95 (26.87)	31.54 (40.75)	2.68 (32.79)	0.18	40.26 (19.24)	26.47 (19.48)	−11.74 (22.58)	<0.001	20.43 [8.85; 33.48]	0.0007
AHI-NREM,/hour	25.83 (16.22)	26.81 (23.70)	−5.74 (22.04)	0.69	21.52 (14.67)	15.86 (19.75)	−3.08 (10.55)	0.07	0.52 [-6.12; 9.80]	0.88
Time spent with SaO2 < 90%, *min*	1.65 (4.24)	1.67 (4.21)	0.00 (2.12)	0.78	0.85 (1.50)	0.55 (1.30)	−0.11 (1.91)	0.38	0.25 [-0.61; 1.35]	0.47
Mean SaO2, %	94.00 (2.00)	94.00 (2.00)	0.00 (2.00)	0.93	94.00 (1.00)	95.00 (2.00)	0.00 (2.00)	0.48	0 [-1; 1]	0.65
Arousal index events,/hour	19.31 (12.38)	22.50 (9.71)	3.73 (16.49)	0.13	20.96 (11.22)	20.58 (11.70)	−0.50 (14.46)	0.67	4.47 [-1.75; 10.73]	0.12
Oxygen desaturation Index,/hour	22.13 (22.83)	27.39 (15.57)	4.11 (23.69)	0.12	22.29 (17.63)	14.94 (14.52)	−1.38 (22.42)	0.29	8.86 [0.15; 17.50]	0.05
TST, minutes	433.00 (96.00)	437.00 (104.00)	2.00 (79.00)	0.50	438.00 (81.00)	447.00 (107.00)	14.00 (71.00)	0.47	1 [-32; 33]	0.99
Sleep efficiency, %	75.05 (21.62)	75.65 (15.39)	−0.90 (17.05)	0.61	79.40 (16.78)	77.28 (16.94)	1.01 (16.03)	0.80	−2.07 [-8.39; 5.81]	0.60
N1–N2, %	62.34 (10.79)	64.75 (14.09)	−1.28 (11.51)	0.54	66.90 (13.80)	62.49 (15.41)	−3.70 (13.04)	0.006	3.52 [-1.03; 8.18]	0.13
N3, %	15.40 (11.81)	16.15 (10.74)	0.80 (9.30)	0.33	13.98 (8.01)	16.60 (10.49)	2.23 (7.97)	0.02	−1.94 [-5.43; 1.00]	0.13
REM, %	19.30 (10.68)	20.00 (8.66)	−2.48 (7.21)	0.69	20.25 (5.69)	21.57 (9.70)	1.71 (8.86)	0.10	−2.50 [-5.69; 0.60]	0.11
PLMS index,/hour	1.45 (5.95)	3.72 (17.86)	0.21 (17.98)	0.06	3.93 (6.14)	4.50 (15.79)	0.56 (9.65)	0.11	0.28 [-2.81; 4.43]	0.82
Objective daytime sleepiness outcome										
MSLT, seconds	1032.00 (246.00)	915.00 (312.00)	−18.00 (202.50)	0.28	972.00 (444.00)	1050.00 (192.00)	54.00 (288.00)	0.02	−136.50 [-264.00;-24.00]	0.02

[a] Indicates medians change between follow-up and baseline.
[b] Indicates medians change difference between the control group and the intervention groupAHI: Apnea Hyponea Index; MSLT: Multiple Sleep Latency Test; PLMS: Periodic Limb Movements of Sleep; REM: Rapid Eye Movement; SaO2: Oxygen Saturation; TST: Total Sleep Time.

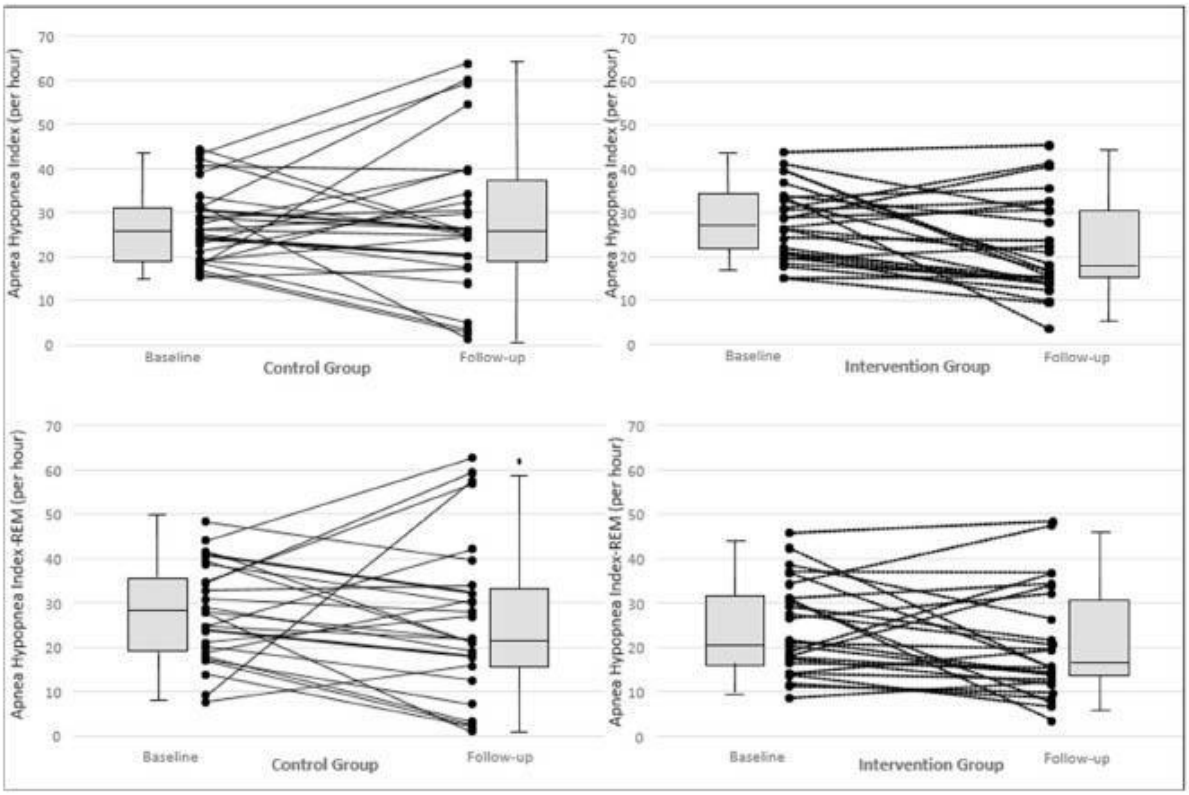

Fig. 2. Individual trajectories of apnea/hypopnea index (AHI) and AHI in REM sleep at baseline and after 8 weeks in patients in IG and CG groups. Results are shown as individual level and with a box–whisker plot, with median and 25th quartile of AHI.

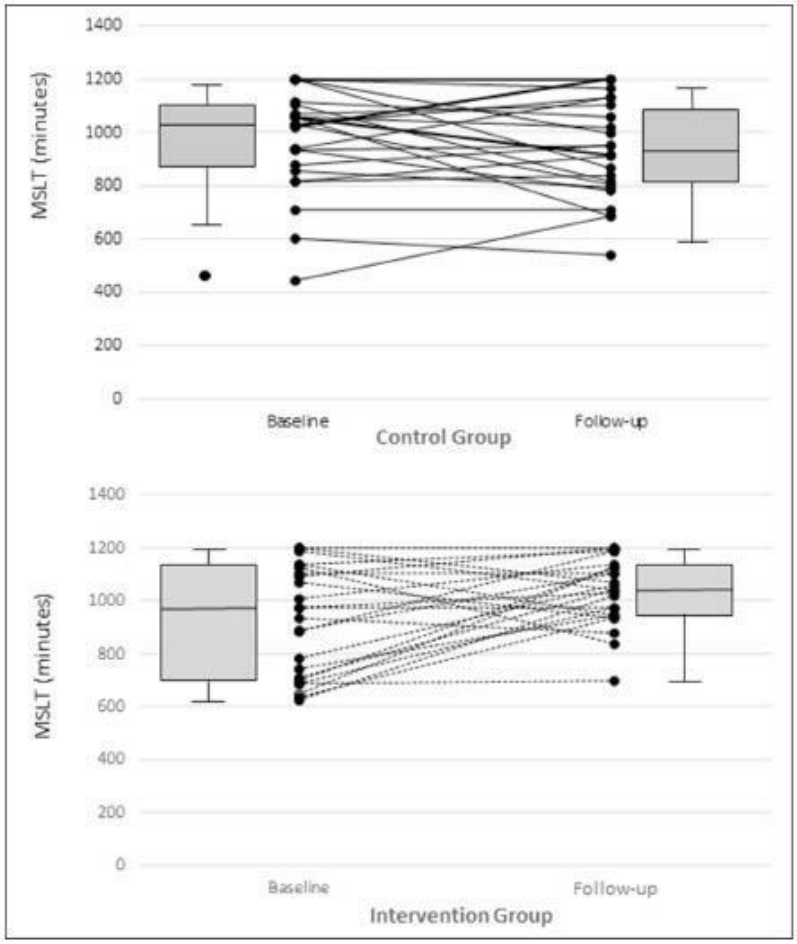

Fig. 3. Individual trajectories of mean sleep latency on the multiple sleep latency test (MSLT) at baseline and after 8 weeks in patients in IG and CG groups. Results are shown as individual level and with a box–whisker plot, with median and 25th quartile of MSL.

nightly CPAP use is often considered an adequate adherence to therapy, however it does not cover the early morning hours associated with REM OSA at risk for cardiovascular and metabolic risks.

We reported a clinically meaningful increase in cycle endurance time after IET, reflecting an improvement of exercise tolerance and training adaptations at follow-up. This result is consistent with those obtained after respiratory rehabilitation in patients with chronic obstructive pulmonary disease [42]. This is a noteworthy result as OSA patients have reduced maximal aerobic capacity and intensity of physical activity below recommendations [40]. The low levels of physical activity in patients with OSA may relate to fatigue, EDS, obesity, exercise intolerance and neurocognitive problems that may all contribute to cardiovascular disorders. Although CPAP reduces EDS and improves quality of life, a recent meta-analysis showed that CPAP did not increase physical activity [15].

Our study also aimed to identify OSA subgroups likely to greater improvement after IET and found that females were associated with the highest decrease in AHI although a limited number of females participated in this study. In contrast, obese, non-sleepy (ESS≤ 10), moderate OSA and patients aged above 55 years were associated with the largest decrease of AHI in REM sleep. Accordingly, obese middle-aged and elderly patients with moderate OSA, often associated with cardiometabolic comorbidities, may be the target population that would benefit the most from IET.

There are limitations in our study. First, the low sample size, the possible underestimated effect size, the high number of drop-outs in the two groups could have affect the magnitude of the results; however this study is the largest randomised study evaluating the efficacy of an IET program in patients with moderate to severe OSA with assessment of EDS by questionnaire and MSLT. The sample size calculation is based on an old study [25] with different duration and design than our study that may have underestimated the effect size; however it was one of the only study available when the current study was planned. The duration of exercise training is also questionable, it may have been too short (eight-week duration) to obtain maximal effects, and to assess on long-term maintenance on both increased physical activity levels and OSA severity; although recent analyses reported that the length of the intervention was not associated with changes in AHI [14,42,43]. Second, physical activity level was assessed at baseline by the Voorrips questionnaire and not by objective measure because the trial was designed long time ago. However, a significant increase in cycle

Table 4
Changes in on weight, metabolic, sleep, psychological and endurance parameters between baseline and 8-week follow-up in per-protocol population.

Variable	Control Group (N = 27)				Intervention Group (n = 27)					
	Baseline	Follow-up	Within-Group Difference[a]		Baseline	Follow-up	Within-Group Difference[a]		Between-Group Difference[b]	
	Median (IQR)	Median (IQR)	Median (IQR)	p	Median (IQR)	Median (IQR)	Median (IQR)	p	Median [95%CI]	p
Anthropometric and metabolic parameters										
Weight, kg	87.40 (11.90)	88.20 (9.60)	0.50 (2.80)	0.45	89.60 (13.40)	89.40 (11.50)	−1.45 (2.60)	0.006	−1.7 [-2.8;-0.4]	0.0009
Glycemia, mmol/L	5.50 (0.60)	5.10 (0.90)	−0.20 (0.60)	0.09	5.10 (1.20)	5.25 (1.10)	−0.25 (0.55)	0.03	−0.2 [-0.5; 0.2]	0.39
Cholesterol total, g/L	2.14 (0.61)	2.10 (0.49)	0.02 (0.37)	0.65	2.15 (0.45)	2.00 (0.47)	−0.08 (0.30)	0.05	0.05 [-0.06; 0.16]	0.31
Fatigue, depression, anxiety and sleep measurements										
Fatigue Mental score	9.00 (3.00)	8.00 (2.00)	0.00 (2.00)	0.69	8.00 (2.00)	7.00 (2.00)	−2.00 (4.00)	0.001	2 [1; 3]	0.002
Fatigue Physical score	16.00 (4.00)	15.50 (4.00)	0.00 (4.00)	0.79	16.00 (6.00)	10.50 (6.00)	−6.00 (9.00)	<0.0001	6 [3; 9]	0.0003
HAD-Depression	6.00 (6.00)	5.00 (6.00)	−0.50 (2.00)	0.54	5.00 (5.00)	3.00 (4.00)	−3.00 (3.00)	0.0002	2 [1; 4]	0.007
HAD-Anxiety	8.00 (5.00)	8.00 (5.00)	0.00 (4.00)	0.99	8.00 (6.00)	6.00 (6.00)	−1.00 (5.00)	0.06	1 [-1; 3]	0.17
ISI Score	13.00 (9.00)	12.50 (8.00)	−1.50 (4.00)	0.50	13.00 (6.00)	7.50 (8.00)	−4.00 (9.00)	0.0008	4 [1; 7]	0.03
ESS score	9.00 (7.00)	10.00 (8.00)	0.00 (3.00)	0.99	10.00 (7.00)	8.00 (6.00)	−2.00 (6.00)	0.004	2 [0; 4]	0.05
Endurance test and Voorrips score										
Endurance Test, sec	261.00 (275.00)	480.00 (583.00)	138.00 (225.00)	<0.001	423.00 (462.00)	1590.00 (1455.00)	1120.00 (1296.00)	<0.001	−695 [-1200;-344]	<0.0001
Voorrips score	4.90 (4.60)	3.50 (4.40)	0.40 (2.56)	0.30	4.06 (4.89)	5.44 (5.46)	1.92 (4.16)	<0.001	−1.59 [-3.69;-0.36]	0.02

ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; HAD-Depression: Hospital Anxiety Depression- Depression sub-scale; HAD-Anxiety: Hospital Anxiety Depression- Anxiety sub-scale.
[a] Indicates medians change between follow-up and baseline.
[b] Indicates medians change difference between the control group and the intervention group.

Table 5
Changes in Apnea hypopnea index and Apnea hypopnea index in REM sleep in response to the individualized exercise training program by participant characteristics in intention to treat population.

Variable	Control Group N = 32			Intervention Group N = 32			Between-Group Difference[b]	
	Within-Group Difference[a]			Within-Group Difference[a]				
	n	Median (IQR)	p	n	Median (IQR)	p	Median [95%CI]	p
Apnea hypopnea index								
Sex								
Male	30	−1.19 (9.97)	0.29	25	−5.53 (12.52)	0.02	2.23 [-2.96; 9.67]	0.50
Female	4	10.65 (21.57)	0.13	9	0.00 (5.50)	0.44	14.98 [3.78; 36.60]	0.03
Age, in years								
<55	17	0.00 (13.49)	0.38	19	0.00 (15.40)	0.19	0.00 [-7.60; 10.99]	0.99
≥55	17	0.00 (16.62)	0.71	15	−5.50 (8.27)	0.006	5.84 [-0.78; 16.07]	0.09
BMI, kg/m^2								
<30.0	14	−1.21 (19.77)	0.91	14	0.00 (7.39)	0.58	0.00 [-7.68; 10.99]	0.98
≥30.0	19	0.00 (12.86)	0.86	20	−5.75 (13.65)	0.008	5.53 [-1.53; 15.82]	0.14
ESS								
≤10	18	−1.61 (17.68)	0.78	18	−5.35 (17.71)	0.06	5.89 [-2.66; 18.09]	0.19
>10	16	0.00 (13.33)	0.68	15	−3.29 (11.23)	0.08	1.64 [-6.30; 9.39]	0.60
AHI/h								
[15–30]	21	0.00 (9.78)	0.77	20	−1.99 (6.79)	0.23	2.25 [-2.43; 7.59]	0.33
≥30	13	−0.78 (17.29)	0.56	14	−8.36 (23.93)	0.03	5.45 [-7.69; 20.53]	0.61
Apnea hypopnea index in REM sleep								
Sex								
Male	30	0.00 (22.04)	0.80	25	−8.90 (21.27)	0.002	11.09 [0.64; 23.93]	0.02
Female	4	23.69 (25.66)	0.13	9	−11.38 (15.90)	0.03	33.18 [14.50; 53.77]	0.02
Age, in years								
<55	17	0.00 (14.16)	0.97	19	−8.90 (25.56)	0.005	10.73 [0; 27.35]	0.07
≥55	17	6.65 (22.96)	0.13	15	−11.09 (20.89)	0.01	17.61 [5.85; 30.93]	0.01
BMI, kg/m^2								
<30.0	14	0.00 (22.96)	0.91	14	−3.07 (13.79)	0.18	4.11 [-8.65; 20.83]	0.43
≥30.0	19	1.81 (30.59)	0.21	20	−12.06 (22.55)	<0.001	21.27 [8.85; 36.98]	0.002
ESS								
≤10	18	0.06 (26.78)	0.27	18	−11.56 (15.89)	0.001	14.97 [3.09; 31.27]	0.01
>10	16	0.91 (26.78)	0.85	15	−8.90 (21.27)	0.02	11.67 [-3.22; 27.54]	0.12
AHI/h								
[15–30]	21	1.81 (17.10)	0.20	20	−11.88 (23.41)	<0.001	16.45 [5.98; 30.40]	0.002
≥30	13	0.00 (22.27)	0.99	14	−6.28 (12.50)	0.05	7.59 [-5.95; 28.82]	0.21

[a] Indicates medians change between follow-up and baseline.
[b] Indicates medians change difference between the control group and the intervention group.

endurance time was found after IET. The use of actimeters would have been of interest to control for any spontaneous physical activity that participants did outside the structured sessions. Third, CG is not a real control group as patients benefited to educational sessions including diet balance that may be a confounding factor limiting the observed changes in the group with IET. Fourth, we included only adults with moderate-to-severe OSA, low physical activity level, without psychotropic drugs intake that may limit the generalizations of our findings. Finally, the subgroup analyses could be limited by the low number of subjects in each subgroup (such as the gender effect).

In conclusion, while the primary outcome was not reached, this is the first randomised controlled trial demonstrating that individualized exercise training improved objective measure of sleepiness and AHI in REM sleep in patients with moderate-to-severe OSA. Personalized exercise training also improved weight, severity of fatigue, insomnia and depressive symptoms. However, the mechanisms underlying the relationships between physical activity, OSA in REM sleep, and sleep remain unclear. Further studies are required to optimize treatment strategies and personalize therapy to achieve long-term benefits as function of OSA phenotypes.

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CRediT authorship contribution statement

F. Bughin: Investigation, Data curation, Writing - original draft. **M. Desplan:** Investigation, Data curation, Funding acquisition, Writing - review & editing. **C. Mestejanot:** Investigation, Data curation, Writing - review & editing. **M.C. Picot:** Methodology, Validation, Resources, Writing - review & editing. **F. Roubille:** Investigation, Data curation, Writing - review & editing. **D. Jaffuel:** Investigation, Data curation, Writing - review & editing. **J. Mercier:** Methodology, Validation, Writing - review & editing. **I. Jaussent:** Methodology, Formal analysis, Writing - review & editing. **Y. Dauvilliers:** Funding acquisition, Writing - original draft, Conceptualization, Supervision.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.02.008.

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Etude 2 : Impact du syndrome d'apnées du sommeil sur le remodelage ventriculaire de patients avec infarctus aigu du myocarde. Etude SAS-IDM.

Prérequis

L'infarctus du myocarde (IDM) correspond à une nécrose ischémique du myocarde secondaire à une occlusion aigue d'une artère coronaire. Le diagnostic comporte une symptomatologie clinique et une augmentation des biomarqueurs cardiaques (troponine ultrasensible) associée à des anomalies de l'électrocardiogramme et/ou l'identification d'un thrombus coronaire à l'angiographie et/ou une imagerie démontrant la perte de myocarde viable(Thygesen et al. 2018). L'IDM peut toucher le ventricule gauche (VG) ou le ventricule droit (VD). Le terme IDM rassemble les IDM avec sus décalage du segment ST (STEMI) et les IDM sans sus décalage du segment ST (NSTEMI), distinction essentielle étant donné qu'elle conditionne la stratégie thérapeutique.

Le pronostic des IDM s'est nettement amélioré ces trois dernières décennies notamment grâce à l'utilisation croissante des stratégies de reperfusion, des traitements éprouvés (bêta-bloquants, aspirine et statines notamment) et des avancées thérapeutiques(Ibanez et al. 2018; Tardif et al. 2019). Cependant, les patients présentant un IDM ont un risque accru de nouveaux évènements cardiovasculaires majeurs (ECM) incluant des évènements coronariens, des arythmies, des accidents vasculaires cérébraux, une insuffisance cardiaque.

Le remodelage ventriculaire, survenant chez certains patients ayant présenté un IDM, correspond à des modifications structurelles et fonctionnelles cardiaques et est associé avec le développement d'une insuffisance cardiaque(Cheng et Vasan 2011) et un moins bon pronostic(Reindl et al. 2019). Les mécanismes du remodelage comprennent des changements cellulaires (nécrose myocardique, inflammation) et extracellulaires entrainant une fibrose du myocarde ainsi que des modifications neuro-hormonales impliquant le système nerveux sympathique et le système rénine-angiotensine-aldostérone (Bhatt, Ambrosy, et Velazquez 2017). Ces phénomènes entrainent une augmentation du volume cardiaque et notamment du volume télédiastolique du ventricule gauche (VTdVG) et du volume télésystolique du ventricule gauche (VTsVG)(Bulluck et al. 2020).

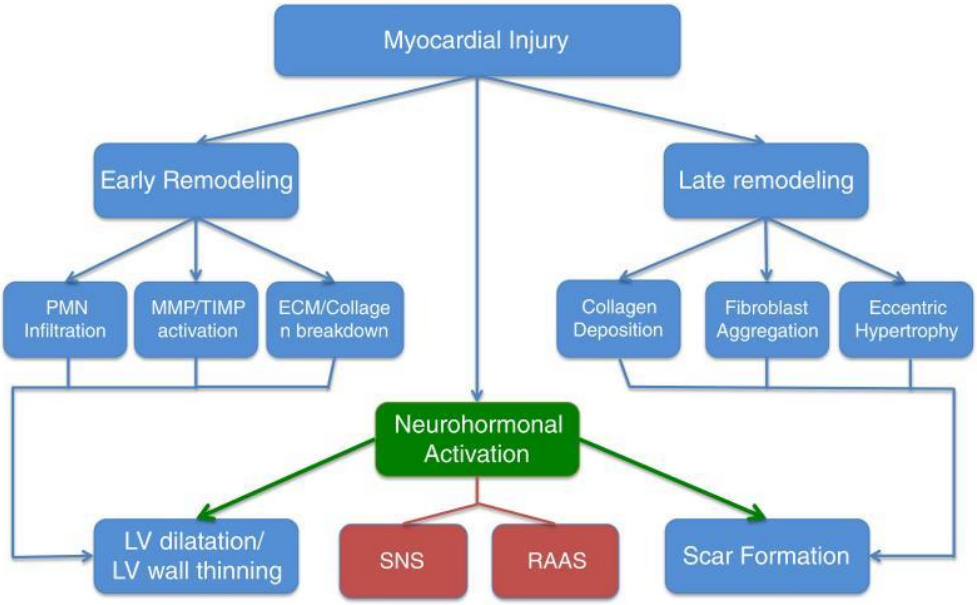

Figure 8. Mécanismes impliqués dans le développement du remodelage ventriculaire après un IDM. Bhatt, Curr Cardiol Rep, 2017.

L'imagerie par résonance magnétique (IRM) cardiaque est un examen de référence pour évaluer le remodelage ventriculaire. Elle permet d'évaluer le VG et le VD et de mesurer notamment la fraction d'éjection et les volumes télésystoliques et télédiastoliques. Elle permet également d'étudier la viabilité myocardique et la perfusion. Par rapport à l'échographie cardiaque, l'IRM a une moindre variabilité inter observateur(Hoffmann et al. 2014).

La prévalence du SAHOS est élevée chez les patients ayant présenté un IDM(Morra et al. 2017). Chez les patients avec un IDM, les conséquences physiopathologiques du SAHOS (hypoxie intermittente, modification des pressions intra thoraciques, hyperactivité sympathique, inflammation, stress oxydant) pourraient favoriser le remodelage ventriculaire mais les données sont peu nombreuses(Buchner et al. 2014; Fisser et al. 2020). Par ailleurs, l'impact pronostic de la présence d'un SAHOS chez les patients avec un IDM n'est pas clairement établi(Xie et al. 2018 ; Sánchez-de-la-Torre et al. 2019).

L'hypothèse de cette étude est que le SAHOS pourrait aggraver le remodelage pathologique qui suit l'IDM et serait un des principaux facteurs d'évolution péjorative.

Article

Impact of Obstructive Sleep Apnea Syndrome on the Ventricular Remodeling After Acute Myocardial Infarction

F Bughin, H Kovacsik, I Jaussent, K Solecki, J Vanoverschelde, H Zarqane, J Mercier, F Gouzi[1], F Roubille, Y Dauvilliers

Papier en voie de soumission

Objectifs

Comparer le remodelage ventriculaire évalué par IRM cardiaque dans les 6 mois suivant un infarctus du myocarde (IDM) entre les patients avec un SAHOS (IAH≥5/h) et sans SAHOS (IAH <5/h).

Méthodes

SAS-IDM est une étude monocentrique réalisée au CHU de Montpellier.

Les patients inclus étaient des patients admis pour IDM avec une IRM cardiaque réalisée à 5 ± 2 jours démontrant un infarctus sévère (≥5/17 segments du ventricule gauche (VG) présentant un rehaussement tardif). Une polysomnographie a été réalisée 21±10 jours après l'IDM et les patients ont été classés selon leur IAH : absence de SAHOS (IAH<5/h), SAHOS léger à modéré (IAH 5-29,9) et SAHOS sévère (IAH ≥30/h). Une IRM cardiaque était réalisée à 6 mois après l'IDM.

Le critère de jugement principal était la différence de remodelage ventriculaire gauche (évalué par les volumes télésystolique et télédiastolique du VG en IRM cardiaque) à 6 mois après un IDM entre un groupe de patients sans SAHOS (IAH<5/heure) et un groupe de patients avec un SAHOS (IAH ≥5/h).

Les critères de jugement secondaires étaient l'association entre les paramètres de remodelage ventriculaire gauche et droits avec les paramètres cliniques, biologiques et polysomnographiques.

Résultats

Parmi les 47 patient inclus dans l'étude, 7 patients n'avaient pas de SAHOS, 17 avaient un SAHOS léger, 12 un SAHOS modéré et 11 un SAHOS sévère. 85 % étaient des hommes avec un âge médian de 57,4 ans (min=33,6 ; max=74,4) et un indice de masse corporelle médian de 25,2 kg/m² (min=18,5 ; max=33,1).

Aucune différence significative entre les groupes n'a été trouvée concernant les caractéristiques démographiques, cliniques et biologiques des patients, à l'exception du taux de CRP et du score de dépression BDI.

À 6 mois, aucune différence significative n'a été observée entre les patients avec un SAHOS et les patients sans SAHOS pour les volumes télésystolique et télédiastolique du VG. Aucune association n'a été mise en évidence entre les différents paramètres du remodelage du VG et du VD que ce soit avec les différents marqueurs polysomnographiques de sévérité du SAHOS (AHI, AHI en REM, index de désaturations) ou avec les paramètres clinques tels que la somnolence diurne.

Conclusion et discussion

Notre étude n'a pas démontré d'association entre les marqueurs de sévérité du SAHOS (IAH, IAH-REM, index de désaturations, somnolence) et le remodelage ventriculaire à six mois après un infarctus aigu du myocarde.

Nous avons retrouvé une prévalence élevée du SAHOS dans cette population avec 40/47 patients (85%) ayant un IAH ≥ 5/heure. Le nombre de patients avec un remodelage ventriculaire gauche était aussi élevé avec 19/47 (40%) patients présentant une augmentation du volume télédiastolique du VG ≥ 12% entre l'inclusion et 6 mois. Cette proportion importante peut être liée au fait d'avoir inclus des patients avec un IDM sévère.

Contrairement à l'hypothèse initiale, nos résultats plaident pour l'absence d'effet du SAHOS sur le remodelage ventriculaire après un IDM. En raison du lien entre remodelage ventriculaire

et morbidité cardiovasculaire après un IDM(Reindl et al. 2019), cela pourrait être interprété comme une absence de risque cardiovasculaire accru en cas de SAHOS chez les patients avec un IDM. Ces résultats sont en accord avec les résultats de deux études récentes qui ont mis en évidence d'une part l'absence d'augmentation du risque cardiovasculaire 36 mois après un IDM chez des patients avec un IAH ≥ 15/heure sans somnolence(Xie et al. 2018) et d'autre part l'absence d'efficacité de la PPC pour diminuer les évènements cardiovasculaires majeurs chez des patients non somnolents avec un IDM et un SAHOS(Sánchez-de-la-Torre et al. 2019).

Impact of Obstructive Sleep Apnea Syndrome on the Ventricular Remodeling After Acute Myocardial Infarction

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ABSTRACT

Background: Obstructive sleep apnea syndrome (OSA) is common in patients with acute myocardial infarction (AMI). Whether OSA impacts on the ventricular remodeling post-AMI and is associated with negative prognosis remains unclear.

Objective: to compare cardiac ventricular remodeling assessed by cardiac magnetic resonance (CMR) imaging within 6 months after AMI between patients based on the presence and severity of OSA.

Methods: This prospective study conducted at the University Hospital of Montpellier included 47 patients (85 % male, median age 57 years (IQ_{25-75} 51-65), median BMI 25.4 kg/m² (23.2-28.2) with moderate to severe AMI from May 2015 to January 2020. They all underwent CMR at inclusion and at 6 months after an AMI, and a polysomnography (PSG) performed 3 weeks after AMI. Clinical (daytime sleepiness and quality of life), biological (inflammation), imaging and PSG (apnea hypopnea index (AHI), NREM and REM sleep, O2 desaturation) parameters were collected. Ventricular parameters changes were compared between patients as function of AHI, AHI in REM and NREM sleep , O2 desaturation and daytime sleepiness .

Results: No significant differences were observed for left and right ventricular remodeling parameters between OSA and no OSA patients. Moreover, there was no association between the markers of OSA severity (AHI-REM,ODI, sleepiness) and the ventricular remodeling.

Conclusions: Obstructive sleep apnea syndrome (OSA) was not associated with ventricular remodeling in patients with acute myocardial infarction.

ClinicalTrials.gov identifier NCT02439294

INTRODUCTION

Ischemic heart disease constitute the first cause of death in adults in most developed countries[1]. Even though death rates following acute myocardial infarction (AMI) have fallen substantially in the past decades with the therapeutic advances [2], survivors of AMI remained at risk of cardiovascular events including death, recurrent MI[3], heart failure[4], arrhythmias, angina, and stroke. These adverse events may be underpinned by a ventricular remodeling, defined by the structural and functional changes of the myocardium occurring after the cardiac injury[5]. Therefore, this ventricular remodeling appeared as a key factor of the patient's prognosis after AMI [6]. Identifying the risk factors of the post-AMI ventricular remodeling is thus a critical step in research aiming to improve the patient's prognosis in AMI. Obstructive sleep apnea (OSA) could constitute such a risk factor of post-AMI ventricular remodeling. Indeed, OSA is a sleep breathing disorder that increases the risk of cardiovascular diseases[7,8] and is highly prevalent in patients with AMI [9,10].

A pejorative role of OSA on post-AMI ventricular remodeling has been hypothesized via its negative impact on clinical outcome in patients with AMI. Indeed, studies have shown that the presence of OSA may worsen the prognosis of patients admitted for MI both in the short[11] and long term[12,13]. Each episode of upper airway obstruction and respiratory efforts during sleep causes arousals and sleep fragmentation, and leads to an increase of the sympathetic activity, systemic inflammation and oxidative stress, and changes in left ventricular transmural pressure [14]. All these factors have been identified as deleterious for the development of ventricular remodeling[15]. However, these results have been challenged by studies showing the cardio protective role of sleep apnea during AMI, via an ischemic preconditioning[16].

Rare studies showed that sleep-disordered breathing (SDB) was associated with cardiac remodeling after AMI[17,18]. One cardiac magnetic resonance (CMR) study showed that SDB could worsen pathological remodeling following the AMI. However, in this study the sample size was low, the follow-up was

limited to three months, and patients with either obstructive or central sleep apnea syndrome were included. The second study re-evaluated the CRM images with an alternative method on a subpopulation sample from the first study. Both studies did not assess the impact of clinical parameters such as excessive daytime sleepiness (EDS) and quality of life, the impact of apnea/hypopnea in REM and NREM sleep independently, O2 desaturation, and the biological parameters (e.g. the low grade inflammation). Altogether, the impact of OSA on the ventricular remodeling post-AMI remains to be further studied.

The aim of this study was to assess the association between OSA and the cardiac ventricular remodeling post-AMI, in comparing the changes in cardiac morphology using CMR within 6 months after AMI in patients based on the presence and severity of OSA characterized by AHI, AHI in REM and NREM sleep, O2 desaturation and EDS.

METHODS

Study design

This prospective study included patients admitted for AMI to the cardiological Intensive Care Unit (ICU) of the University Hospital of Montpellier (France). Cardiac magnetic resonance imaging (CMR) was scheduled 5±2 days after the percutaneous coronary intervention (PCI) and at six months. Polysomnography was carried out 21±10 days after the PCI and patients were classified according to their AHI: no OSA (AHI<5/h), mild to moderate OSA (AHI 5-29.9) and severe OSA (AHI ≥30/h). A clinical standardized evaluation including sleep parameters was performed for all patients. Blood samples carried out on the day of admission for AMI.The study was conducted in accordance with the CONSORT ethical guidelines and was approved by the local ethics committee (CPP Sud-Mediterrannee IV, N° ID-RCB: 2015-A00079-40).). All participants gave their written informed consent. ClinicalTrials.gov identifier NCT02439294.

Study population

The inclusion criteria for this study were as follows: adults aged between 18 and 89 years, hospitalized in Intensive Care Units for AMI (detection of rise and/or fall of cardiac biomarkers with a least symptoms of ischaemia, ECG changes or imaging abnormality[19]), confirmed by coronary angiography. Score of delayed enhancement CMR should be greater than or equal to 5 segments of 17. Key exclusion criteria were a mild infarction (rate of delayed enhancement CMR less than or equal to 4 segments of 17), patient previously treated with continuous positive airway pressure (CPAP) prior MI, sleep apnea syndrome whose central part was predominant (> 50%), implantation of a cardiac device, or other contraindications for CMR.

Outcomes

The primary endpoint was the difference in left ventricular remodeling assessed by the changes of end-diastolic and end-systolic left ventricular volumes in CMR after 6 months of AMI between a group of patients without OSA (AHI<5/hour) and with OSA (AHI ≥ 5/h).

Secondary outcomes were the association between of CMR-based left and right ventricular remodeling parameters and clinical, biological and polysomnographic parameters.

Measures

Cardiac magnetic resonance imaging

All patients had CMR at baseline (median=6 days Interquartile Range (IQR)= [5-9] days) after the AMI. The second CMR was performed in a median delay of 6.28 months IQR= [6.04-7.09]. All CMR studies were performed on a 1.5 T AREA® system (Siemens, Erlangen, Germany) using vectocardiogram monitoring and a phased-array cardiac receiver coil. Localizers and left ventricular functional assessment were performed using steady-state free-processing sequences in the three axes of the heart. Multiplanar T2 STIR acquisition to study of oedema and area at risk. In the short-axis orientation, the left ventricle was completely encompassed by contiguous

slices with coverage of the entire left ventricular (LV) and right ventricular (RV), reference method for calculating both right and left ventricular, end-systolic and end-diastolic volumes, myocardial mass and left ventricular ejection fraction (LVEF). Calculation of end-systolic volume (ESV), end-diastolic volume (EDV) and ejection fraction (EF) in multiphase series was done using CVI42 software (Circle Cardiovascular Imaging, US). Based on a recent study of Bulluck et al, [20] a cardiac remodeling was defined as an increase of left ventricular end-diastolic volume (LVEDV) ≥12% after 6 months.

Inversion-Recovery and PSIR sequences were acquired 10 min after administration of 0.2 mmol/kg gadolinium-based contrast agent (Dotarem®, Guerbet, Roissy CdG, France) to assess the extent of the infarction (number of segments), the transmurality and the presence of no reflow. Comparative planimetry between the extent of late enhancement and T2 oedema for a calculation of the area at risk was done. The viability criteria studied were transmural enhancement, wall thickness LV and the presence of no-reflow. All the examinations were interpreted by experienced radiologists.

Polysomnography

All patients underwent a polysomnography in the sleep laboratory in Gui de Chauliac, Montpellier University hospital, in a median delay of 28 days IQR=[24-36] from AMI. PSG included EEG leads, electrooculogram, electromyography of chin and tibialis anterior muscle, electrocardiogram, nasal cannula/pressure transducer, mouth thermistor, chest and abdominal bands, and pulse oximeter. Obstructive/central apneas were defined as an airflow cessation (>90%) for more than 10 seconds associated with/without thoracoabdominal movements, and hypopnea as airflow reduction of more than 30% associated with a drop in SpO2 of more than 3% or a micro-arousal. Sleep stage, micro-arousals, periodic limb movements (PLM), and respiratory events were scored manually according to standard criteria[21].Mild, moderate and

severe OSA were respectively defined by an AHI below 5, between 15 and 29.9, and greater or equal to 30 events per hour of sleep. Apnea central syndrome, defined by an AHI ≥ 5/hour with more than 50% of respiratory events of central origin, was a non-inclusion criterion.

Blood test

Blood samples were taken on the day of admission for AMI to measure glycemia, CRP, HbA1c, cholesterol (HDL and LDL), triglycerides, hs-troponin T, CPK, NT-proBNP, creatinine, ionogram.

Self-reported questionnaires

Epworth severity scale[22] . This questionnaire assesses EDS through 8 items or situations common or frequently found in everyday life during which the propensity to fall asleep or sleepiness is measured on a scale from 0 to 3. The score is noted from 0 to 24. A score of >10 defines the presence of EDS.

Insomnia Severity Index[23]. This questionnaire estimates the severity of insomnia symptoms over the past month. It includes seven items scored between 0 and 4 with a total score between 0 and 28. The severity of insomnia symptoms is a function of the total score: not clinically significant between 0 and 7, mild between 8 and 14, moderate between 15 and 21 and severe between 22 and 28.

EQ5D[24]. The EQ-5D is a preference-based health survey assessing five health dimensions (with three levels of problems) and an overall health visual analog scale (EQ-VAS) which assesses the respondent's self-rated health status on a graduated (0–100) scale, with higher scores for higher health-related quality of life.

Beck depression inventory[25] . This 21-item questionnaire describes the patient's mood over the 2 weeks preceding the visit. Each item is scored from 0 to 3 with a total score between 0 and

63. A score between 10 and 18 indicates minor, 19 and 29 moderate, 30 and 63 severe depressive symptoms.

Power Calculations

In the absence of studies carried out with a comparable methodology at time of the development of the protocol (in 2013), statistical power was based on the estimated distribution of left ventricular remodeling at 6 months in a group of patients with AMI with a mean of 84 ml and a standard deviation of 29 [26]. Therefore, 72 patients (24 patients without OSA and 48 patients with OSA) provided a power of 0.80 for detecting a between-group difference in the left ventricular remodeling of 25% at 6-months (mean of the left ventricular remodeling at 6 months of 84 ml in patients without OSA and 63 ml for patients with OSA) using a 2-sided, a ratio 1-2 with a significance level of 0.05. The rate of lost to follow-up being estimated at 20%, a total of 87 patients was therefore necessary for this study.

Statistical analysis

The characteristics of the study population were described using number and percentage for categorical variables and medians and (minimum value- maximum value) or interquartile range (IQR) for continuous variables due to their distributions mostly skewed according to Shapiro-Wilk test. Non-parametric statistical tests were used due to the small sample size (less than 30 in each group). The Mann-Whitney test were performed to compare continuous variables of two groups of AHI and the Kruskal-Wallis test to compare the four groups. Chi-square or Fisher's exact tests were used to compare categorical variables between the groups of AHI. When comparisons were statistically significant between groups, two-by-two comparisons were carried-out, using a correction for multiple comparisons with the Bonferroni method. Changes in each outcome between baseline and six-month follow-up were compared between the groups using a Mann-Whitney U test. For the between-group differences, 95% Confidence Intervals (CI) were constructed. To compare differences between baseline and six-month

follow-up within group, Wilcoxon signed-rank tests were used. Spearman's rank order correlations were used to determine associations between continuous variables. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with SAS version 9.4.

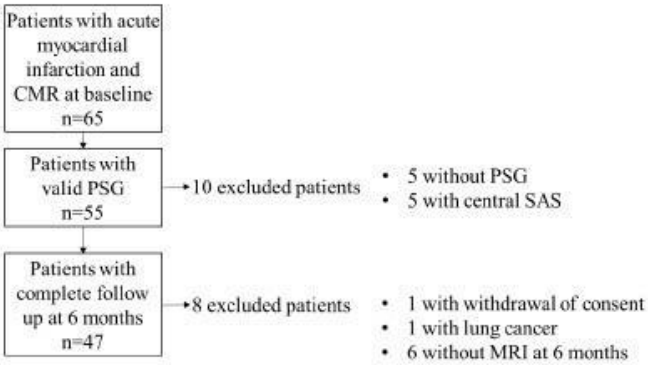
RESULTS

Between May 2015 and January 2020, consecutive patients who underwent percutaneous coronary intervention to treat AMI were screened. Overall, 65 patients were eligible for the prospective study. Among them, 18 patients were excluded due to the absence of CMR at 6 months (n = 6) or polysomnography recording (n = 5), a SAS with predominant central part (n=5), a lung cancer (n=1) or a consent withdrawal (n=1) (Figure 1). The final analysis included 47 patients, divided into four groups: no OSA (AHI<5/h, n=7), mild (5≤AHI<15/h, n=17), moderate (15≤AHI<30, n=12) or severe OSA (AHI ≥ 30/h, n=11). Among the 11 patients with severe OSA, CPAP was offered to all subjects but only one patient used CPAP more than 2 hours per night at 6 months.

Of the patients included, 85% were male with a median age of 57.43 years (min=33.60; max=74.41) and a median body mass index of 25.18 kg/m²(min=18.52; max=33.14). Infarct related artery was left anterior descending, circumflex artery and right coronary artery for respectively 40 (85%), 4 (9%) and 6 (13%) of patients.

The severity of AMI was confirmed by the large proportion of patients with non-viability criteria on the initial CMR: 34/47 (72%) patients had no reflow and 44/46 (96%) patients had transmural enhancement ≥ 75%.

Figure 1 Flow Chart



Baseline demographic, clinical and biological characteristics according to the severity of AHI

No between-group differences were found according to demographic, clinical and biological characteristics of the patients except for higher level of CRP and a better quality of life in patients with an AHI≥15/h (n=23) compared to patients with AHI < 15/hour (n=24) (Table 1). Moreover, these patients had higher AHI in REM and in NREM and higher oxygen desaturation and micro-arousal indexes (Table 2).

Outcome measures at 6 months

No significant differences were observed between OSA and no OSA patients for left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV). Given the small number of patients, we divided the patients into two groups based on the AHI (AHI < 15/h and AHI ≥ 15/h) for the secondary outcomes (Table 3).. We found no differences in LV and RV remodeling parameters either at 6 months or for the difference between baseline and 6 months (Figure 2).

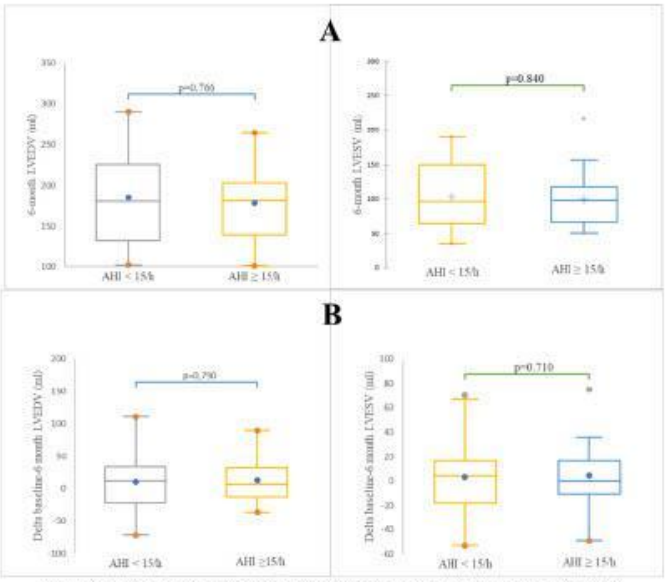


Figure 2: Differences between patients with AHI <15/h and patients with AHI ≥15/h for :
A/6-month left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) ;
B/ Changes between baseline and 6-month in LVEDV and LVESV

By analysing the phenotypes of interest with groups of patients based on their levels of REM-AHI, NREM-AHI, or oxygen desaturation index (ODI), and EDS we found no significant difference in the changes in in LV and in RV parameters at 6 months (Figure 3). We obtained similar results when we considered EDS associated with AHI ≥5/h or ≥ 15/h. Moreover, there were no significant associations between changes in parameters of CMR-based ventricular remodeling and clinical (e.g. insomnia and depressive symptoms and quality of life), polysomnography (e.g. sleep efficiency, total sleep duration, N3 and REM sleep percentages and microarousal index) and biological (inflammation, lipids and glycemia).

Among our population, 19 patients (40%) had an increase of LVEDV ≥12% between baseline and 6 months. These patients had a lower rate of slow deep sleep (p=0.026) and a higher rate of CK peak (p=0.048) compared to patients without remodeling. However, no differences in

OSA severity (AHI, REM-AHI, NREM-AHI, O2 desaturation and EDS) were found between patients who remodelled or not their left ventricle.

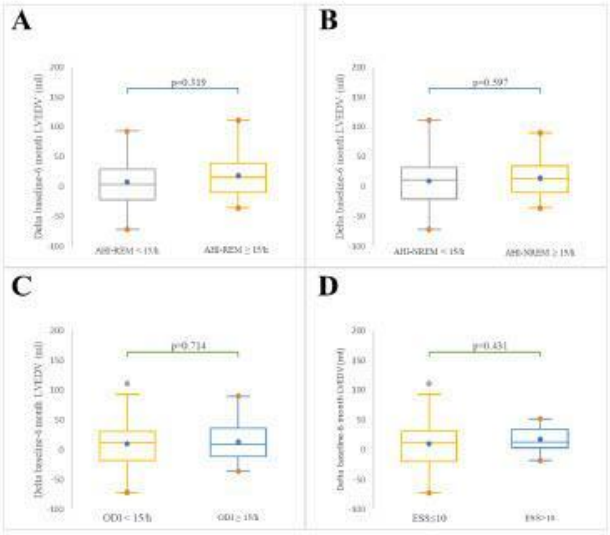


Figure 3: Changes between baseline and 6-month in LVEDV between patients with A/AHI-REM <15/h and ≥15/h ; B/AHI-NREM <15/h and ≥15/h ; C/ Oxygen Desaturation Index (ODI) <15/h and ≥15/h ; D/ Epworth Sleepiness Scale (ESS) ≤ 10 and >10

DISCUSSION

Our study found no association between the markers of OSA severity (AHI, AHI-REM, ODI, AHI and EDS) and ventricular remodeling at six months or between baseline and six months after acute myocardial infarction (AMI).

We found a high frequency of OSA in our population with 85% of patients having an AHI ≥5/hour and 49% having moderate to severe OSA. These results were in agreement with the widely reported prevalence of OSA in patients with AMI[9,10]. Moreover, 40% of AMI patients displayed a ventricular remodeling characterized by an increase of ≥ 12% of LVEDV[20]. This frequency was even higher compared to other studies[20], probably due to the inclusion of severe AMI patients (CMR delayed enhancement score ≥5/17 segments).

Our study failed to show any significant difference in the left or right ventricle remodelling between severity groups of OSA patients. Our results may contrast with the association reported between OSA and ventricular remodelling; [17,18] however this previous studies performed PSG earlier after AMI, 3 to 5 days vs 34±17 days in our study. Performing a sleep study early after AMI may reveal a high frequency of obstructive and central apnea/hypopnea events, that may decrease over time[27,28]. Thus, the timing of the polysomnography may have precluded our study of an overestimation bias of sleep respiratory events during AMI.

Our study could be interpreted as a lack of effect of OSA on the ventricular remodelling assessed at 6 months after AMI. Given the weight of the ventricular remodelling on the cardiovascular morbidity post-AMI[29], this lack of effect of OSA could translate into an absence of increased risk of major cardiovascular events post-AMI in OSA patients. One prospective study revealed that in the absence of EDS, AMI patients with moderate to severe OSA (AHI ≥15/h) were not associated with an increased probability of major cardiovascular events at 36 months [30]. However, in our study, EDS was not associated with significant increased risk of major cardiovascular events. Also, a randomized controlled trial in AMI patients reported that treating OSA with CPAP did not reduce the frequency of major cardiovascular events [31].

Besides the post-AMI condition, sleep cohort studies and meta-analyses reported associations between OSA and the long-term ventricular remodeling[32]. In the Wisconsin sleep cohort study, OSA was associated with a slight decrease in LV systolic function when reevaluated 18.0±3.7 years after the OSA diagnosis. Moreover, mean nocturnal SpO2 saturation and percent sleep time with SpO2< 90% were independent predictors of LV mass and LV wall thickness[33]. In a large, community-based cohort study using CMR imaging, Javaheri et al. showed an increased LV mass with increasing AHI categories, but no association between OSA severity and LVEF, 10 years after the diagnosis. In this study, SpO2 was associated with LV mass to volume ratio[34]. These two cohort studies showed a role of intermittent hypoxia on the ventricular hypertrophy.

Yet, the duration of the intermittent hypoxia exposure has not been assessed in post-AMI studies and could be shorter. In addition, the intermittent hypoxia related to OSA could have cardioprotective effects in AMI patients[16]. *In vivo* intermittent hypoxia conditioning has shown to improve the post-ischemic cardiac function in animal model[35].

Our study had several strengths. CMR is considered the reference method for evaluating ventricular remodeling with low inter-reader variability[36] and the high reproducibility[37]. Different definitions of adverse LV remodelling exist, however we used LVEDV and LVESV as primary outcome because of their good predictive value for long-term clinical outcomes[15,20]. We assessed all parameters related to OSAS severity including clinical, PSG and biological parameters.

Our study has some limitations. The main limitation is the sample size, with recruitment being lower than initially planned that can be explained by the inability to recruit patients during the Covid-19 pandemic. Achieving the expected sample size would have shown no significant effect of OSA severity on the post-AMI ventricular remodeling. A post hoc power analysis showed that 1032 patients would be required to reach a power of 0.8 with a significant level of 0.05. Only one patient (9%) with severe OSAS used CPAP for more than two hours per night at six months. This finding was in agreement with the ISAAC study[31] that highlighted the limited impact of CPAP in this specific population. Finally, this study addressed the cardiac remodeling of structure and functional parameters as a function of OSA, with a limited population of subjects with results which may be not generalizable, and which remain limited to 6 months and therefore not in the long-term.

CONCLUSION

Our study showed no significant differences in the ventricular remodeling assessed by CMR between groups of OSA patients of different severity 6 months after the AMI. No associations

were found between AHI in REM and NREM sleep, O2 desaturation and low grade inflammation and LV and RV remodeling. These results question the need and timing of the sleep assessment and post AMI OSAS and highlight the complexity of the relationships between OSA and post-AMI morbi-mortality.

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Authors contribution

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Table 1. Baseline demographic, clinical, biological characteristics according to the severity of Apnea-Hypopnea Index

	Apnea-Hypopnea Index						Apnea-Hypopnea Index		
	<5/h Group 0 N=7	**[5-15[/h** Group 1 N=17	**[15-30[/h** Group 2 N=12	**≥30/h** Group 3 N=11			**<15/h** **N=24**	**≥15/h** **N=23**	
Variables	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**p**	**Post-Hoc comparisons**	**n (%)**	**n (%)**	**p**
Female, Gender	2 (28.57)	3 (17.65)	2 (16.67)	0 (0.00)	0.36		5 (20.83)	2 (8.70)	0.42
Age, years[1]	7 ; 50.79 (33.60 ; 70.38)	17 ; 55.95 (46.72 ; 67.91)	12 ; 60.44 (45.13 ; 74.41)	11 ; 62.05 (42.22 ; 73.43)	0.17		24 ;54.31 (33.60 ; 70.38)	23 ;60.65 (42.22 ; 74.41)	0.09
BMI, kg/m2[1]	7 ; 23.44 (18.52 ; 28.70)	16 ; 25.73 (19.38 ; 32.65)	10 ; 27.27 (20.76 ; 32.00)	11 ;25.31 (23.51 ; 33.14)	0.29		23 ;24.58 (18.52 ; 32.65)	21 ;26.18 (20.76 ; 33.14)	0.14
Systolic BP, mmHg[1]	7 ; 117.00 (87.00 ; 133.00)	17 ; 110.00 (79.00 ; 163.00)	11 ;120.00 (90.00 ; 145.00)	11 ;123.00 (100.00 ; 162.00)	0.53		24 ;111.50 (79.00 ; 163.00)	22 ;121.00 (90.00 ; 162.00)	0.20
Diastolic BP, mmHg[1]	7 ; 73.00 (60.00 ; 90.00)	17 ; 71.00 (28.50 ; 100.00)	11 ;70.00 (39.70 ; 78.00)	11 ;66.80 (10.10 ; 99.00)	0.78		24 ;72.00 (28.50 ; 100.00)	22 ;69.00 (10.10 ; 99.00)	0.38
Diabetes, Yes	0 (0.00)	3 (17.65)	1 (8.33)	0 (0.00)	0.50		3 (12.50)	1 (4.55)	0.61
Hypertension, Yes	2 (28.57)	6 (35.29)	5 (41.67)	4 (36.36)	0.97		8 (33.33)	9 (39.13)	0.68
Hypercholesterolemia, Yes	3 (42.86)	2 (12.50)	4 (36.36)	7 (63.64)	0.05		5 (21.74)	11 (50.00)	0.05
Current smoker, Yes	3 (42.86)	9 (52.94)	8 (72.73)	2 (18.18)	0.08		12 (50.00)	10 (45.45)	0.76
Family history of CA, n (%)	4 (57.14)	6 (35.29)	4 (33.33)	4 (40.00)	0.74		10 (41.67)	8 (36.36)	0.71
TIMI-flow before PCI					0.11				0.05
Grade 0	5 (83.33)	11 (84.62)	6 (85.71)	3 (42.86)			16 (84.21)	9 (64.29)	
Grade 1	0 (0.00)	0 (0.00)	1 (14.29)	3 (42.86)			0 (0.00)	4 (28.57)	
Grade 2	1 (16.67)	2 (15.38)	0 (0.00)	1 (14.29)			3 (15.79)	1 (7.14)	
TIMI-flow after PCI					0.39				0.46
Grade 0	0 (0.00)	0 (0.00)	1 (11.11)	0 (0.00)			0 (0.00)	1 (5.26)	

	Apnea-Hypopnea Index						Apnea-Hypopnea Index		
	<5/h Group 0 N=7	**[5-15[/h** Group 1 N=17	**[15-30[/h** Group 2 N=12	**≥30/h** Group 3 N=11			**<15/h N=24**	**≥15/h N=23**	
Variables	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**p**	**Post-Hoc comparisons**	**n (%)**	**n (%)**	**p**
Grade 3	7 (100.00)	15 (100.00)	8 (88.89)	10 (100.00)			22 (100.00)	18 (94.74)	
CRP, mg/L[(1)]	7 ; 1.70 (0.30 ; 25.20)	17 ; 5.40 (0.70 ; 106.40)	11 ;9.30 (1.30 ; 56.70)	11 ;37.40 (2.20 ; 128.60)	0.02	Gr0<Gr3	24 ;4.40 (0.30 ; 106.40)	22 ;11.70 (1.30 ; 128.60)	0.01
Hs-troponine T, ng/L[(1)]	7 ; 1300.00 (10.70 ; 17459.00)	17 ; 3311.00 (122.80 ; 15138.00)	11 ;2899.00 (6.10 ; 9124.00)	10 ;4022.50 (114.30 ; 14445.00)	0.43		24 ;2870.50 (10.70 ; 17459.00)	21 ;3594.00 (6.10 ; 14445.00)	0.64
CK (CPK) , U/L[(1)]	7 ;650.00 (126.00 ; 9272.00)	14 ;976.50 (132.00 ; 8224.00)	10 ;552.00 (122.00 ; 5182.00)	11 ;414.00 (128.00 ; 4884.00)	0.65		21 ;782.00 (126.00 ; 9272.00)	21 ;414.00 (122.00 ; 5182.00)	0.41
ACE inhibitor/ARB intake, Yes	7 (100.00)	15 (88.24)	11 (91.67)	10 (90.91)	0.99		22 (91.67)	21 (91.30)	0.99
β-blocker intake, Yes	7 (100.00)	15 (88.24)	11 (91.67)	8 (72.73)	0.49		22 (91.67)	19 (82.61)	0.42
Statins intake, Yes	7 (100.00)	15 (88.24)	11 (91.67)	10 (90.91)	0.99		22 (91.67)	21 (91.30)	0.99
ESS[(1)]	7 ;5.00 (0.00 ; 13.00)	17 ;7.00 (0.00 ; 15.00)	11 ;4.00 (0.00 ; 18.00)	10 ;7.00 (0.00 ; 19.00)	0.83		24 ;6.00 (0.00 ; 15.00)	21 ;6.00 (0.00 ; 19.00)	0.63
ISI score[(1)]	7 ; 6.00 (0.00 ; 14.00)	17 ;8.00 (1.00 ; 23.00)	12 ;4.50 (0.00 ; 15.00)	11 ;11.00 (1.00 ; 23.00)	0.13		24 ;8.00 (0.00 ; 23.00)	23 ;7.00 (0.00 ; 23.00)	0.26
BDI-II total score[(1)]	7 ;5.00 (0.00 ; 10.00)	17 ;11.00 (0.00 ; 39.00)	11 ;4.00 (0.00 ; 15.00)	11 ;6.00 (0.00 ; 22.00)	0.02	Gr1>Gr2	24 ;9.50 (0.00 ; 39.00)	22 ;4.00 (0.00 ; 22.00)	0.08
EQ5D-VAS[(1)]	6 ;62.50 (30.00 ; 80.00)	16 ;50.00 (30.00 ; 90.00)	12 ;65.00 (40.00 ; 90.00)	11 ;65.00 (50.00 ; 80.00)	0.09		22 ;50.00 (30.00 ; 90.00)	23 ;65.00 (40.00 ; 90.00)	0.02

[(1)] continuous variables were expressed as number; median (minimum value;maximum value)

Abbreviations: BMI = Body Mass Index, BDI-II = Beck Depression Inventory-II, EQ5D = European Quality of Life 5-dimensions questionnaire, ESS = Epworth sleepiness scale VAS = visual analog scale.

Table 2. Baseline polysomnographic characteristics according to the severity of Apnea-Hypopnea Index

	Apnea-Hypopnea Index						Apnea-Hypopnea Index		
	<5/h Group 0 N=7	**[5-15[/h** Group 1 N=17	**[15-30[/h** Group 2 N=12	**≥30/h** Group 3 N=11			**<15/h** **N=24**	**≥15/h** **N=23**	
Variables	**n; median (min-max)**	**n; median (min-max)**	**n; median (min-max)**	**n; median (min-max)**	**p**	**Post-Hoc comparisons**	**n; median (min-max)**	**n; median (min-max)**	**P**
Apnea-Hypopnea Index in REM	7 ; 2.24 (0.00 ; 12.25)	16 ; 12.63 (0.00 ; 46.29)	12 ;11.67 (1.37 ; 51.25)	10 ;38.02 (3.87 ; 59.98)	0.004	Gr0<Gr3	23 ;10.65 (0.00 ; 46.29)	22 ;19.38 (1.37 ; 59.98)	0.02
Apnea-Hypopnea Index in NREM	7 ; 1.30 (0.49 ; 2.59)	17 ; 7.33 (0.00 ; 11.20)	12 ;24.82 (13.07 ; 31.99)	10 ;45.88 (34.40 ; 58.47)	<0.0001	Gr0<Gr1<Gr2<Gr3	24 ;4.06 (0.00 ; 11.20)	22 ;31.39 (13.07 ; 58.47)	<0.0001
Oxygen desaturation index	7 ; 1.41 (0.39 ; 5.36)	17 ; 7.21 (0.33 ; 16.90)	12 ;17.11 (5.06 ; 26.60)	10 ;35.59 (4.09 ; 51.21)	<0.0001	Gr0<Gr1<Gr2<Gr3	24 ;5.56 (0.33 ; 16.90)	22 ;21.18 (4.09 ; 51.21)	<0.0001
SaO2, %	7 ; 96.00 (93.00 ; 98.00)	17 ; 95.00 (91.00 ; 97.00)	12 ;95.00 (87.00 ; 97.00)	9 ;95.00 (91.00 ; 97.00)	0.29		24 ;95.00 (91.00 ; 98.00)	21 ;95.00 (87.00 ; 97.00)	0.65
Microarousal index, /hour	7 ; 11.30 (4.26 ; 17.01)	17 ; 9.92 (4.03 ; 84.00)	12 ;17.60 (4.66 ; 25.84)	9 ;31.45 (18.30 ; 46.87)	0.0001	Gr0,Gr1,Gr2<Gr3	24 ;11.29 (4.03 ; 84.00)	21 ;22.26 (4.66 ; 46.87)	0.0001
N3 (%)	7 ; 16.39 (12.37 ; 21.69)	17 ; 21.83 (4.90 ; 35.84)	12 ;18.63 (4.81 ; 35.16)	10 ;12.94 (0.00 ; 20.72)	0.06		24 ;19.27 (4.90 ; 35.84)	22 ;15.38 (0.00 ; 35.16)	0.23
Total sleep time (minutes)	7 ; 425.00 (329.00 ; 512.00)	17 ; 371.00 (229.00 ; 517.00)	12 ;362.00 (227.00 ; 464.00)	11 ;400.00 (324.00 ; 640.00)	0.45		24 ;379.00 (229.00 ; 517.00)	23 ;373.00 (227.00 ; 640.00)	0.75
Sleep efficiency (%)	7 ; 85.14 (65.50 ; 95.07)	17 ; 78.22 (40.63 ; 91.76)	12 ;76.44 (45.91 ; 89.82)	10 ;77.26 (63.12 ; 94.44)	0.81		24 ;79.03 (40.63 ; 95.07)	22 ;76.44 (45.91 ; 94.44)	0.92

Abbreviations: NREM = Non rapid Eye Movement sleep; REM = Rapid Eye Movement sleep; N3 = non-REM sleep stage 3

Table 3. Changes in cardiac remodeling between baseline and 6-month follow-up in patients with baseline apnea hypopnea index <15/hour and patients with baseline apnea hypopnea index≥15/hour

	Among patients with baseline AHI<15/hour N=24				Among patients with baseline AHI≥15/hour N=23					
	At baseline	At 6-month follow-up	Within-Group Difference[1]		At baseline	At 6-month follow-up	Within-Group Difference[1]		Between-group difference[2]	
	Median (IQR)	Median (IQR)	Median (IQR)	p	Median (IQR)	Median (IQR)	Median (IQR)	p	Median [95%CI]	p
LV end-diastolic volume (ED) (mL)	183.50 (50.50)	180.50 (95.00)	-11.50 (56.50)	0.22	155.00 (56.00)	181.00 (80.00)	-7.00 (50.00)	0.11	3.50 [-18.00;24.00]	0.79
LV end-systolic volume (mL)	110.00 (55.00)	96.00 (86.50)	-4.00 (36.00)	0.92	95.00 (41.00)	98.00 (55.00)	0.00 (28.00)	0.42	3.50 [-14.00;19.00]	0.71
LVEF(%)	42.00 (12.00)	45.00 (18.00)	-3.00 (13.00)	0.09	42.00 (8.00)	46.00 (14.00)	-3.00 (11.00)	0.25	-1.00 [-6.00;4.00]	0.66
LV ejection volume (mL/m2)	39.00 (8.00)	44.60 (13.85)	-4.50 (13.75)	0.05	34.20 (7.70)	42.00 (14.00)	-4.00 (12.00)	0.13	-2.00 [-7.80;5.00]	0.60
LV cardiac output (L/min)	4.68 (1.16)	4.66 (1.38)	0.04 (1.52)	0.93	4.70 (1.09)	4.59 (1.29)	0.09 (1.13)	0.77	-0.11 [-0.87;0.55]	0.68
LV cardiac index (L/min/m2)	2.52 (0.43)	2.35 (0.62)	-0.02 (0.82)	0.91	2.42 (0.64)	2.47 (0.65)	0.01 (0.59)	0.55	-0.04 [-0.41;0.32]	0.87
RV end-diastolic volume index (mL)	120.50 (43.50)	128.50 (35.00)	-6.00 (26.00)	0.48	115.00 (31.00)	129.00 (57.00)	0.00 (46.00)	0.31	3.00 [-15.00;22.00]	0.68
RV end-systolic volume (mL)	49.50 (26.00)	54.50 (18.50)	-5.00 (19.50)	0.65	52.00 (26.00)	54.00 (37.00)	-2.00 (23.00)	0.93	-0.50 [-11.00;10.00]	0.92
RVEF(%)	58.50 (6.50)	59.00 (10.50)	-0.50 (10.50)	0.60	56.00 (8.00)	57.00 (14.00)	-2.00 (11.00)	0.20	3.00 [-2.00;8.00]	0.22

Etude 3 : Impact pronostic des troubles du sommeil chez des patients avec insuffisance cardiaque. Etude PRO-TSIC.

Prérequis

L'insuffisance cardiaque (IC) est un syndrome clinique fréquent secondaire à un trouble cardiaque structurel ou fonctionnel cardiaque qui altère la capacité du ventricule à se remplir ou à éjecter du sang. Les causes sont multiples et incluent les maladies du myocarde, de l'endocarde ou du péricarde, les valvulopathies, les arythmies, les maladies coronariennes ou encore les désordres métaboliques(Yancy et al. 2013). La maladie coronarienne représente la cause principale d'IC. Il existe trois classes d'IC : 1) IC à fraction d'éjection modérément altérée définie par une fraction d'éjection ventriculaire gauche (FEVG) entre 40 et 50%, 2) l'IC à fraction d'éjection diminuée (FEVG < 40 %) et 3) l'IC à fraction d'éjection préservée (FEVG > 50 %)(Ponikowski et al. 2016).

La prévalence de l'IC est estimée à 1-2% de la population adulte. Elle est probablement sous-estimée. En effet, chez des adultes de plus de 65 ans, on retrouve des signes d'IC à l'échographie dans 11.8% des cas(Groenewegen et al. 2020). L'IC est associée à une altération de la qualité de vie et la **survenue d'événements cardiovasculaires indésirables majeurs** est fréquente, conduisant fréquemment à une hospitalisation qui est un marqueur important de mauvais pronostic(Malik et al. 2020). Les patients hospitalisés ont une survie médiane de 2.1 ans (K. S. Shah et al. 2017).

Le traitement de l'IC comprend la prise en charge de la maladie sous-jacente (coronaropathie, valvulopathie,…), les règles hygiéno-diététiques (notamment le régime hyposodé), les traitements médicamenteux (bétabloquants, inhibiteurs de l'enzyme de conversion de l'angiotensine, inhibiteurs de l'angiotensine et de la néprilysine, inhibiteurs des cotransporteurs sodium-glucose de type 2), la réhabilitation cardiaque, la resynchronisation ou encore la transplantation cardiaque(Yancy et al. 2017; McDonagh et al. 2021).

Les patients avec une IC ont fréquemment des comorbidités non cardiaques qui sont associées à une augmentation des hospitalisations, de la durée d'hospitalisation et de la mortalité(Bhatt

et al. 2020). **L'identification et la prise en charge de ces comorbidités** est donc essentielle afin d'améliorer le pronostic. **Les troubles du sommeil** sont fréquents avec plus de 50% des patients présentant une insomnie(Kanno et al. 2016), 4 à 40% un syndrome des jambes sans repos (SJSR) (Zilberman et al. 2010) et 25 à 66% des troubles respiratoires du sommeil (Javaheri et al. 2017). De plus, 60 à 75% des patients rapportent un sommeil de mauvaise qualité et 35% utilisant régulièrement des hypnotiques(Jorge-Samitier et al. 2020). Plusieurs études ont mis en évidence que la présence de ces désordres du sommeil est associée à une altération de la qualité de vie et du pronostic.

- Le syndrome d'apnées du sommeil, obstructif ou central, non traité, est associé avec une augmentation de la survenue des évènement cardiovasculaires majeurs(Damy et al. 2012).
- Le sommeil de mauvaise qualité est associé à une altération de la qualité de vie et de l'humeur, à une augmentation des symptômes dépressifs et à une augmentation de la morbidité et de la mortalité cardiovasculaire(K. S. Lee et al. 2016).
- La prise de benzodiazépines est liée à une augmentation du taux de réhospitalisations(Sato et al. 2020).

Hormis pour les troubles respiratoires du sommeil, les études étudiant les liens entre qualité du sommeil et le pronostic cardiovasculaire chez les patients avec IC sont limitées par un suivi de courte durée.

Sur la base de la littérature, l'hypothèse de l'étude PRO-TSIC (Impact PROnostic des Troubles du Sommeil chez l'Insuffisant Cardiaque) était de de mettre en évidence que les troubles du sommeil sont liés à un pronostic cardiovasculaire à long terme plus défavorable chez les patients atteints d'IC.

Article

Prognostic impact of sleep patterns and related-drugs in patients with heart failure

F Bughin, I Jaussent, B Ayoub, S Aguilhon, N Chapet, S Soltani, J Mercier, Y Dauvilliers, F Roubille

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Objectifs

Etudier à long terme l'association entre les troubles du sommeil et la survenue d'événements cardiovasculaires majeurs (ECM) chez des patients avec une IC.

Méthodes

Etude monocentrique longitudinale. Les patients inclus dans cette étude sont les patients suivis dans le Département de Cardiologie du CHU de Montpellier et diagnostiqués avec une insuffisance cardiaque selon les critères de 2016 de la société européenne de cardiologie. Les patients inclus ont rempli à l'inclusion des auto-questionnaires validés sur la somnolence, la fatigue, l'insomnie, la qualité du sommeil, les rythmes du sommeil, les symptômes anxieux et dépressifs, et la prise de médicaments agissant sur le système nerveux central (SNC).

Le critère de jugement principal est la survenue d'un ECM évalué par un critère composite associant la mortalité, l'hospitalisation, la transplantation cardiaque ou l'implantation d'un défibrillateur.

Résultats

119 patients (29.4% de femmes) ont été inclus et suivi pendant une durée médiane de 888 jours.

Après ajustement pour l'âge, la survenue d'un ECM était associée avec les scores d'insomnie et de qualité du sommeil, une diminution de l'efficacité du sommeil et du temps de sommeil

total (TST), une augmentation de la latence d'endormissement ou encore la prise de médicaments agissant sur le SNC. Cependant, après ajustement sur la FEVG et l'hypercholestérolémie, les seuls paramètres significatifs étaient la diminution du TST et la prise de médicaments agissant sur le SNC.

Conclusion et discussion

La prise de médicaments agissant sur le SNC et la diminution du TST sont indépendamment associées à une augmentation du risque d'ECM chez des patients atteints d'IC.

Cette étude est la première à notre connaissance à étudier au long terme l'association entre les caractéristiques et les troubles du sommeil et le pronostic cardiovasculaire chez des patients avec une IC. Elle souligne la nécessité de réaliser un interrogatoire détaillé des patients avec IC comprenant notamment des questionnaires sur les habitudes, la qualité et les troubles du sommeil ainsi qu'une anamnèse médicamenteuse détaillée.

Les médicaments agissant sur le SNC regroupent les hypnotiques (benzodiazépines, zolpidem et zopiclone) ainsi que les antidépresseurs. Nous avons choisi de regrouper ces médicaments en une seule entité étant donné que leurs apports sont souvent combinés et que leurs effets respectifs sur le SNC sont difficiles à différencier. La mise en évidence d'une association entre la prise de ces médicaments et l'augmentation des ECM est un message important pour la prise en charge des patients avec une IC et rejoint les résultats d'une étude récente(Sato et al. 2020). Les mécanismes incriminés sont multiples et pas encore totalement élucidés. D'une part, ces médicaments pourraient altérer le pronostic en favorisant le déclin cognitif, la somnolence diurne, la diminution des performances psychomotrices(Enomoto et al. 2020) ou encore en entrainant une dépression respiratoire(Kang, Galuska, et Ghassemzadeh 2021). D'autre part, les nombreuses comorbidités présentes chez les patients utilisant ces médicaments(Jaussent et al. 2013) pourraient également jouer un rôle dans la détérioration du pronostic.

Le temps de sommeil total (TST) est également un facteur important à rechercher à l'interrogatoire étant donné la mise en évidence d'une association entre la diminution du TST d'une heure et l'augmentation des ECM. L'augmentation du risque cardiovasculaire en

population générale en cas de TST abaissé est décrite dans certaines études(Yin et al. 2017) mais pas retrouvée de manière systématique(Kwok et al. 2018).

Cette étude a certaines limites. D'une part, nous avons utilisé des auto-questionnaires sans évaluation objective du sommeil (et notamment des troubles respiratoires du sommeil). D'autre part, en analyse univariée, les diurétiques étaient associés avec une augmentation du risque d'ECM. Les diurétiques étant étroitement associés à la FEVG, nous ne les avons pas inclus dans le modèle multivarié étant afin d'éviter un surajustement.

Les résultats de cette étude soulignent l'importance d'interroger les patients avec une IC sur la qualité de leur sommeil, la présence d'éventuels troubles du sommeil et sur la prise de médicaments du SNC.

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Article

Prognostic impact of sleep patterns and related-drugs in patients with heart failure

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Abstract:
Sleep disturbances are frequent among patients with heart failure (HF). We hypothesized that self-reported sleep disturbances are associated with a poor prognosis in patients with HF.
A longitudinal study of 119 patients with HF was carried out to assess the association between sleep disturbances and the occurrence of major cardiovascular events (MACE). All patients with HF completed self-administered questionnaires on sleepiness, fatigue, insomnia, quality of sleep, sleep patterns, anxiety and depressive symptoms, and central nervous system (CNS) drugs intake . Patients were followed for a median of 888 days. Cox models were used to estimate the risk of MACE associated with baseline sleep characteristics.
After adjustment for age, the risk of a future MACE increased with CNS drugs intake, sleep quality and insomnia scores as well with increased sleep latency, decreased sleep efficiency and total sleep time. However, after adjustment for left ventricular ejection fraction and hypercholesterolemia the HR failed to be significant except for CNS drugs and total sleep time.
CNS drugs intake and decreased total sleep time were independently associated with an increased risk of MACE in patients with HF. Routine assessment of self-reported sleep disturbances should be considered to prevent the natural progression of HF.

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Keywords: heart failure 1; sleep disturbances 2 ; sleep patterns 3; central nervous system drugs 4; sleep quality 5

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1. Introduction

Heart failure (HF) is a common clinical syndrome characterized by inability of the ventricle to fill with or eject blood. HF is a major public health problem with a constantly increasing prevalence[1], a loss of quality of life, and a high mortality rate[2]. Major adverse cardiac events (MACE) are frequent in the history of HF and often lead to hospitalization which is an important marker for poor prognosis[3].

Patients with HF often have several non-cardiac comorbidities which are associated with an impaired quality of life and a poorer prognosis[4]. Identifying and treating the factors

contributing to the progression of HF are therefore essential goals for an optimized management. Sleep disturbances are frequent with 60-75% of patients with HF complaining of poor sleep quality, more than 50% of insomnia[5,6] and 35% using regularly hypnotics[7]. The frequency of restless legs syndrome (RLS) varies between 4 and 40% depending on the studies[8,9]. Sleep-disordered breathing are also common (25-66%) in HF patients[10]. The natures and causes of sleep disorders are numerous and often associated in patients with HF, together with the potential for side effects of CNS drugs[11]. Patients with HF and poor sleep quality have increased deterioration in quality of life, alertness, and mood with a higher level of depressive symptoms[12]. A greater morbidity and mortality is also observed in patients with HF and poor quality sleep[12], sleep breathing disorders[13] or taking benzodiazepines[6]. However most of these studies were limited by short-term follow-up or the use of simple questions instead of validated questionnaires to assess sleep disturbances in this population.

Based on the previous reported studies, we hypothesized that sleep disturbances are linked to a poorer long-term cardiovascular prognosis in patients with HF. Here we aimed to evaluate the association between baseline self-reported sleep characteristics using a comprehensive battery of validated questionnaires and CNS drug intake in 119 patients with HF over a period of 888 days.

2. Materials and Methods

Study Design and Population

This study was a longitudinal study on the occurrence of non-fatal and fatal MACE in patients with HF. All participants were admitted to the Cardiology Department, University Hospital Center of Montpellier. The study was approved by the local ethics committee (Institutional Review Board, Montpellier University Hospital, IRB-MTP_2020_05_202000496) (ClinicalTrials.gov identifier NCT04653883).

119 patients with HF with a median age of 69 years [range=44-89] of whom 29.41% were women were included. These patients were followed in the Cardiology Department of the Montpellier University Hospital and diagnosed with HF according to the 2016 criteria of the European Society of Cardiology[14]. All patients filled in the questionnaires upon admission to a cardiology day hospital or outpatient clinic.

Patients were recruited between October 2016 and February 2020 and were followed up to the first non-fatal cardiovascular event, death or were censored at March 1, 2020, whichever came first.

Measures

Cardiac pathology, treatment and clinical data were collected on the patient's computerized medical record by the physicians. The cardiovascular and CNS drugs assessments were carried out by patients and physicians.

A self-administered questionnaire on sleep habits was completed by all patients in order to collect bedtime, waketime, sleep latency, total sleep time (TST), sleep efficiency (i.e. ratio of the TST compared to the time in bed). RLS was defined using the International RLS Study Group (IRLSSG) criteria. Standardized questions addressed the presence of the four minimal diagnostic criteria of the IRLSSG 1/ Do you feel or have you ever felt an irresistible urge to move your legs? 2/ If you feel or you have ever felt an irresistible urge to move your legs, does it begin or become worse during periods of rest or inactivity, such as sitting or lying down? 3/ If you feel or you have ever felt an irresistible urge to move

your legs, does it get better, at least partially, by movements such as walking or stretching your legs? 4/ If you feel or you have ever felt an irresistible urge to move your legs, does-it begin or become worse during the evening or the night? A positive answer to all four questions was required for a presumed diagnosis of RLS[15].

All patients also completed the following standardised questionnaires:

Pittsburgh Sleep Quality Index-PSQI[16]

This questionnaire evaluates the quality of the patient's sleep during the last month before the visit. It is composed of 19 questions concerning 7 items, each item being scored between 0 and 3. The global score therefore varies from 0 to 21 and a high score corresponds to poor quality sleep. A score greater than or equal to 5 defines poor quality sleep.

Epworth Sleepiness Scale-ESS[17]

This questionnaire assesses excessive daytime sleepiness (EDS) through 8 different items or situations common or frequently found in everyday life during which the propensity to fall asleep or sleepiness is measured on a scale from 0 to 3. The score is noted from 0 to 24. A score of >10 defines the presence of excessive daytime sleepiness

Chalder Fatigue scale[18]

The 11-item Chalder fatigue scale is divided into two components: one that measures physical fatigue (7 questions) and one that measures mental fatigue (4 questions). A global binary fatigue score of 3 or less represents scores of those who are not fatigued, with scores of 4 or more equating to severe fatigue.

Insomnia Severity Scale-ISI[19]

This questionnaire estimates the severity of insomnia symptoms over the past month. It includes seven items scored between 0 and 4 with a total score between 0 and 28. The severity of insomnia symptoms is a function of the total score: not clinically significant between 0 and 7, mild between 8 and 14, moderate between 15 and 21 and severe between 22 and 28.

Beck Depression Inventory- BDI[20]

This 21-item questionnaire describes the patient's mood over the 2 weeks preceding the visit. Each item is scored from 0 to 3 with a total score between 0 and 63. A score between 10 and 18 indicates minor depression, 19 and 29 moderate depression, 30 and 63 severe depression.

Berlin Questionnaire[21]

This questionnaire is designed to identify people at risk of OSA. The questionnaire is self-administered and consists of 10 questions in three categories related to the presence and severity of snoring, frequency of daytime sleepiness, and the presence of obesity or hypertension. Patients have a 'high risk' of OSA if there are 2 or more categories where the score is positive.

CVD Outcome

Occurrence of MACE included death, hospitalization for heart failure, unplanned revascularization, heart transplantation and implantation of a defibrillator or circulatory assistance.

Mortality data were obtained from the public database of INSEE (Institut national de la statistique et des études économiques). Morbidity data were collected from computerized medical record data. These data were verified by the physicians in charge of these patients.

Statistical analysis

Participants' characteristics are presented as median [minimum value; maximum value] for continuous variables, or number and percentages for categorical variables.

Cox proportional hazard models with delayed entry and age of the patients as the time scale were used to estimate hazard ratios (HR) and their CI. Demographic and clinical characteristics associated with risk of future MACE at $p<0.05$ were included in Cox proportional hazard models to estimate the HR for the relationships between each sleep and mood characteristics and risk of future MACE. In the case of multiple events during follow-up, the first event was considered in the survival analysis. Two multivariate models were successively performed: 1) adjustment for left ventricular ejection fraction (LVEF), and hypercholesterolemia and 2) further adjustment for CNS drugs. When appropriate, the interaction terms were tested using the Wald-x2 test. The log-rank test was used to compare the Kaplan-Meier estimate curves for cardia-event free survival with events being right-censored.

Association between baseline characteristics and CNS drugs intake were compared using the chi-square and Mann-Whitney U tests. Significance level was set at $p<0.05$. Analyses were performed using SAS statistical software (version 9.4 SAS Inc, Cary, North Carolina).

3. Results

Among the 119 patients, respectively 60.50%, 50.00% and 36.75% had hypercholesterolemia, hypertension and diabetes and 28.21% were obese. (Table 1). A HF with reduced ejection fraction (HFrEF) was diagnosed for 46% of the patients. The primary cause of heart failure was ischemic heart disease in 57% of patients. 60.50% of patients used angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), 61.34% beta-blockers and 62.18% diuretics. 24.37% took these 3 drugs together.

At baseline, 63.46% complained of poor sleep quality, 21% reported moderate to severe insomnia symptoms, 28.70% an excessive daytime sleepiness and 10.81% had both insomnia symptoms and EDS. RLS was diagnosed in 5.56% of the patients. 35.09% of patients were at high risk for OSA. Around 30% were short sleeper (<7 hours/night), 18% long sleeper (≥9 hours/night) and 46% reported a sleep efficiency <85%. Overall, 36 patients (30%) took central nervous system (CNS) drugs (benzodiazepines, Z-drugs (zolpidem and zopiclone) and antidepressant) (Table 2).

Over a median of 888 days follow-up [5-1470], 37 (31.09%) future MACE were observed, including 21 (17.65%) fatal events, 14 (11.76%) acute cardiac failure and 2 (0.02%) cardiac transplantation.

Each baseline socio-demographic and clinical characteristics of the patients according to the occurrence of MACE events during the follow-up are given in table 1. The risk of future MACE increased in patients with a lower level of LVEF and with more hypercholesterolemia and in patients taking diuretics. We did not include this parameter in the multivariate model given a risk of overfitting.

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Table 1. Demographic and clinical characteristics of patients according to the occurrence of a CV event during the follow-up.

	Whole sample		Occurrence of CV events					
	N=119		No N=82		Yes N=37		Model 0	
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**HR [95% CI]**	**p**
Sex, Female %	35	29.41	25	30.49	10	27.03	0.79 [0.38;1.64]	0.531
BMI, kg/m2 [a]	117 ; 26.56 (18.21 ; 50.24)		81 ; 26.17 (18.21 ; 50.24)		36 ; 27.43 (18.36 ; 49.44)		1.03 [0.97;1.09]	0.352
LVEF, % [a] HR for 10% increase	116 ; 40.00 (15.00 ; 70.00)		79 ; 43.00 (18.00 ; 70.00)		37 ; 30.00 (15.00 ; 60.00)		0.74 [0.57;0.96]	0.021*
Hypertension, Yes	59	50.00	39	48.15	20	54.05	1.08 [0.57;2.07]	0.807
Diabetes mellitus, Yes	43	36.75	26	32.10	17	47.22	1.60 [0.83;3.09]	0.159
Hypercholesterolemia, Yes	72	60.50	43	52.44	29	78.38	2.79 [1.28;6.11]	0.010*
Current smoker, Yes	43	36.44	33	40.74	10	27.03	0.57 [0.28;1.19]	0.133
BDI- score total [a]	112 ; 10.50 (0.00 ; 39.00)		77 ; 9.00 (0.00 ; 38.00)		35 ; 13.00 (3.00 ; 39.00)		1.03 [0.99;1.06]	0.139
CFS – Total score [a]	115 ;8.00 (0.00 ; 14.00)		80 ; 7.00 (0.00 ; 14.00)		35 ; 9.00 (2.00 ; 14.00)		1.09 [0.99;1.20]	0.078

* significant value

[a] Continuous variables were expressed as number, median (minimal value; maximal value)

Model 0 : adjusted for age (timescale)

Abbreviations: ACEI= angiotensin-converting enzyme inhibitors; ARA= angiotensin II receptor antagonists ; BMI=Body Mass Index; OSA= Obstructive Sleep Apnea; BDI= Beck depression inventory ; CFS= Chalder Fatigue Scale; LVEF= Left Ventricular Ejection Fraction

Association between sleep parameters, mood disturbances, CNS drugs intake and future MACE

Each baseline sleep parameters, mood disturbances and CNS drugs the patients according to the occurrence of MACE events during the follow-up are given in table 2.After adjustment for age, the risk of a future MACE increased with CNS drugs intake, PSQI and ISI

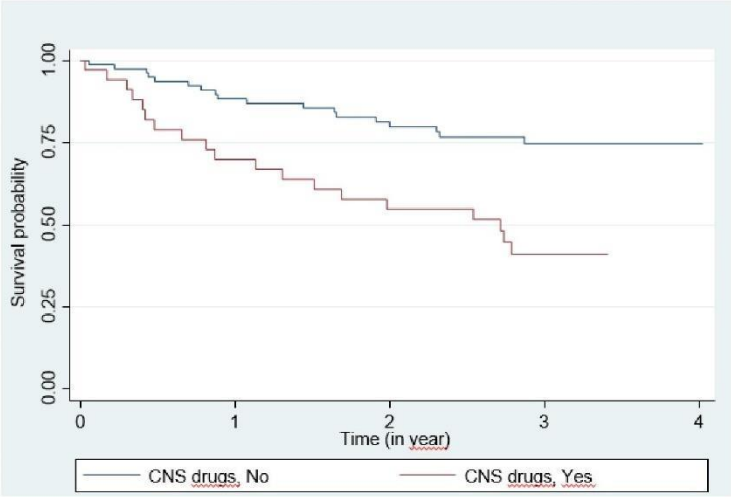
scores as well as increased sleep latency and decreased sleep efficiency. We also found an increased occurrence of fatal and non-fatal MACE when total sleep time was reduced by one hour. When potential confounders were entered into the model (model 1, Table 2), the HR were reduced and failed to be significant except for CNS drugs and total sleep time. Similar trends were found however for ISI and PSQI scores. When further adjusting for CNS drugs, the associations became not significant (model 2, Table 2).

No interaction was found for future MACE event between CNS drugs intake and sleep disturbances.

Patients with HF who were taking CNS drugs had a lower LVEF (p=0.02) and more hypercholesterolemia (p=0.03). Moreover, they got worse scores for BDI (p<0.01), ISI (p=0.02), PSQI (p<0.01) and fatigue dimension of Chalder fatigue scale (p=0.02). Finally, these patients had a lower sleep efficiency (p=0.04).

The Kaplan-Meier survival curves showed that cardiac event-free survival differed in patients who took CNS drugs vs not (p=0.001) (Figure 1).

Figure 1. Survival curve of patients with HF according to CNS drugs intake; MACE events.



4. Discussion

Our study reported that sleep disturbances and CNS drugs intake are associated with a poor prognosis in patients with HF with long term follow-up.

This study emphasizes the importance of a detailed drug history in the population of HF patients. Indeed, the main finding of this study was the higher risk of MACE in patients who were taking CNS drugs. CNS drugs include benzodiazepines, Z-drugs and antidepressants (AD). We have chosen to bring these drugs together in a single entity given that their intake is often combined and their respective effects on the CNS are difficult to differentiate. While the relationship between hypnotic use and long-term mortality is not well established in the general population[22] a recent study found that the use of benzodiazepines was an independent predictor of rehospitalisation for HF patients[6]. The poorer prognosis of patients taking these drugs could be related to their potential side

effects such as cognitive decline, daytime sleepiness, impairment in psychomotor performance[23] or respiratory depression[24]. The numerous comorbidities associated with the use of CNS drugs[22] and with patients with HF as confirmed in the present study could increase the risk of mortality and cardiovascular morbidity.

We also found an increased occurrence of fatal and non-fatal MACE when total sleep time was reduced by one hour. Short sleep duration (<7 hours) is frequently found in the general population[25] and is associated with all-cause mortality [26] although this link is not found in all studies[27].Moreover, self-reported short sleep (<6 hours) is associated with high risk of developing HF in men with cardiovascular disease[28].

Table 2. Self-reported sleep parameters and central nervous system (CNS) drugs intake in patients as function of the occurrence of CV events during the follow-up.

	Whole sample		Occurrence of CV events									
			No N=82		Yes N=37		Model 0		Model 1		Model 2	
Variable	n	%	n	%	n	%	HR [95% CI]	p	HR [95% CI]	P	HR [95% CI]	P
CNS drugs, Yes	36	30.25	17	20.73	19	51.35	3.03 [1.59;5.79]	<0.001*	2.37 [1.22;4.59]	0.010*		
ESS score [a]	115 ; 7.00 (0.00 ; 22.00)		80 ; 6.00 (0.00 ; 22.00)		35 ; 9.00 (0.00 ; 22.00)		1.03 [0.97;1.09]	0.303	1.04 [0.98;1.11]	0.187	1.04 [0.98;1.11]	0.234
ESS score, >10	33	28.70	21	26.25	12	34.29	1.31 [0.65;2.64]	0.448	1.62 [0.80;3.27]	0.178	1.45 [0.71;2.93]	0.307
ISI score [a]	115 ; 8.00 (0.00 ;28.00)		79 ; 7.00 (0.00 ; 21.00)		36 ; 11.00 (1.00 ; 28.00)		1.07 [1.01;1.12]	0.012*	1.05 [1.00;1.10]	0.048*	1.03 [0.98;1.09]	0.197
ISI score,>14	24	20.87	14	17.72	10	27.78	1.52 [0.73;3.15]	0.261	1.22 [0.58;2.56]	0.593	0.96 [0.45;2.07]	0.921
BQ score, ≥2	40	35.09	25	32.05	15	41.67	1.29 [0.67;2.51]	0.449	1.41 [0.72;2.74]	0.313	1.05 [0.51;2.13]	0.903
RLS, ≥4	6	5.56	4	5.56	2	5.56	1.20 [0.29;5.03]	0.798	1.22 [0.29;5.09]	0.785	1.43 [0.34;6.03]	0.630
PSQI score [a]	104 ;6.00 (0.00 ; 16.00)		71 ; 6.00 (0.00 ; 14.00)		33 ; 7.00 (1.00 ; 16.00)		1.10 [1.01;1.20]	0.028*	1.09 [1.00;1.19]	0.059	1.05 [0.95;1.15]	0.362
PSQI score, ≥5	66	63.46	42	59.15	24	72.73	1.29 [0.67;2.51]	0.268	1.31 [0.60;2.84]	0.496	0.94 [0.40;2.18]	0.882
Sleep latency, min [a] HR For 15 min Increase	117 ; 15.00 (0.00 ; 150.00)		80 ; 15.00 (0.00 ; 150.00)		37 ; 30.00 (0.00 ; 90.00)		1.11 [0.97;1.28]	0.127	1.09 [0.94 ;1.25]	0.255	1.10 [0.95;1.28]	0.201
Sleep latency, min												
<30	70	59.83	54	67.50	16	43.24	1	0.033*	1	0.091	1	0.071

	Whole sample		Occurrence of CV events									
			No N=82		Yes N=37		Model 0		Model 1		Model 2	
Variable	n	%	n	%	n	%	HR [95% CI]	p	HR [95% CI]	P	HR [95% CI]	P
[30-60[	25	21.37	16	20.00	9	24.32	1.54 [0.68;3.48]		1.47 [0.65;3.36]		1.13 [0.48;2.65]	
>60	22	18.80	10	12.50	12	32.43	2.72 [1.28;5.74]		2.34 [1.09;5.01]		2.38 [1.10;5.14]	
TST, hour [a]	119 ; 7:30		82 ; 7:52		37 ; 7:00		1.26 [1.02;1.55]	0.030*	1.27 [1.01;1.58]	0.037*	1.22 [0.97;1.52]	0.092
HR For 1 hour decrease	(3 :00 ;11:45)		(3:00 ; 12:00)		(3:15 ; 10:15)							
TST, ≤7 hours	57	47.90	34	41.46	23	62.16	1.84 [0.95;3.58]	0.072	1.72 [0.88;3.36]	0.111	1.41 [0.70;2.84]	0.333
Efficiency, % [a]	118 ; 87.50		81 ; 88.57		37 ; 82.35		0.79 [0.65;0.97]	0.022*	0.85 [0.69 ;1.05]	0.135	0.99 [0.97;1.01]	0.353
HR for 10% increase	(35.29 ; 100.00)		(35.29 ; 100.00)		(38.24 ; 100.00)							
Efficiency ≥85%	63	53.39	45	55.56	18	48.65	0.82 [0.43;1.57]	0.551	1.02 [0.53;1.97]	0.947	1.31 [0.66;2.62]	0.440

* significant value

[a] Continuous variables were expressed as number, median (minimal value; maximal value)

Model 0 : adjusted for age (timescale)

Model 1: adjusted for age (timescale), left Ventricular Ejection Fraction (%) and hypercholesterolemia.

Model 2: adjusted for covariates in model 1 plus CNS drugs intake.

Abbreviations: BQ=Berlin questionnaire, ESS=Epworth Severity Scale, HR=Hazard Ratio, ISI=Insomnia Severity Index, PSQI=Pittsburgh Sleep Quality, Index TST=Total Sleep Time, RLS=Restless legs syndrome

In unadjusted analysis, high sleep latency, poor sleep efficiency, poor sleep quality and insomnia symptoms severity were associated with a poorer prognosis in patients with HF.. Sleep latency and sleep efficiency are good indicators of sleep quality[29] and should be evaluated to characterize the sleep of patients with HF. Our results were consistent with previous studies for total sleep time [30] and sleep quality[12,28,31]. However, several important differences exist between these studies and ours. First, these studies were secondary analyses, with no primary objective of exploring sleep problems in patients with HF. Secondly, the sleep assessment was often carried out with a single item or a single questionnaire, and never with a comprehensive battery of sleep questionnaires [12].

We did not find any significant results with factors frequently associated with an increased cardiovascular risk. First, sleepiness is a factor of severity in the presence of sleep breathing disorders and is associated with mortality and CVD morbidity[32,33] but it does not appear to be linked to the prognosis of heart failure patients in this study. We did not find any association with the presence of restless legs syndrome, although studies have shown an increase in mortality due to CVD associated or not with periodic leg movements[34–36].

There are some limitations in this study. The assessment of sleep parameters was only self-reported causing possible recall bias and a lack of accuracy in responses. However, we used validated questionnaires, which are simple tools that can be used by a large number of practitioners, to assess for sleepiness, fatigue, insomnia symptoms, RLS, proxy of OSA, quality of sleep, anxiety and depressive symptoms. In contrast, the presence of sleep apnea was not evaluated objectively, as no polysomnography were available for this specific study, and the Berlin questionnaire is not very specific in patients with cardiovascular diseases[37]. Finally, the use of diuretics was associated with the occurrence of MACE in univariate analysis, but we did not include this parameter in the multivariate model, because of the risk of overfitting. Indeed, LVEF was closely linked to the use of cardiological drugs with a lower LVEF in patients taking diuretics or beta blockers. Diuretics are used to control symptoms in patients with HF, especially fluid overload, but without effect on mortality**[38]**. Moreover, approximately 80% of patients with HF are taking diuretics with frequent changes in dosage**[39]**, which makes their integration in the multivariate model irrelevant.

5. Conclusions

Our findings suggest that CNS drugs intake and decreased total sleep time were associated with an increased risk of fatal and non-fatal MACE in patients with HF. These results emphasize the importance of routinely screening for sleep symptoms and CNS drugs intake, especially in patients with severe HF to propose a specific management to improve the quality of life and prevent the natural progression of HF.

Supplementary Materials:

Author Contributions: FB :drafting/revising the manuscript for content, including medical writing for content; interpretation of data analysis; acquisition of data. IJ: performing statistical analysis; interpretation of data analysis; revising the manuscript for content. FR, YD: drafting/revising the manuscript for content, including medical writing for content; study concept or design; interpretation of data analysis, study supervision and coordination. BA, SS : data curation. SA: investigation. NC: data curation.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study

Data Availability Statement: Data would be provided under reasonnable request

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Conflicts of Interest: The authors declare no conflict of interest.

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PARTIE 3 : SYNTHESE DES TRAVAUX ET PERSPECTIVES

Les travaux présentés dans la partie 2 de ce document apportent donc des éléments de réponse aux objectifs de cette thèse.

Pour rappel, le premier objectif est d'**améliorer la compréhension des liens physiopathologiques et cliniques entre les troubles du sommeil, et notamment le SAHOS, et les maladies cardiovasculaires**.

- L'étude **SAS-IDM** a confirmé la prévalence très élevée de SAHOS chez les patients ayant présenté un infarctus du myocarde sévère et n'a pas mis en évidence d'association entre la présence d'un SAHOS et le remodelage ventriculaire.
- L'étude **PRO-TSIC** a démontré une augmentation de la survenue d'évènements cardiovasculaires majeurs chez des patients avec une insuffisance cardiaque prenant des médicaments agissant sur le système nerveux central et présentant une diminution du temps de sommeil.

Le deuxième objectif est de **préciser les impacts cliniques et physiopathologiques de différents traitements du SAHOS**.

- L'étude **REEVASAS** a mis en évidence qu'un réentrainement à l'effort individualisé pendant 8 semaines améliorait les marqueurs de sévérité du SAHOS et notamment la somnolence diurne, l'IAH en sommeil paradoxal (IAH-REM) mais aussi la fatigue et les symptômes d'insomnie et de dépression.

Les projets en cours devraient également apporter des éléments de réponse afin de compléter cette réflexion.

- L'étude **CARDIOXSAS** évalue les liens entre SAHOS et marqueurs physiopathologiques (stress oxydant, inflammation, fonction endothéliale, activité sympathique) chez des patients coronariens stables ainsi que l'impact du traitement par PPC sur ces marqueurs (Objectifs 1 et 2).

- L'étude **m-Rehab OSA** va étudier l'efficacité d'un programme de téléréhabilitation associé à la PPC sur les marqueurs de sévérité du SAHOS chez des patients obèses (Objectif 2).

Les réponses apportées par nos travaux et la littérature récente font constater qu'il existe encore de nombreuses inconnues dans les connaissances concernant les liens entre troubles du sommeil et maladies cardiovasculaires. Les projets en cours et à venir doivent apporter des éléments de réponse à un **troisième objectif** plus ambitieux, rassemblant les deux précédents, qui est de **proposer une approche diagnostique et thérapeutique du SAHOS basée sur la médecine de précision**.

Alors que le SAHOS est considéré comme un facteur de risque cardiovasculaire indépendant, son association avec l'augmentation du risque cardiovasculaire chez des patients avec une maladie coronarienne reste débattue. Notre étude SAS-IDM a mis en évidence que la présence d'un SAHOS n'était pas associée au remodelage ventriculaire chez des patients avec un IDM alors que deux études récentes n'ont pas objectivé d'augmentation de l'incidence des évènements cardiovasculaires en cas de SAHOS chez des patients avec un IDM(Xie et al. 2018; Sánchez-de-la-Torre et al. 2019).

Le SAHOS regroupant un ensemble de patients très hétérogène, il est de plus en plus évident qu'utiliser l'IAH comme seul critère pour définir le SAHOS et déterminer sa sévérité est réducteur et ne permet pas de déterminer la population avec un risque cardiovasculaire augmenté et donc la thérapeutique adaptée.

La **symptomatologie** est essentielle afin de mieux caractériser la population. Notamment la présence d'une **somnolence diurne excessive** chez les patients avec un SAHOS est associée à une augmentation du risque cardiovasculaire aussi bien en population générale que chez des patients avec un IDM(Mazzotti et al. 2019; Xie et al. 2018). (Figure).

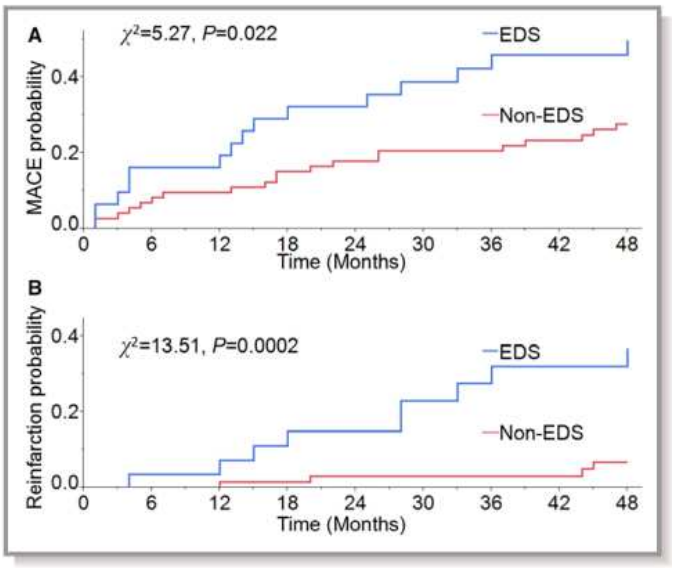

Figure 9. Probabilité d'évènements cardiovasculaires majeurs et de récidive après un IDM chez des patients somnolents et non somnolents. Xie, J Am Heart Assoc., 2018.

La prise en compte des **antécédents personnels** permet également un meilleur phénotypage des patients. Des analyses post-hoc de l'étude ISAAC ont mis en évidence que la présence d'un SAHOS était associée à une augmentation de la survenue d'évènement cardiovasculaires chez des patients présentant un syndrome coronaire aigu sans antécédent de maladie coronarienne contrairement aux patients avec des antécédents cardiovasculaires(Zapater et al. 2020).

La médecine de précision implique d'intégrer également **d'autres paramètres de l'enregistrement du sommeil,** reflétant plus précisément la physiopathologie du SAHOS.

- Les paramètres reflétant l'**hypoxie intermittente** (HI) sont importants à prendre en compte. Dans deux études de cohorte, la charge hypoxique, nouvelle mesure de l'HI représentant l'aire sous la courbe de désaturation en référence à la saturation avant l'évènement, était associée à la mortalité cardiovasculaire(Azarbarzin et al. 2019).
- Les marqueurs de la **balance sympatho-vagale** peuvent également participer à une meilleure caractérisation de la population. Des marqueurs témoignant d'une augmentation du tonus sympathique, tels que l'index de l'intervalle R-R et la variabilité de fréquence cardiaque suivant les évènements respiratoires, ont été associés à une augmentation de la morbidité et de la mortalité cardiovasculaire(Sankari et al. 2019; Azarbarzin et al. 2021).

- Une courte durée moyenne des évènements respiratoires, témoignant d'un **seuil d'éveil abaissé,** est associée à une augmentation de la mortalité chez les hommes et chez les femmes(Butler et al. 2019).
- **L'IAH en sommeil paradoxal** est également un facteur à prendre en considération. Des études ont objectivé une association entre un SAHOS en sommeil paradoxal et la prévalence et l'incidence de l'HTA ainsi qu'un lien avec l'insulinorésistance(Mokhlesi et al. 2015; Rishi et Rishi 2021).

Nos travaux et la littérature confirment donc la nécessité d'évoluer vers une médecine personnalisée, de précision, tenant compte de la symptomatologie, des comorbidités et des antécédents, des paramètres physiopathologiques ainsi que des caractéristiques polysomnographiques.

La meilleure caractérisation des patients avec un SAHOS, qui constituent une population très hétérogène, doit permettre d'identifier les patients présentant un risque cardiovasculaire augmenté et d'adapter la thérapeutique afin de diminuer ce risque.

Etude 4 : Téléréhabilitation et SAHOS : Impact d'un programme de téléréhabilitation associé à la PPC sur les marqueurs de sévérité du syndrome d'apnées hypopnées obstructives du sommeil. Etude prospective, randomisée, contrôlée, multicentrique. Etude m-Rehab OSA.

Papier en voie de soumission

Généralités sur le projet m-Rehab

Le projet m-Rehab est un projet de recherche et développement qui consiste à développer une solution de téléréhabilitation pour les maladies chroniques et d'étudier l'efficacité de cette solution par l'intermédiaire de deux études randomisées contrôlées : l'étude m-Rehab OSA et l'étude m-Rehab BPCO (projet financé par la DGOS dans le cadre d'un PREPS-programme de recherche sur la performance du système de soins). Le porteur principal du projet et coordonnateur principal de l'étude m-Rehab BPCO est le Professeur Maurice Hayot.

Le projet a été financé à hauteur de 1.092.072 euros par la Région Occitanie et les fonds FEDER dans le cadre de l'appel à projets Recherche et Société(s) 2018. Le projet est porté par l'Université de Montpellier dans le cadre d'un consortium associant différents laboratoires (PhyMedExp INSERM U1046-CNRS UMR9214, Laboratoire de Génie informatique et Ingénierie de Production - LGI2P, IMT Mines Alès, Laboratoire Montpellier Recherche en Management (MRM), laboratoire Euromov) et les cliniques du Souffle du groupe Korian.

La première étape du projet qui consistait au développement de la solution de téléréhabilitation (Figure 10) s'est déroulée entre mars 2019 et septembre 2021. La société qui a développé la solution est la solution Avis2Santé.

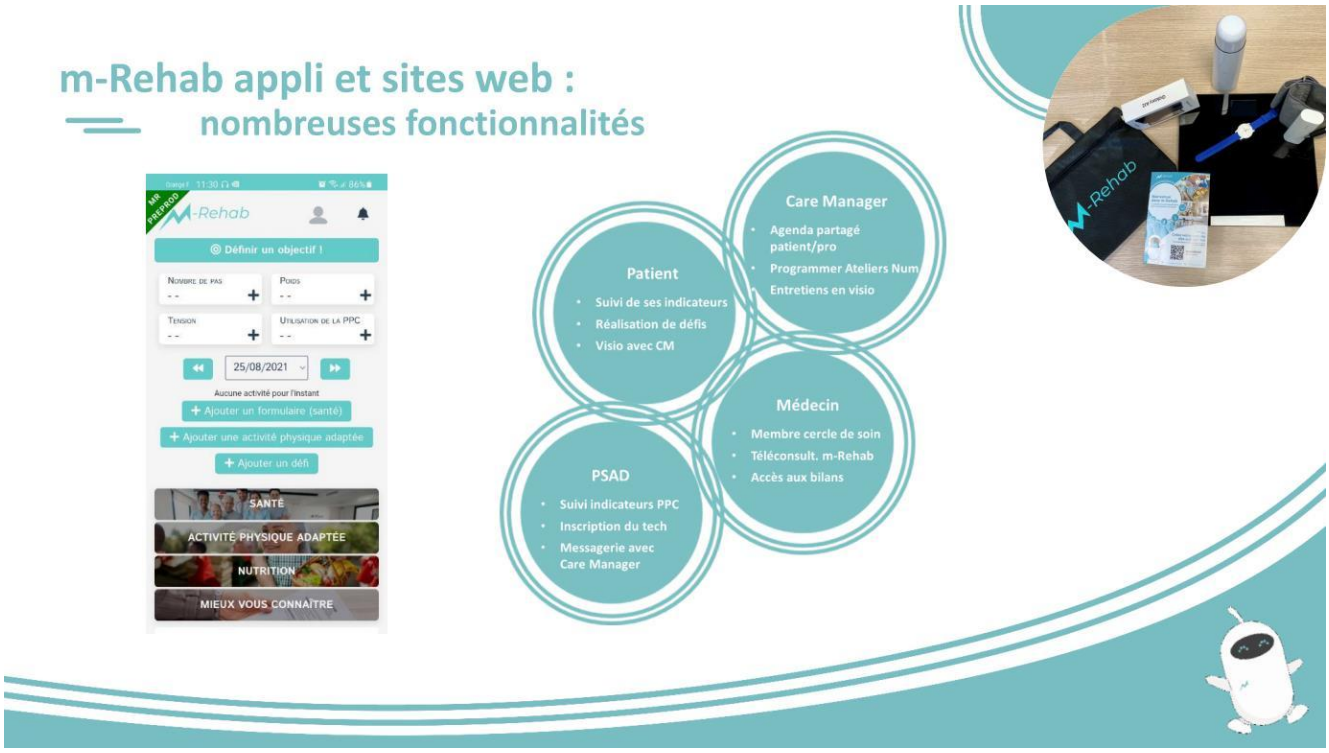

Figure 10. m-Rehab, solution de téléréhabilitation pour les maladies chronique, est une plateforme d'échange entre le patient et son cercle de soins. Des objets connectés permettent la remontée quotidienne des données de santé.

Prérequis pour l'étude m-Rehab OSA

Le SAHOS est un trouble respiratoire du sommeil fréquent et est associé à de nombreuses complications dont notamment la somnolence diurne excessive(Prasad et al. 2018), une altération de la qualité de vie(Pichel et al. 2004) et des complications métaboliques et cardiovasculaires(Javaheri et al. 2017).

L'obésité, définie par un IMC ≥ 30 kg/m², est un des facteurs de risque majeurs de SAHOS(Terry Young, Peppard, et Gottlieb 2002). Le SAHOS et l'accumulation de masse grasse exercent un effet synergique négatif sur le système cardio-vasculaire à travers différents mécanismes. Parmi ceux-ci, l'inflammation joue un rôle prépondérant. L'accumulation de masse grasse et le SAHOS sont associés de manière indépendante à un état inflammatoire systémique(Ferrante 2007; K. Li et al. 2017) . La C-reactive protéine ultrasensible (CRP us),

protéine de la famille des pentraxines synthétisée par le foie, est un témoin précis du statut inflammatoire et est associée avec une augmentation de la morbidité cardio-vasculaire(Ridker 2007).

Le traitement de choix du SAHOS est la PPC qui permet une normalisation de l'IAH, une amélioration de la qualité du sommeil, de la somnolence diurne ou encore de la qualité de vie(Patil et al. 2019). L'effet de la PPC sur la pression artérielle (PA) est limité avec une diminution de 2 mmHg en moyenne de la PA systolique moyenne et une efficacité qui peut être supérieure sur les mesures de PA nocturne(Posadas et al. 2020). Par ailleurs, aucune étude randomisée contrôlée n'a démontré un effet protecteur de la PPC en prévention primaire ou secondaire des maladies cardiovasculaires(McEvoy et al. 2016). Ces résultats décevants pourraient être expliqués notamment par une faible observance au traitement. En effet, malgré les améliorations technologiques, la durée d'utilisation de la PPC reste insuffisante(Cistulli et al. 2019) alors que certaines études montrent qu'une observance moyenne supérieure à 4 heures par nuit est nécessaire pour obtenir une efficacité sur la PA(Bratton et al. 2015) et sur la réduction de certains évènements cardiovasculaires(Javaheri et al. 2019).

Par ailleurs, les modifications du mode de vie sont recommandées dans la prise en charge du SAHOS afin de diminuer sa sévérité et ses complications(Epstein et al. 2009; Hudgel et al. 2018). Le réentrainement à l'effort permet de diminuer la sévérité du SAHOS, la somnolence diurne et d'améliorer l'aptitude physique aérobie(Mendelson, Bailly, et al. 2018; F. Bughin et al. 2020) alors que la perte pondérale améliore la TA, l'insulinorésistance, l'hypertriglycéridémie et l'inflammation(Chirinos et al. 2014) chez les patients obèses avec SAHOS sévère. La réhabilitation, intervention globale et individualisé incluant le réentraînement à l'effort, l'éducation thérapeutique, les changements de comportement(Spruit et al. 2013), a un effet bénéfique sur la sévérité du SAHOS et les composantes du syndrome métabolique qui y sont associés(Desplan et al. 2014; Dobrosielski et al. 2017).

Les avancées technologiques de ces dernières années, particulièrement dans le domaine des technologies de l'information et de la communication ont amené des nouveaux outils dédiés à la prise en charge des pathologies chroniques. Nous avons démontré dans une étude pilote

que la téléréhabilitation (TR) chez des patients obèses était faisable avec une bonne satisfaction des patients et permettait d'améliorer la qualité de vie et des marqueurs du risque cardiométabolique(François Bughin et al. 2021).

Dans le cadre du SAHOS, la téléconsultation s'est révélée aussi efficace que la consultation présentielle sur l'observance de la PPC avec un bon rapport coût efficacité(Isetta et al. 2015). En outre, alors que le visionnement de vidéos éducatives ne permet pas d'améliorer l'observance au traitement(Guralnick et al. 2017), le télésuivi avec retours vers le patient sur l'utilisation de la PPC entraîne une augmentation significative de l'utilisation du traitement sans effet cependant sur la somnolence ou la qualité de vie(Hwang et al. 2017; Aardoom et al. 2020). L'utilisation d'une plateforme multimodale avec remontée de différents objets connectés (podomètre, tensiomètre) permet une amélioration de l'observance et de la somnolence sans toutefois augmenter le nombre de pas ni améliorer la PA(J.-L. Pépin et al. 2018) .

Aucune étude n'a étudié dans le SAHOS l'impact d'une solution complète de TR associant un programme d'activité physique, de nutrition, d'éducation thérapeutique tout en tenant compte des dimensions motivationnelles, comportementales et psychosociales propres à la réhabilitation.

Nous proposons donc de démontrer l'impact d'une solution de TR associée à la PPC sur les marqueurs de sévérité du SAHOS.

Objectifs

Objectif principal : Evaluer à six mois l'efficacité sur les marqueurs de sévérité du SAHOS (somnolence diurne, qualité de vie, pression artérielle, inflammation) d'un programme de TR associé à la PPC comparativement à la PPC seule, chez des patients obèses présentant un SAHOS sévère.

Méthodes

Etude prospective, randomisée à deux bras parallèles, contrôlée interventionnelle versus prise en charge de référence, multicentrique, en ouvert.

Deux groupes de 90 patients chacun seront constitués : un groupe utilisant la solution de TR associée à la PPC et un groupe contrôle suivant une prise en charge habituelle (PPC et conseils hygiéno diététiques).

Les patients inclus seront des patients de 30 à 75 ans, avec un IMC supérieur à 30kg/m² et un IAH ≥30/heure.

Les principaux critères de non-inclusion sont : présence de contre-indications à la réalisation d'un réentraînement à l'effort ; présence d'une maladie inflammatoire, infectieuse ou néoplasique active ; refus d'utiliser un smartphone ou un dispositif numérique ; impossibilité d'accéder à une connexion internet à domicile.

Nous utiliserons plusieurs critères principaux selon un test séquentiel hiérarchisé. Dans l'ordre, les critères successifs seront : Evolution entre l'inclusion et 6 mois 1/Somnolence diurne (Questionnaire d'Epworth) 2/Qualité de vie (Questionnaire FOSQ) 3/ Pression artérielle (PA systolique nocturne) 4/ Inflammation (CRP).

Le nombre de sujets nécessaires est de 90 patients par groupe. L'analyse principale sera l'analyse univariée, en intention de traiter. Les analyses secondaires comprendront une analyse en intention de traiter des critères de jugement secondaires, une analyse multivariée des critères d'efficacité et une analyse en per protocole.

L'étude est prévue sur 15 mois dont 9 mois d'inclusion et 6 mois de suivi avec des visites prévues à l'inclusion et à 6 mois ainsi que des téléconsultations à 1 et 3 mois. Les visites d'inclusion et finale comprendront un enregistrement du sommeil, un prélèvement sanguin, des mesures anthropométriques, des questionnaires et une épreuve d'effort. Une actimétrie de 7 jours et un Holter tensionnel sont prévus à l'inclusion et à la fin de l'étude.

Une étude ancillaire compassionnelle sera réalisée à la fin des 6 mois de suivi pour permettre aux 90 patients du groupe contrôle d'utiliser la solution de TR et prolonger le suivi des 90 patients du groupe expérimental sur 6 mois.

Description de l'intervention

Les patients du groupe expérimental seront traités par PPC (PRISMA, LOEWENSTEIN®) et auront accès au programme de TR m-Rehab®. Le programme de TR se compose des éléments suivants :

- Applications mobiles et site web utilisables sur smartphone et tablette pour le patient. Ils permettent le recueil de données, l'éducation thérapeutique et l'administration de conseils et programmes en AP et nutrition par l'intermédiaire de questionnaires en ligne et d'appareils connectés. Le but étant de provoquer des modifications comportementales chez les patients notamment en favorisant l'autogestion (empowerment ou self monitoring du patient). Les données d'utilisation de la PPC (observance, fuites, IAH résiduel) seront disponibles.
- Solution de téléconsultation pour le patient et le médecin.
- Solution de visioconférence pour les professionnels impliqués dans le suivi des patients
- Interface web pour les professionnels de santé permettant le recueil et le suivi des différents paramètres en activité physique et en nutrition ainsi que la progression dans les activités d'éducation thérapeutique. Les données d'utilisation de la PPC (observance, fuites, IAH résiduel) seront disponibles.
- Objets connectés de marque Withings® : montre connectée, balance, tensiomètre

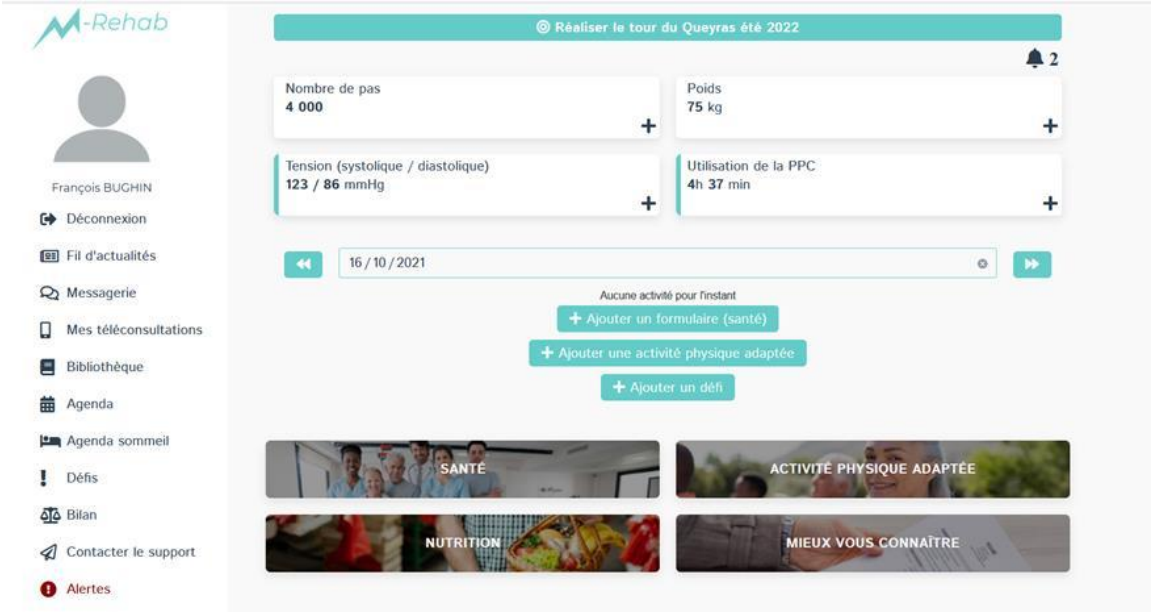

Figure 11. Page d'accueil de la solution m-Rehab pour le patient.

Les patients seront suivis par un care manager, professionnel qui fera le lien entre les patients, la plateforme de TR et les différents professionnels de soins et de santé. Il accompagnera les patients tout au long de leur programme de TR en favorisant l'adoption de comportements de santé favorables. La fréquence des interventions sera dégressive au cours du suivi : 60 minutes la première semaine, 30 minutes hebdomadaire jusqu'à la douzième semaine et 30 minutes toutes les deux semaines lors des trois derniers mois.

Les patients du groupe contrôle seront traités par PPC (PRISMA, LOEWENSTEIN) et recevront lors de la consultation initiale les conseils habituels en activité physique adaptée et en nutrition.

Etat d’avancement du projet

Mises en place sur les différents centres en août et septembre 2021.

Première inclusion le 27 septembre 2021.



Figure 12. Mise en place et inclusions de l'étude m-Rehab OSA.

Article

Impact of a telerehabilitation program associated with CPAP on severity markers of obstructive sleep apnea syndrome.

Study protocol for a randomized, controlled, multicenter study

F Bughin, M Mendelson, D Jaffuel, B Ayoub, F Roubille, J Mercier , N Molinari, P Pomies, Y Dauvilliers , N Heraud, M Hayot *and the member of the consortium m-Rehab*

Papier en voie de soumission

Impact of a telerehabilitation program associated with CPAP on severity markers of obstructive sleep apnea syndrome.

Study protocol for a randomized, controlled, multicenter study

Acronym: m-Rehab OSA

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ABSTRACT

Background: Obstructive sleep apnea syndrome (OSA) is a common sleep breathing disorder associated with adverse health outcomes including excessive daytime sleepiness, impaired quality of life and an increase in the risk of cardiovascular events. Continuous positive airway pressure (CPAP) is the reference treatment, but its cardiovascular and metabolic benefits are uncertain. Interventions aimed at improving patient's lifestyle behaviours are therefore recommended in the management of OSA. However, access to these interventions is limited and their effectiveness seem to be limited over time. Telerehabilitation (TR) is a promising approach that has only been the subject of pilot studies in OSA.

Methods: This study is a randomized controlled multicenter trial in which 180 obese patients with severe OSA will be randomized to a telerehabilitation lifestyle intervention (TR and CPAP) or to a control (CPAP) group. As the main endpoint, we will use a sequential hierarchical criterion including sleepiness, quality of life, nocturnal systolic blood pressure and inflammation respectively.

Discussion: m-Rehab OSA is the first study to examine the effectiveness of a TR lifestyle program in OSA. We hypothesize that a TR lifestyle intervention associated with CPAP for 6 months will be more effective than CPAP alone on markers of the severity of OSA. A medico-economic analysis will assess the efficiency of the intervention. Massive data analysis (data mining) will allow us to better understand the motivational barriers and levers of patients to use CPAP and to modify their behaviors.

Trial Registration : Clinicaltrials.gov Identifier: NCT050499281. Registration data: September 20th, 2021

KEYWORDS : Obstructive sleep apnea syndrome, Obesity, Sleepiness, Cardiovascular risk, Quality of life, Hypertension, Telemedicine, Telerehabilitation, Randomized controlled trial

INTRODUCTION

Obstructive sleep apnea (OSA) is a frequent sleep respiratory disorder and is associated with many complications, including excessive daytime sleepiness[1], impaired quality of life[2], metabolic and cardiovascular complications[3].

Obesity, defined by a body mass index (BMI) ≥ 30 kg/m², is a major risk factor for OSA[4]. OSA and the accumulation of body fat exert a synergistic negative effect on the cardiovascular system through various mechanisms. Among these mechanisms, inflammation plays a major role. Fat accumulation and OSA are independently associated with a systemic inflammatory state[5,6]. The ultrasensitive C-reactive protein (hs CRP), a protein of the pentraxin family synthesized by the liver, is an accurate indicator of the inflammatory status and is associated with an increase in cardiovascular morbidity[7].

The first line treatment for OSA is continuous positive airway pressure (CPAP), which normalizes the apnea-hypopnea index (AHI), improves sleep quality, daytime sleepiness and quality of life[8]. The effect of CPAP on blood pressure (BP) is limited with an average decrease of between 2 and 2.5 mmHg of systolic or diastolic BP[9]. Furthermore, the cardiovascular benefit of OSA treatment with CPAP remains undefined since randomized controlled trials (RCT) failed to demonstrate a protective effect of CPAP in secondary prevention of cardiovascular disease[10,11]. These disappointing results could be partly explained by adherence to CPAP treatment which is often insufficient[12] while an average compliance greater than 4 hours per night is necessary to obtain efficacy on BP[13] and on the reduction of certain cardiovascular events[14]. Telemonitoring and eHealth interventions could improve adherence to CPAP[15,16]. The use of a multimodal telemonitoring platform at CPAP initiation, improves CPAP adherence and sleepiness without increasing the number of steps per day or decreasing the BP[17].

However, improved cardiovascular prognosis is not always related to CPAP adherence[10] and the development of combined treatment strategies is necessary for the management of OSA and its comorbidities[18]. A recent trial examining the effects of a comprehensive and individualized intervention including exercise training, therapeutic patient education and behaviour changes has shown a beneficial effect on the severity of OSA and the associated components of metabolic syndrome[19].The technological advances of recent years, particularly in the field of information and communication technologies (ICT) have brought new tools dedicated to the management of chronic diseases. We demonstrated in a pilot study that telerehabilitation (TR) in obese patients was feasible, provided good patient satisfaction, and improved quality of life and markers of cardiometabolic risk[20].

To our knowledge, no study has examined the impact of a complete TR intervention combining physical activity, nutrition and therapeutic patient education while considering the motivational, behavioural and psychosocial dimensions specific to rehabilitation in patients with OSA and obesity. We therefore propose to demonstrate the impact of a TR solution associated with CPAP on markers of OSA severity.

This paper describes the rational and design of the multicentric, randomized controlled trial (RCT) we have designed to address these points.

Objectives of the study

Primary objective

The aim of our RCT is to assess the potential benefits in severe OSA patients with obesity of a 6-month TR program implemented at CPAP initiation, compared to usual care with CPAP, on severity markers of OSA evaluated by a hierarchical test sequence including in the following order: sleepiness, quality of life, nocturnal systolic blood pressure and inflammation (CRP).

Secondary objectives

The secondary objectives are to evaluate the effects of the 6-month TR program compared to CPAP alone on:

- Sleep habits and disorders based on self-administered questionnaires (sleepiness, fatigue), adherence to CPAP and sleep architecture
- Physical activity levels and exercise tolerance
- Motivation to physical activity, based on self-administered questionnaires (also evaluated at 3 months): expectations of results, self-efficacy, perception of risks, intentions, planning, self-efficacy to barriers, habits, and social support
- Nutritional and metabolic aspects: hunger and satiety sensations, anthropometric characteristics, and biological data
- BP multiple parameters based on 24-hour ambulatory blood pressure monitoring

A medico-economic assessment is also planned.

In the TR group only, we also aim to evaluate:

- Usability of the TR digital solution[21]
- Usage of the TR during the 6-month period: the extraction of data from the digital solution, and the data-mining analysis will allow to study the relationships between the TR digital solution usage and the effects of TR program in the TR group.

Methods

Study design

The present study is a multicentre randomized, controlled, parallel, trial involving thirteen centres in France.
180 newly diagnosed patients with severe OSA and obesity will be randomly allocated to CPAP with TR or CPAP alone (control group). All subjects will be requested to provide written informed consent before study entry. Data will be collected at baseline and after 4, 12, and 24 weeks.

Patients randomized to the control group will be informed that, at the end of the 6-month protocol, they will be offered a 6-month period usage of the TR digital solution developed for the study. Patients in the intervention group will have the opportunity to continue the TR intervention for an additional 6-month period. Satisfaction, usability, and patient experience will be assessed to improve the digital solution in an ergonomic and functionality points of view.

The study was approved by the ethics committee (CPP IDF IV – France. IDRCB : 2020-A02100-39). ClinicalTrials.gov identifier NCT050499281. This protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013[22] and the reporting will respect the CONSORT (Consolidated Standards of Reporting Trials) statement for non-pharmacologic trials[23].

Study Population

Inclusion criteria: Patients eligible for participation to the study will be:

- Adults aged between 30 and 75 years
- with severe OSA, defined by an apnea hypopnea index (AHI) ≥ 30/h
- and obese (BMI ≥30 kg/m²)

Exclusion criteria are:

- OSA treated by CPAP or mandibular advancement device in the 3 months preceding inclusion
- Presence of contraindications to perform exercise training (neuromuscular disease, orthopaedic cause, acute coronary syndrome or stroke in the previous three months).
- Active infection, chronic inflammatory disease, cancer under treatment. Systemic treatment with immunosuppressants or corticosteroids
- Participation in a rehabilitation program scheduled in the next 6 months of inclusion
- Predominantly central sleep apnea syndrome (AC> 50%)
- Heart failure with Left Ventricular Ejection Fraction <40%
- Bariatric surgery in the previous 6 months or bariatric surgery project in the 6 months
- Alcohol> 14 drinks per week
- Refusal to use a smartphone or digital device
- Inability to access an internet connection at home.
- Inability to understand and / or answer questionnaires.

Randomisation

180 obese patients with OSA will be randomly allocated to a TR program with CPAP (intervention group) or to a CPAP (control group).

The randomization sequence will be computer-generated using random blocks in an order unknown by the investigators. The list is established by a statistician and is only accessible by personnel in

charge of randomization. Although participants cannot be blinded to their treatment, both interventions are presented as active interventions.

Randomization between the 2 arms will be stratified based on study center and on the baseline Epworth Sleepiness Scale[24] (ESS) value (>14 vs. ≤14), with a 1:1 ratio.

Statistical analysis plan

The number of patients contacted for the study and the number of subjects included and randomized in each group will be reported on a study flow chart. Premature stops (lost to follow-up, death, study withdrawals) and their reasons will be reported as well as any deviations from the protocol.

An initial descriptive analysis of each group will be carried out. For qualitative variables, this description will include the number as well as the frequency of the different modalities. Concerning the quantitative variables, the description will include the number, the mean, the standard deviation, the median as well as the extreme values according to the distribution.

The comparability of the 2 groups will be verified for all the initial characteristics likely to influence the results. In the event of non-comparability on one or more parameters, an adjustment will be made on this or these parameters for the comparisons between groups of judgment criteria.

Analysis of the primary outcome measure: The variation in the evolution of the various main criteria will be compared between the 2 groups using a nonparametric means comparison test (Mann-Whitney test) or if the distribution turns out to be Gaussian and the conditions application are verified, a parametric test (Student's T).

Analysis of secondary endpoints: The qualitative variables will be compared by a Chi-square test. Otherwise, if the conditions for performing this test are not met, Fisher's exact test will be used.

The quantitative variables will be compared between the two groups. In the case of Gaussian variables, by a student's t test or an analysis of variance. In the case of non-Gaussian variables, by a Wilcoxon-Mann-Withney test

Longitudinal data (quality of life scores, physical activities) will be modeled by a mixed regression with the patient effect as a random variable. A linear regression model modeling the variation of the longitudinal endpoints will be fitted to the covariates having at least one trend ($p < 0.15$) to the difference between the two arms of the study. A forward type procedure will be implemented to obtain a final multivariate model.

Management of missing data: The IPTW method will be used. The lost to follow-up will be considered using a weighting on the inverse of the probability of being censored.

Sample size calculation

The calculations are made by taking a power of 80% and alpha risk at 5%. Our assumptions are that:

- For the Epworth Sleepiness Scale, the difference between the two arms will be 2 points ± 4 [8,17]. Thus, 80 subjects per study arm are needed
- For the FOSQ, the difference will be 1.5 points +/- 2.5 [25]. Thus, 59 subjects per study arm are necessary,
- For nocturnal systolic BP, the difference will be 10 points +/- 20[26]. Thus, 63 subjects per study arm are required.
- For CRP, the difference will be 8 points +/- 16 [26]. Thus, 63 subjects per study arm are necessary.

In order to consider a rate of participants lost to follow-up and unusable data of around 25%, we propose to include in this study n= 180 subjects (90 per arm).

Intervention

Patients in both groups will be treated with CPAP (PRISMA SMART max LOWENSTEIN, Hamburg, Germany). The CPAP settings will be made by the doctor in charge of the patient. The CPAP can be in fixed mode or in auto-titrating mode.

Control group

Patients will receive the usual advice on adapted physical activity and nutrition during the initial consultation. For physical activity, patients will be advised to achieve the World Health Organization (WHO) recommendations of physical activity (i.e. at least 150–300 minutes of moderate-intensity aerobic physical activity per week), to decrease sedentary time and increase the daily number of steps.

Intervention group

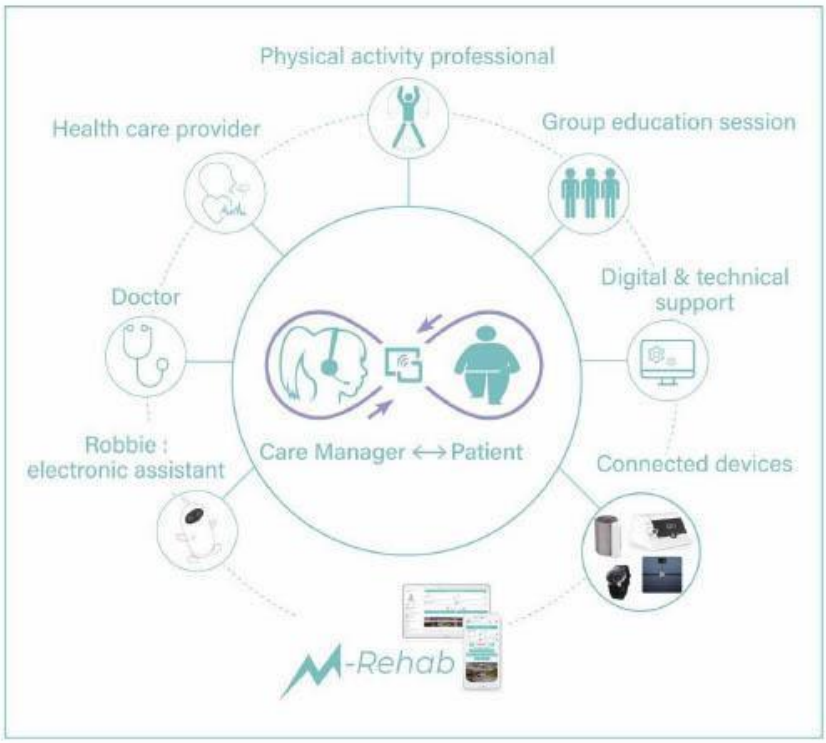
Patients will have access to the m-Rehab® telerehabilitation program, a digital solution we have designed et developed for the present study.

Multimodal interventions will implemented and the "care manager" will play a key role by providing coordination and tracking the home-based telerehabilitation intervention. Patients will have the possibility to request a consultation with his/her sleep specialist via medical teleconsultation, with the health-care provider (for CPAP follow-up) and with the m-Rehab technical support team for the use of the digital solution.

During the course of the TR intervention, feedback will be available to the patient via various connected devices: smart watch for the measurement of steps per day; connected weight scale; and connected tensiometer. Data from the CPAP device will also be transmitted in the patient application and web site.

Figure 1 shows the global model of m-Rehab digital solution and organisation. The organization and content of the telerehabilitation program is fully described in the supplementary information file with screenshots of the patient solution.

Figure 1: General organization of the telerehabilitation with m-Rehab digital solution. The patient and the care manager are in contact via the video-conferencing solution on the patient's m-Rehab application or via the patient website, and via the website for the care manager. The multiple possibilities of contact between the patient and her/his circle of care are summarized. The connected devices are also represented. **(For more information, see supplementary dat**



Outcome measures

All assessments made at baseline will be realised at the end of follow-up.

The data will be collected by personnel attached to the research group who have previously been instructed in the procedures to follow and who are not aware of patients' randomization.

Outcome measures are indicated in table 1.

Sleepiness: Epworth Sleepiness Scale (ESS)

This questionnaire assesses excessive daytime sleepiness (EDS) through 8 different items or situations common or frequently found in everyday life during which the propensity to fall asleep or sleepiness is measured on a scale from 0 to 3. The score is noted from 0 to24. A score of >10 defines the presence of excessive daytime sleepiness[24].

Quality of life: Functional Outcomes of Sleep Questionnaire (FOSQ)

This specific sleep questionnaire evaluates the effect of excessive sleep and daytime sleepiness on activities of daily living. The FOSQ contains 30 elements and is divided into 5 scales: activity level, alertness, intimate and sexual relations, productivity general and social outcomes. A change of 2 or more points in the FOSQ score is considered to indicate clinically significant improvement in daily functioning[27].

Nocturnal systolic blood pressure

Ambulatory blood pressure monitoring (ABPM) will be performed with MOBIL-O-GRAPH device, Germany. BP is measured every 15 minutes, daytime and every half hour at night. Each recording will be validated according to the following quality criteria: size of the cuff adapted to the diameter of the arm, recording time of 24 hours and including at least 48 valid measurements and no more than two missing time slots. In the event of non-validation, it will be proposed to the patient to replace the device. The following parameters will be collected: systolic BP, diastolic BP, mean BP (in mmHg) and frequency heart rate (in beats per minute), over 24 hours, day (8 am-11pm), night (11 pm-8am), in position sitting / lying and standing during the activity period (10 am-8pm). Additional measurement trains will be analyses. Night-time drops in systolic BP, diastolic BP and heart rate will be calculated.

Blood sample

Blood samples will be taken after an overnight fast on inclusion and during the final assessment. It includes CRP, blood count numbering, renal function and an ionogram, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, fasting blood sugar, glycosylated haemoglobin or HbAc1, CRP and insulinemia

Anthropometric parameters

Anthropometric measurements will be taken in the morning after 12 hours of fasting. The following parameters will be collected: height (m), weight (kg), calculation of the body mass index (BMI) in kg / m^2, hip, waist and neck measurements (cm).

Polysomnography

Sleep recordings are made in the sleep laboratory or at the patient's home. PSG included several EEG leads (C3-A2, C4-A1, O1-A2, O2-A1), right and left electrooculogram, electromyography of chin and tibialis anterior muscle, electrocardiogram, nasal cannula/pressure transducer, mouth thermistor, chest and abdominal bands, and pulse. The following data are collected: architecture of sleep (stages of sleep, sleep efficiency, micro-arousal index), polysomnographic markers of OSA (AHI, AHI-REM, AHI-NREM, Desaturation index, average SpO2, time spent under a SpO2 of 90%).

Actigraphy

Evaluation will be realized by an Actigraph Gt3X triaxial accelerometer worn for 7 days on the hip. The following data will be collected: duration of time in moderate to vigorous physical activity, sedentary time, number of daily steps, intensity and distribution of PA during the day / week, energy expenditure, sleep time and sleep efficiency.

Cardiopulmonary exercise testing

Maximum incremental stress test on a bicycle ergometer. Using a12-lead electrocardiogram and a gas exchange analysis system with a cycle system cycle. Maximum criteria will be determined in accordance with international stress testing standards. The variables of interest will be the maximum oxygen uptake at peak (maximum VO2), the maximum power and the ventilatory threshold.

Endothelial function: endoPat

Examination will be carried out in the morning (upon awakening). Peripheral Arterial Tone (PAT) is considered a witness to endothelial function. In practice, the patient is semi-lying down, hands on a table, in a room between 21 ° C and 24 ° C. A plethysmographic sensor is placed on the end of a finger measuring pulse wave amplitude. A sensor is placed on each of the 2 index. A first measurement of the arterial tone is carried out. A 5-minute ischemia is performed on the right by a cuff inflated to 50 mmHg above systolic BP. When the ischemia is over, a new bilateral measurement is performed for 5 minutes. This makes it possible to calculate the post / pre ratio ischemia on the right. To overcome systemic variations, this ratio is normalized by the measurements of the arm witness (left).

Adherence to CPAP

Data on the use and efficacy of CPAP will be collected by healthcare providers either during the visit to the patient's home or via remote monitoring. Data from CPAP at 1 month (residual AHI, leaks, deep sleep indicator) will be collected to assess whether it is associated with adherence at 6 months.

Motivational self-reported questionnaires

Questionnaires on perceived risk, expectations of consequences, self-efficacy, intentions, planning, self-efficacy against barriers, social support and questionnaire relating to the automatic nature of behaviour.

Others self-reported questionnaires

Idiopathic Hypersomnia Severity Scale[28], Fatigue Severity Scale[29], Insomnia Severity Index[30], Pittsburgh Sleep Quality Index[31], Hospital Anxiety and Depression scale[32], International physical activity questionnaire[33].

Data mining

Supervised classification: recall and precision. Unsupervised classification: Silhouette coefficient and Dunn index.

Medico-economic endpoint

The medico-economic judgment criterion will be the incremental cost-utility ratio at 6 months. The utility will be derived from the EQ5D (EuroQol five dimensions questionnaire)[34].

Table 1. Primary and secondary outcomes

	Baseline	4w	12w	24 w
Primary				
Sleepiness (ESS)	X			X
FOSQ	X			X
Nocturnal systolic BP (ABPM)	X			X
CRP (blood sample)	X			X
Secondary				
Polysomnography	X			
Anthropometric parameters	X			X
Self-reported questionnaires	X	X	X	X
Actigraphy	X			X
Cardiopulmonary exercise testing	X			X
endoPat	X			X
Assessment of adherence to CPAP		X	X	X
Data mining				X*
Economic evaluation				X

ABPM: Ambulatory blood pressure monitoring ; CPAP: Continuous positive airway pressure; ESS: Epworth Sleepiness Scale; FOSQ : Functional Outcomes of Sleep Questionnaire
* TR group specific analysis

DISCUSSION

We have designed a multicentric randomized, controlled, parallel, clinical trial to study the effects of a comprehensive 6-month telerehabilitation program, in patients with obesity and severe OSA, compared to CPAP usual care, at the initiation of CPAP. This article presents a detailed description of the multicentre randomized controlled trial.

Severe OSA and obesity have common characteristics and comorbidities, such as sleep disturbances, increased cardiometabolic risks (metabolic syndrome, diabetes, hypertension and other cardiovascular diseases), reduced physical activity levels, detrimental nutritional behaviour, and needs for better self-management for their disease. In both cases, and *a fortiori* when combined in the same patient, promotion of regular physical activity and a healthy diet, is essential in the control of the disease. Introducing comprehensive lifestyle interventions[35] is therefore recommended in OSA with obesity. Gathered in a structured, multidisciplinary program, this defines rehabilitation[36,37] which can also be administered via ICT and is called telerehabilitation (TR). TR has been studied in several chronic conditions like chronic obstructive diseases[38], cardiac diseases[39] or obesity[20] but, to the best of our knowledge, our study called "m-Rehab OSA" is the first trial to study TR in patients with OSA and obesity. Interventions combining CPAP and TR programs may therefore be a promising approach to improve the consequences of OSA, but need to be rigorously tested which is the goal of the RCT we presently propose. In addition, addressing the problem of compliance to CPAP as soon as possible upon initiation, is challenging for physicians due to lack of time, lack of patient knowledge on sleep disorders and management, and finally due to the predominance of initial barriers centred on technical aspects (mask – leaks, noise, etc)[40,41].

We have designed a set of digital solutions including a website for professionals and patients and an application on smartphone for patients. We called it "m-Rehab" to summarize the concept of "mobile telerehabilitation", in the same way than m-health or e-health: providing a rehabilitation course to patients via ICT, allowing access to the program to gain mobility anywhere, close to patient living place. Our first experience in telerehabilitation for obese patients, revealed the need of an individual human home care intervention to complete the program[20] . Therefore, we have conceived a human centred management by introducing remote coordination via a "care manager"[42]. Many organisational home-care services or telemonitoring interventions have been studied in chronic diseases[43], and case management seems to be effective on positive outcomes[42]. We believe that such a remote service in telerehabilitation will play a facilitating role to develop individualized action plans for increasing physical activity levels, improving nutritional behaviour and CPAP adherence, for solving problems or remove barriers allowing patients to adopt favourable health behaviours.

The m-Rehab 6-month program includes several interventions aimed at reaching patient-oriented outcomes via a rehabilitation model: increase patient health education, particularly in sleep and nutritional disorders, promote regular physical activity, and improve nutritional behaviours. Feed-back from connected medical devices (connected watch, scale, tensiometer) or from the CPAP device, will only be here to help the patient track each of these dimensions and to think about what he/she can/wants to do. m-Rehab course is not conceived as a "45-min 3 times per week exercise training program" or an "active weigh loss diet program". The m-Rehab digital solution and human care management aims to provide a behavioural and educative oriented approach that can encourage the patient to engage in long-term beneficial health changes.

We have designed a randomized, controlled trial, a multiple evaluation criterion, a reference method in therapeutics evaluation in human disease. The effects of a new, original intervention have to evaluated by a basic comparison with the usual care in a given disease. In our model, the blind modality is not conceivable because of two main challenges. The first was to consider patient deception when randomized in the control usual care arm of the study. This could cause higher volunteer dropouts in the control group or encourage them to them to adopt an alternative digital solution of exercise training, for example. To avoid these risks, we will propose the use of the digital solution during 6 months at the end of the 6-month control period, shortly after the randomization process. Second, is the lack of blindness in such a study design which could represent a bias in the evaluation procedures. To avoid this, the questionnaires used in the present study will only be self-administered via an online platform that is different from the TR digital solution (MHLink) for both groups,. In addition, the primary outcome of the study will be independent of the operator (24-hour ABPM, CRP dosage), therefore not based on any operator or patient influence. Finally, we have chosen a hierarchical testing strategy[44] based on 4 different dimensions including sleepiness, quality of life, BP and an inflammation marker. It is quite challenging to reach statistical significance in this type of interventional telerehabilitation trial. However, we believe that to be convincing TR should take into account the multiple dimensions of TR in chronic disease.

In conclusion, the m-Rehab OSA study is a rigorously designed multicentric RCT evaluating the effects of a multidimensional telerehabilitation program aimed at engaging patients with obesity and severe OSA in a physically active lifestyle, and healthy diet behaviours, using an original and human centred digital solution. The potential success of this program will open new area in patient daily and ubiquitous care.

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Etude 5 : Evolution du stress oxydant chez des patients coronariens avec un syndrome d'apnées obstructives du sommeil de gravité modérée sous traitement par pression positive continue. Etude CardioX-SAS.

Papier en préparation-Résultats préliminaires

Prérequis pour l'étude CardioX-SAS

Le SAHOS est une pathologie respiratoire du sommeil très fréquente, caractérisée par la répétition de collapsus complets (apnées) ou incomplets (hypopnées) des voies aériennes supérieures, d'une durée minimale de dix secondes, avec la persistance d'efforts respiratoires. Ces phénomènes entraînent une hypoxémie et une hypercapnie intermittentes, des micro-éveils avec une fragmentation du sommeil et une variation de la pression intra thoracique. La sévérité du SAHOS est fonction de l'index d'apnées- hypopnées (IAH) recensées par heure (léger entre 5 et 15, modéré entre 15 et 30 et sévère lorsque l'IAH est supérieur à 30/heure) et du degré de somnolence diurne(Berry et al. 2012). Le SAHOS est reconnu comme un facteur de risque cardiovasculaire indépendant(Jose M. Marin et al. 2005; Javaheri et al. 2017).

Le traitement de référence du SAHOS est la PPC. En France, la PPC est remboursée dans le SAHOS en cas de symptomatologie et d'IAH ≥ 30 heure ou ≥ 15/heure associé à une fragmentation du sommeil (index de microéveils ≥ 10/heure) ou à une maladie cardiovasculaire ou respiratoire sévère. Cependant, si l'efficacité du traitement par PPC a largement été démontrée notamment sur la sévérité du SAHOS ou la somnolence diurne(Patil et al. 2019), l'efficacité de la PPC pour la prévention secondaire des maladies cardiovasculaires n'a pas été établie par des études randomisées contrôlées(McEvoy et al. 2016; Peker et al. 2016).

La médecine du sommeil évolue vers une médecine de précision afin d'identifier les patients avec un SAHOS qui pourraient bénéficier du traitement par PPC pour diminuer leur risque cardiovasculaire. L'amélioration des connaissances des mécanismes physiopathologiques liant le SAHOS aux complications cardiovasculaires pourrait permettre d'identifier des

biomarqueurs permettant un endotypage des patients afin d'améliorer la démarche diagnostique et thérapeutique.

Parmi les mécanismes physiopathologiques avancés pour expliquer le lien entre SAHOS et maladies cardiovasculaires, le stress oxydant, secondaire à l'hypoxie intermittente, semble jouer un rôle prépondérant notamment en favorisant la dysfonction endothéliale, facteur clef du développement de l'athérosclérose(Badran, Ayas, et Laher 2014).

Le stress oxydant est caractérisé par un déséquilibre de la balance entre les systèmes oxydants et les capacités antioxydantes d'un organisme, résultant dans la formation excessive d'espèces oxygénées réactives (EOR) qui peuvent endommager les lipides, les protéines et les acides nucléiques. Les patients avec un SAHOS présentent une production accrue de EOR, une diminution des défenses antioxydantes et donc une augmentation des marqueurs du stress oxydant(Maniaci et al. 2021). Plusieurs études ont mis en évidence une diminution des marqueurs du stress oxydant avec le traitement par PPC mais cet effet n'est pas constamment retrouvé(Campos-Rodriguez et al. 2019; Stanek, Brożyna-Tkaczyk, et Myśliński 2021).

Peu d'études ont étudié les liens entre SAHOS et stress oxydant chez les patients avec une cardiopathie ischémique(Fiedorczuk, Stróżyński, et Olszewska 2020) et à notre connaissance aucune étude n'a évalué l'impact du traitement par PPC sur le stress oxydant chez des patients avec une maladie coronarienne stable.

Nous proposons donc d'évaluer, dans le cadre d'une étude prospective randomisée contrôlée, l'effet d'un traitement par PPC pendant 12 semaines sur les marqueurs du stress oxydant chez des patients avec une maladie coronarienne et un SAHOS modéré.

Méthodes

Design de l'étude

CardioX-SAS est une étude monocentrique randomisée, contrôlée, en double aveugle.

Deux groupes de patients ont été constitués : un groupe interventionnel traité par pression positive continue et un groupe contrôle sous sham PPC. Les patients inclus sont des patients de 30 à 80 ans, avec une maladie coronarienne stable depuis plus de 3 mois et un IAH entre 15 et 29.9/heure.

La randomisation a été effectuée le jour de l'inclusion avec une stratification sur le genre, l'indice de masse corporelle (IMC < 27, IMC≥27 kg/m²) et la consommation de tabac.

Les patients ont été suivis pendant trois mois de suivi avec des visites le jour de l'inclusion, à 1 mois et à 3 mois.

Une étude ancillaire a été réalisée afin de caractériser le profil biologique et clinique des patients coronariens en fonction de leur IAH (<15/heure, 15-29.9/heure, ≥30/heure).

L'étude a été approuvée par le comité d'éthique (Sud Méditerranée 1– France. IDRCB : 2015-A01439-40). Identifiant ClinicalTrials.gov NCT02893865

Tous les sujets ont fourni un consentement éclairé écrit avant l'entrée dans l'étude.

Objectifs

Le critère de jugement principal est l'évaluation de l'évolution du stress oxydant (évalué par le rapport GSH/GSSG) après 12 semaines de traitement par PPC par rapport à l'inclusion et par rapport au groupe contrôlé.

Les objectifs secondaires comprennent :

- Des critères physiopathologiques : évolution des autres paramètres du stress oxydant, des paramètres inflammatoires, du système rénine angiotensine-aldostérone, de l'activité sympathique et de la fonction endothéliale. Evolution de la troponine et de la BNP.
- Des critères cliniques : évolution du profil tensionnel, des scores aux différents auto-questionnaires

L'étude ancillaire a pour objectif de caractériser au niveau clinique et physiopathologique les patients coronariens en fonction de la présence ou non d'un SAHOS et de la sévérité de celui-ci : absence de SAHOS ou SAHOS léger (IAH <15/heure), SAHOS modéré (15≤IAH<30/heure), SAHOS sévère (IAH ≥ 30/heure).

Population

Les critères d'inclusion étaient :

- Cardiopathie ischémique stable (antécédents d'angioplastie ou stenting, de pontage aorto-coronarien ou de maladie coronarienne traitée médicalement) depuis plus de 3 mois.
- IAH compris entre 15 et 30/heure
- Age compris entre 30 et 80 ans

Les critères d'exclusion étaient :

- Insuffisance cardiaque à fraction d'éjection réduite (FEVG < 45%)
- Maladie inflammatoire chronique ou néoplasie active.
- Index apnées centrales supérieur ou égal à 50% de l'IAH total
- Traitement par PPC ou orthèse d'avancée mandibulaire
- IMC > 40 kg/m²
- Supplémentation nutritionnelle dans les 4 semaines précédant l'étude (antioxydants, vitamines…).
- Traitement par allopurinol ou N-acétylcystéine, dans les 4 semaines précédant l'étude.
- Hypercapnie connue
- Contre- indication à l'utilisation de la PPC : pneumopathie bulleuse, hypotension pathologique, dérivation des voies aériennes, pneumothorax, signes d'infections des sinus ou de l'oreille interne

Intervention

Les patients de l'étude principale ont été randomisés entre deux bras.

Bras n°1 : traitement par PPC avec une pression efficace autopilotée (4-14 cm H2O): PR1 Remstar Auto P-Flex (Philips, USA). Une interface nasale était proposée en première intention et un humidificateur installé en cas d'intolérance au traitement ou de sécheresse nasale. Les patients étaient suivis au domicile par un prestataire de santé à domicile avec appel à 48 heures, visite à une semaine et un mois.

Bras n°2 : traitement par un appareil de pression continue inefficace (sham PPC) : PR1 Remstar Auto P-Flex (Philips, USA).

Nombre de sujets nécessaire

Nous attendions un pourcentage de variation nul dans le groupe contrôle versus 50% de variation dans le groupe PPC. Avec un écart type de la variation commun de 50%, un risque de première espèce de 5% et une puissance de 80%, 16 sujets par bras étaient nécessaires. Afin de tenir compte de patients perdus de vue (20% maximum), nous proposions d'inclure dans cette étude N=40 sujets (20 par bras).

Pour les sous-groupes de l'étude ancillaire, afin d'optimiser la puissance statistique dans les comparaisons, nous proposions d'inclure autant de sujets que dans chacun des bras. Ainsi 20 patients avec IAH<15 et 20 patients avec IAH≥30/heure devaient être inclus.

Plan statistique

Une première analyse des données permet la description de la population totale et par groupe. La normalité de la distribution des variables quantitatives est explorée à l'aide du test de normalité de Shapiro-Wilks, ainsi que des coefficients de Kurtosis et de Skewness.

Les résultats statistiques sont présentés sous forme de moyennes ± écarts-types pour les variables quantitatives dont la distribution est gaussienne, moyennes et intervalles de confiance à 95% anti-transformés pour les variables dont la distribution est gaussienne après une transformation, et médianes et intervalles interquartiles pour les autres variables. Pour les variables qualitatives, les effectifs et les pourcentages associés sont présentés.

Les variables qualitatives sont comparées par un test du Chi-2. A défaut, si les conditions de réalisation de ce test ne sont pas respectées, le test exact de Fisher est utilisé.

Les variables quantitatives sont comparées entre les deux groupes :

- en cas de variables gaussiennes, par un test t de student ou une analyse de variance
- En cas de variables non-gaussiennes, par un test de Wilcoxon-Mann-Withney

Des tests de comparaison de moyennes pour données indépendants sont employés pour répondre à l'objectif principal.

Outre les tests employés pour répondre aux objectifs secondaires, des modélisations permettant de tenir compte de la répétition des mesures pour un même sujets (3 temps d'observation seront ajustées (modèles mixtes ou GEE). Le sujet sera considéré comme une variable aléatoire.

Mesures

Bilan sanguin

Paramètre d'évaluation principal : rapport GSH/GSSG

Le dosage du GSH/GSSG est effectué sur sang total (tube hépariné), traité immédiatement en diluant au demi le sang avec une solution de TCA 10%, EDTA 1mM. Après centrifugation, le surnageant est conservé à -80°C. Le dosage du GSH/GSSG est effectué par LC/MSMS, avec une séparation chromatographique en phase inverse et une détection en ionisation électrospray positive en mode MRM.

- Evolution des autres paramètres du stress oxydant (8 OH déoxy guanosine, isoprostanes urinaires, vitamine C, vitamine E, glutathion total, glutathion peroxydase (GPX), superoxyde dismutase (SOD), catalase).
- Evolution des paramètres inflammatoires (CRP, TNF α, IL6 et IL8), du système rénine angiotensine-aldostérone (rénine et aldostérone plasmatiques) ainsi que de l'activité sympathique (catécholamines urinaires).
- Evolution des paramètres métaboliques : bilan lipidique (triglycérides, cholestérol total, HDL), insulinorésistance (HOMA- Homeostasis Model Accessment of insuline resistance).
- Evolution de la troponine et du BNP.

EndoPat

Évaluation de la fonction endothéliale. Examen réalisé le matin de l'enregistrement polygraphique au laboratoire du sommeil (GDC). Le tonus artériel périphérique (PAT) est considéré comme un témoin de la fonction endothéliale et est un marqueur validé du risque cardio-vasculaire. En pratique, le patient est semi-allongé, mains sur une table, dans une pièce entre 21°C et 24°C. Un capteur pléthysmographique est placé sur l'extrémité d'un doigt

mesurant l'amplitude de l'onde de pouls. Un capteur est placé sur chacun des 2 index. Une première mesure du tonus artériel est réalisée. Une ischémie de 5 minutes est réalisée à droite par un brassard gonflé à 50 mmHg au-dessus de la PA systolique. A la levée de l'ischémie une nouvelle mesure bilatérale en continue est réalisée pendant 5 minutes. Cela permet de calculer le ratio post/pré ischémie à droite. Pour s'affranchir des variations systémiques, ce ratio est normalisé par les mesures du bras témoin (gauche).

Scintigraphie MIBG

Evolution de l'activité sympathique myocardique évaluée par scintigraphie à la ^{123}I-MIBG.

Les patients bénéficient d'une prémédication par 2 comprimés de 65 mg d'iodure de potassium de manière à éviter la fixation d'iode libre sur la thyroïde. Les données scintigraphiques sont acquises immédiatement après puis trois heures après administration intraveineuse de 185 MBq de métaiodobenzylguanidine marquée à l'iode 123. Les acquisitions précoces sont réalisées en mode planaire pour évaluer le rapport de fixation cardio-médiastinal précoce. Les données tardives sont acquises en mode planaire et tomographique pour évaluer le rapport de fixation cardio-médiastinal tardif, le wash-out myocardique du radiotraceur, et pour quantifier son homogénéité de fixation sur chaque segment myocardique. Chaque acquisition dure 5 minutes.

Mesure ambulatoire de la pression artérielle

La mesure ambulatoire de la pression artérielle (MAPA) a été réalisée à V1, le lendemain de l'enregistrement polysomnographique et à la visite 3 par des appareils validés (type I-MAPA® ou Spacelabs). La PA a été mesurée toutes les 15 minutes, le jour et toutes les demi-heures la nuit, par méthode oscillométrique. Chaque enregistrement a été validé selon les critères de qualité suivants : taille du brassard adaptée au diamètre du bras, durée de l'enregistrement de 24 heures et comprenant au moins 48 mesures valides et pas plus de deux tranches horaires manquantes. Les paramètres suivants on été recueillis : PA systolique, PA diastolique, PA moyenne (en mmHg) et fréquence cardiaque (en battements par minute), sur 24 heures, le jour (8H-23H), la nuit (23H-8H), en position assise/couchée et debout sur la période d'activité (10H-20H). Les chutes nocturnes de PA systolique, PA diastolique et de fréquence cardiaque ont été calculées.

Questionnaires

Score d'Epworth : Ce questionnaire couramment utilisé en pratique clinique de façon subjective la somnolence diurne excessive (SDE) grâce à 8 items ou situations différentes communes ou fréquemment retrouvées dans la vie de tous les jours au cours desquelles on mesure la propension à s'endormir ou somnolence sur une échelle de 0 à 3. Le score est noté de 0 à 24. Un score de >10 définit la présence d'une SDE (Johns 1991).

Questionnaire de qualité de vie SF36 : Cette échelle permet une mesure de la qualité de vie. Elle permet d'évaluer l'état général des patients sous la forme de 36 questions. Un score moyen physique (PCS = Physical Composite Score) et un score moyen mental (MCS = Mental Composite Score) peuvent être calculés selon un algorithme établi. Les scores pour chaque domaine vont de 0 à 100, un score plus élevé définissant un état de santé plus favorable(McHorney et al. 1994).

Le tableau des évaluations est détaillé dans la table 13.

Visite	**Visite V0 (Pré-inclusion)**	**Visite 1 (Inclusion)**	**Visite 2**	**Visite 3**
Jours	J0	J30	Mois 1 (J+-14)	Mois 3 (J+-14)
Polygraphie Ventilatoire	X			
Information	X	X		
Polysomnographie		X		X*
Signature du consentement		X		
Randomisation		X*		
Initiation de la PPC		X*		
Questionnaires		X	X	X
Evaluation de l'observance			X*	X*
Prélèvement sanguin		X*		X*
Recueil urinaire		X*		X*
Endopat		X*		X*
MAPA		X		X
Scintigraphie MIBG/Thallium		X		X
Recueil des EIG			X*	X*

* *examens spécifiques à l'étude*

Figure 13. Tableau des évaluations de l'étude CardioX-SAS.

Résultats préliminaires

Description de la population

71 patients ont été inclus entre mai 2016 et mai 2021. 28 patients ont été inclus dans l'étude principale et 43 patients dans l'étude ancillaire.

Les patients de l'étude principale ont été randomisés dans les groupes PPC (n=14) et Sham PPC (n=14). Un patient du groupe Sham PPC est sorti en cours d'étude suite à sa volonté de ne pas poursuivre les examens.

Parmi les 71 patients, 57 (80%) étaient des hommes, l'âge moyen était de 60.2 ± 8.9 ans et l'IMC moyen de 28.6 ± 4.6 kg/m².

Le diagramme des flux est présenté dans la figure 14.

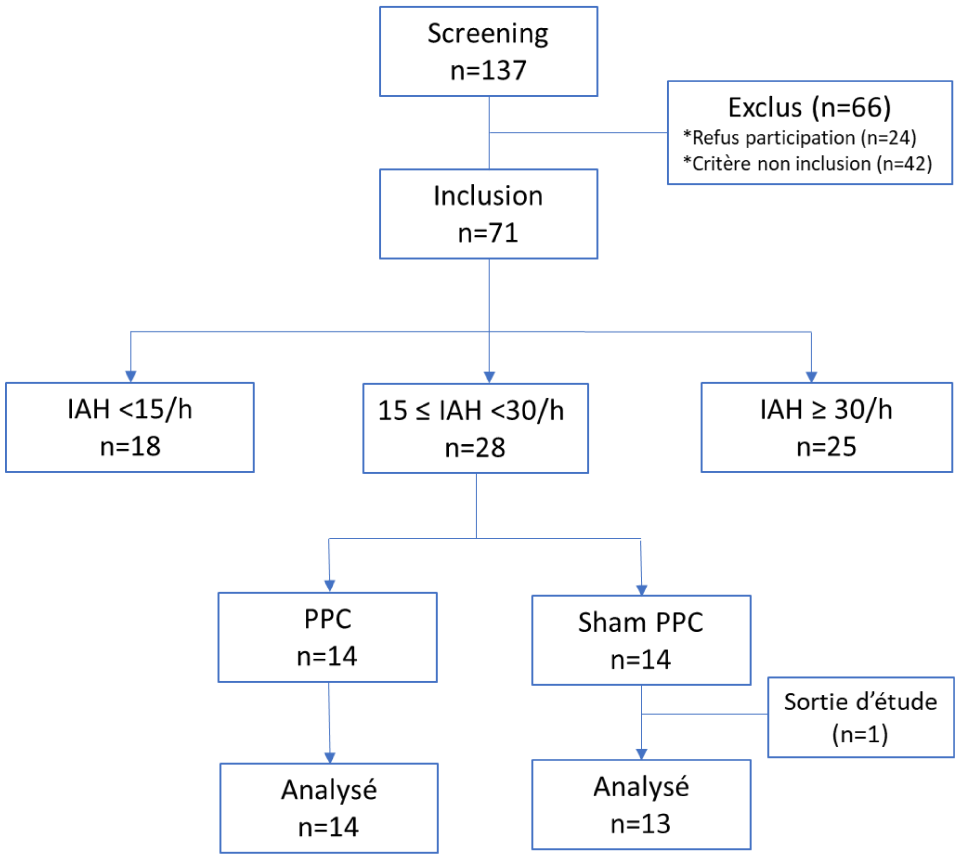

Figure 4. Diagramme des flux de l' étude CardioX-SAS.

Caractéristiques démographiques, cliniques et biologiques selon la sévérité de l'IAH

Parmi les 71 patients, 18 patients n'avaient pas de SAHOS ou avaient un SAHOS léger (IAH <15/heure) , 28 patients avaient un SAHOS modéré (IAH 15-29.9/heure) et 25 patients avaient un SAHOS sévère (IAH ≥ 30/heure).

On note des différences significatives entre les trois groupes pour l'IMC, le rapport cardio médiastinal tardif (scintigraphie MIBG), la proportion de patients diabétiques ou encore quelques paramètres biologiques tels que la glycémie, le HOMA, la CRP ou le taux plasmatique de rénine. Le rapport GSH/GSSG n'était pas significativement entre les trois groupes. Les scores de somnolence, de fatigue et d'insomnie ne sont pas significativement différents entre les trois groupes. L'ensemble de ces résultats sont visibles dans la table 1.

Critère d'évaluation principal : évolution du rapport GSH/GSSG entre l'inclusion et 3 mois entre le groupe PPC et le groupe sham PPC.

Les analyses préliminaires montrent une différence significative de l'évolution du rapport GSH/GSSG entre les deux groupes (p=0.006) avec une augmentation significativement plus importante dans le groupe PPC (Figure 15).

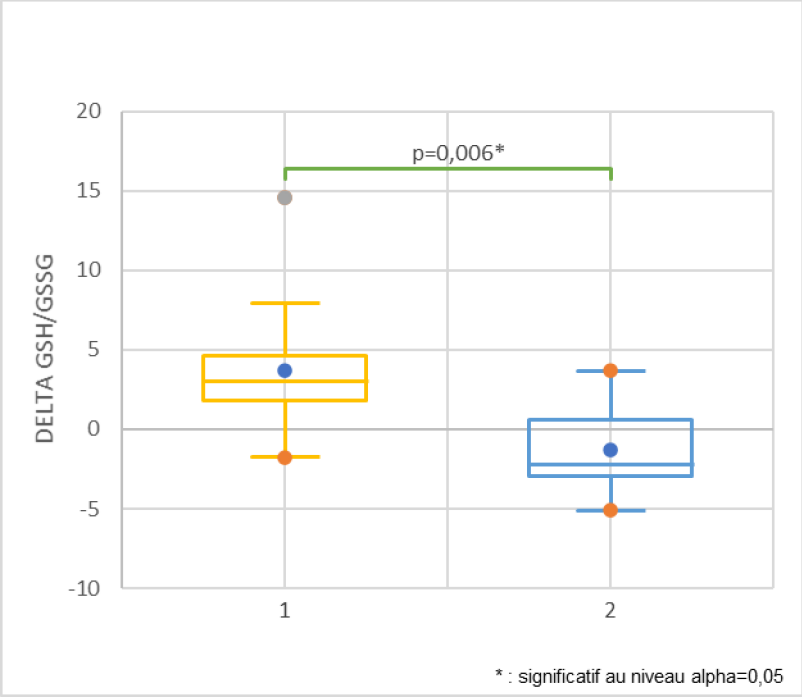

Figure 5.Evolution du rapport GSH/GSSG entre l'inclusion et 3 mois. 1 : groupe PPC. 2/ Groupe sham PPC.

Tableau 1 Caractéristiques démographiques, cliniques et biologiques selon la sévérité de l'IAH

Variable	Population totale (n=71)				IAH < 15/h (n=18)				15 ≤ IAH <30/h (n=28)				IAH >30/h (n=25)				p value
	Moyenne	Ecart type	Min	Max	Moyenne	Ecart type	Min	Max	Moyenne	Ecart type	Min	Max	Moyenne	Ecart type	Min	Max	
Age (ans)	60,2	8,9	37,0	75,0	58,4	9,0	43,0	74,0	60,0	8,3	42,0	75,0	61,6	9,7	37,0	74,0	0,44
IMC (kg/m²)	28,6	4,6	20,6	41,2	25,4	2,3	22,1	29,1	28,3	4,2	20,6	39,8	31,2	4,9	21,8	41,2	<0,0001
IAH study	26,3	15,7	3,4	75,1	8,7	2,8	3,4	13,0	21,5	4,1	15,6	29,8	43,9	11,1	30,8	75,1	<0,0001
Somnolence d'Epworth	8,6	5,2	0,0	22,0	7,5	4,4	1,0	20,0	9,2	5,8	0,0	20,0	8,6	5,1	1,0	22,0	0,570
FFS	32,1	15,4	9,0	63,0	27,4	14,2	9,0	50,0	37,6	15,0	9,0	63,0	28,6	15,2	10,0	63,0	0,189
Index de sévérité de l'insomnie	9,6	6,1	0,0	25,0	6,5	5,0	1,0	15,0	10,9	6,2	0,0	21,0	10,2	6,1	1,0	25,0	0,065
Echelle de sévérité SJSR	7,7	9,1	0,0	27,0	4,5	6,2	0,0	17,0	8,8	9,5	0,0	23,0	8,5	10,1	0,0	27,0	0,396
BDI	8,8	8,3	0,0	37,0	5,9	4,0	0,0	12,0	10,2	9,7	0,0	37,0	9,1	8,5	0,0	34,0	0,456
Rapport CM tardif de la MIBG	1,6	0,2	1,2	2,1	1,7	0,3	1,2	2,1	1,6	0,1	1,4	2,0	1,5	0,2	1,3	1,9	0,017
Wash out de la MIBG (%)	32,0	12,3	2,0	81,0	32,3	9,4	20,0	50,0	30,3	16,7	2,0	81,0	33,4	8,7	16,0	45,0	0,357
Triglycérides (mmol/L)	1,7	0,9	0,6	6,4	1,5	0,7	0,7	3,2	1,7	0,7	0,9	3,4	1,8	1,2	0,6	6,4	0,480
Cholesterol total (mmol/L)	3,9	1,1	1,0	6,8	3,7	1,1	1,7	5,8	4,0	1,0	2,0	5,8	3,7	1,0	1,0	6,8	0,433
Cholesterol HDL (mmol/L)	1,2	0,3	0,6	2,0	1,3	0,3	0,6	1,9	1,3	0,3	0,9	2,0	1,1	0,3	0,6	1,8	0,314
Cholesterol LDL (mmol/L)	2,1	1,2	0,3	8,4	1,9	0,9	0,7	3,9	2,1	0,9	0,4	4,1	2,1	1,6	0,3	8,4	0,453
Glucose (mmol/L)	6,4	2,1	4,5	14,5	5,3	0,6	4,5	6,7	6,1	1,6	4,7	11,4	7,5	2,7	4,8	14,5	0,006
Hémoglobine glyquée (%)	6,2	1,1	4,8	9,7	5,7	0,4	4,8	6,3	6,3	1,2	5,0	9,7	6,4	1,2	4,9	8,7	0,153
HOMA	4,4	3,4	0,1	15,4	2,6	1,1	1,1	4,5	3,7	2,1	0,1	8,9	6,1	4,4	1,5	15,4	0,022

CRP (mg/L)	2,8	3,9	0,3	22,3	0,8	0,6	0,3	2,2	2,9	3,0	0,5	13,6	3,9	5,4	0,3	22,3	0,011
Cuivre (µmol/L)	14,5	2,7	5,0	19,8	14,8	2,6	8,9	18,0	15,1	2,6	10,8	19,8	13,7	2,9	5,0	18,4	0,200
Zinc (µmol/L)	12,7	2,9	9,3	26,2	13,9	4,0	9,9	26,2	12,2	2,7	9,3	20,9	12,4	1,9	9,6	16,0	0,189
Selenium (µmol/L)	43,0	43,0	0,5	119,9	50,4	46,5	0,8	119,9	48,4	41,3	0,7	108,1	31,3	41,9	0,5	117,0	0,427
GSH µM	741,8	241,7	168,0	1520,0	752,5	223,9	304,0	1046,4	709,7	224,7	224,0	1052,0	770,5	277,2	168,0	1520,0	0,673
GSSG µM	152,7	77,7	38,4	384,0	164,6	102,5	38,4	384,0	148,6	54,9	54,4	280,0	148,7	82,2	40,0	320,0	0,903
GSH/GSSG	7,3	5,9	0,5	27,3	8,0	7,2	0,8	27,3	5,9	3,8	0,8	16,0	8,3	6,8	0,5	24,6	0,851
Aldostérone (pmol/lh)	203,0	213,4	3,7	789,5	131,8	215,1	3,7	761,8	236,2	200,4	3,7	747,9	205,7	225,4	3,7	789,5	0,067
Rénine (µU/ml)	67,0	75,4	2,2	310,5	104,7	73,9	4,7	242,1	40,2	47,8	2,4	200,3	74,8	91,3	2,2	310,5	0,023
	n (%)				n (%)				n (%)				n (%)				
Sexe, homme, n (%)	57 (80%)				14 (82%)				21 (72%)				22 (88%)				0,35
Diabète	21 (32%)				1 (7%)				9 (32%)				11 (46%)				0,047
HTA	48 (73%)				8 (57%)				22 (79%)				18 (75%)				0,320
Hypercholestérolémie	53 (80%)				11 (79%)				23 (82%)				19 (79%)				0,950
Antécédents familiaux	19 (27%)				2 (12%)				10 (34%)				7 (28%)				0,240

Discussion

Cette étude est à notre connaissance la première à évaluer l'efficacité de la PPC chez des patients avec une cardiopathie ischémique stable sur les paramètres physiopathologiques du SAHOS modéré.

Les résultats préliminaires montrent que les patients avec un SAHOS modéré et sévère ont un profil biologique différent par rapport aux patients avec un IAH < 15/heure ainsi qu'une différence du rapport cardio médiastinal tardif à la scintigraphie MIBG, pouvant témoigner d'une balance sympatho-vagale différente. Par ailleurs, la PPC semble influencer le rapport GSH/GSSG qui est un excellent marqueur du stress oxydant(Jones et al. 2002).

Ces analyses doivent être complétées d'une part en traitant les autres paramètres biologiques du stress oxydant et de l'inflammation et d'autre part en complétant les analyses statistiques notamment en ajustant sur les paramètres confondants tel que l'IMC et en poursuivant le plan statistique prévu notamment avec un modèle linéaire mixte.

Les résultats de cette étude permettront une meilleure compréhension de l'efficacité de la PPC sur les marqueurs physiopathologiques liant le SAHOS et les maladies cardiovasculaires et doivent permettre d'évoluer vers une médecine de précision dans le cadre de la démarche diagnostique et thérapeutique du SAHOS.

CONCLUSION GENERALE

Ce travail de thèse apporte des éléments de réponse d'une part sur la compréhension des liens physiopathologiques et cliniques entre les troubles du sommeil et les maladies cardiovasculaires et d'autre part sur les impacts cliniques et physiopathologiques des traitements du syndrome d'apnées hypopnées obstructives du sommeil.

Nos travaux confirment la prévalence importante des troubles du sommeil chez les patients avec des comorbidités cardiovasculaires. Alors que le SAHOS est considéré comme un facteur de risque cardiovasculaire dans la population générale, son impact pronostic et l'efficacité de la pression positive continue en prévention secondaire restent débattus. Les résultats de l'étude SAS-IDM, démontrant l'absence d'association entre le SAHOS et le remodelage ventriculaire après un infarctus du myocarde, confirment les doutes sur le rôle pronostic du SAHOS…L'étude PRO-TSIC a confirmé l'importance d'élargir le spectre de l'interrogatoire au-delà des troubles respiratoires du sommeil en objectivant une augmentation des évènements cardiovasculaires majeurs chez des patients avec une insuffisance cardiaque lors de la prise de médicaments agissant sur le système nerveux central et en cas de réduction du temps de sommeil total.

La prévention du risque cardiovasculaire lié au SAHOS comprend la prescription d'interventions non médicamenteuses et notamment d'un réentrainement à l'effort. L'étude REEVASAS a confirmé cet intérêt en démontrant qu'un programme de 8 semaines permettait une amélioration des marqueurs de sévérité du SAHOS en diminuant notamment le degré de somnolence diurne et l'index d'apnées hypopnées en sommeil paradoxal alors que la littérature nous apprend que ces deux paramètres sont liés eux-mêmes à une augmentation du risque cardiovasculaire. Le développement et la validation clinique d'une solution mobile de téléréhabilitation a pour ambition d'objectiver une amélioration des marqueurs de sévérité du SAHOS sur un plus long terme.

Les travaux présentés dans cette thèse et ceux en cours doivent permettre d'évoluer vers une médecine de précision en caractérisant mieux cliniquement et physiopathologiquement le SAHOS qui est une entité complexe et hétérogène.

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ANNEXES

Annexe 1 : Fréquence de l'apnée du sommeil dans la cardiopathie ischémique en phase aiguë : dépistage systématique chez les patients admis en soins intensifs cardiologiques pour syndrome coronaire aigu

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Original article

Prevalence of obstructive sleep apnoea in acute coronary syndrome: Routine screening in intensive coronary care units

Fréquence de l'apnée du sommeil dans la cardiopathie ischémique en phase aiguë : dépistage systématique chez les patients admis en soins intensifs cardiologiques pour syndrome coronaire aigu

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Abstract

Introduction. – Increased evidence has shown that, despite the maximum care afforded to patients admitted with acute coronary syndromes (ACS), a residual risk of mortality remains, in which obstructive sleep apnoea (OSA) appears to be a largely undiagnosed factor, particularly in the intensive cardiac care unit (ICCU). The purpose of this study is to determine whether the systematic screening for sleep-disordered breathing (SDB) is feasible and may be recommended. The aims of our study are to determine: (1) The estimated prevalence of OSA in patients admitted to the ICCU for ACS determined by a validated, user-friendly portable screening device; (2) The feasibility of the screening in this context; (3) To assess any negative impact of OSA on the severity of ACS.

Patients and methods. – This is an observational study of 101 patients admitted to the ICCU for ACS showing no clinical evidence of heart failure (HF). In the 24–72 hours following admission, they underwent an overnight sleep study using a 3-channel portable screening device with automatic analysis.

Results. – Sixty-two out of the 101 patients proved positive to the screening test, and its feasibility was acceptable. OSA patients tended to have greater peak levels of hs-cTnT (3685 ± 3576 ng/L versus 2830 ± 3333 ng/L, $P = 0.08$) than the non-OSA group. Compared with the non-OSA group, OSA patients presented more severe ACS, with a greater average GRACE score at admission of 112.2 ± 26.3 (versus 98.4 ± 19.2, $P < 0.001$). In the OSA group, we found a statistically significant inverse correlation between the apnoea-hypopnea index (AHI) and the left ventricular ejection fraction (LVEF) in the linear regression analysis ($r = -0.26$; $P = 0.037$).

Conclusions. – A systematic screening of patients in the ICCU is acceptable. OSA is frequently found in the acute phase of ischaemic heart disease and its presence is associated with more severe ACS and a poorer left ventricle systolic function.
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Keywords: Acute myocardial infarction; Sleep-disordered breathing; Portable monitoring screening device; Heart failure

Résumé

Introduction. – Actuellement, un grand nombre d'études tend à montrer que, malgré les efforts maximaux destinés aux patients hospitalisés pour un syndrome coronarien aigu, un certain risque résiduel de mortalité persiste, dans lequel les apnées obstructives du sommeil semblent jouer un

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rôle non négligeable et pourtant sous-estimé, surtout aux soins intensifs. Les objectifs de notre étude sont les suivants : (1) Déterminer la prévalence estimée de l'apnée obstructive du sommeil chez les patients admis aux soins intensifs cardiologiques pour syndrome coronarien aigu à l'aide d'un appareil de dépistage validé, simple et intuitif dans l'interprétation des résultats ; (2) Vérifier la faisabilité du *screening* dans ce contexte ; (3) Identifier tout retentissement négatif des apnées obstructives du sommeil sur la sévérité du syndrome coronarien aigu.

Patients et méthodes. – Il s'agit d'une étude observationnelle comprenant 101 patients admis aux soins intensifs cardiologiques pour syndrome coronarien aigu, sans signes cliniques d'insuffisance cardiaque. Dans les 24–72 heures suivant leur admission, les patients ont bénéficié d'un enregistrement nocturne du sommeil à l'aide d'un appareil de dépistage à trois paramètres avec analyse automatique.

Résultats. – Sur 101 patients au total, le test de dépistage était positif pour 62 d'entre eux et sa faisabilité dans le service de soins intensifs a été satisfaisante. Le taux plasmatique de hs-cTnT a une tendance à être plus élevé chez les patients atteints du syndrome d'apnée du sommeil par rapport au groupe non OSA (3685 ± 3576 ng/L versus 2830 ± 3333 ng/L, $p = 0{,}08$). Par rapport au groupe non OSA, les patients qui souffrent d'apnée présentent un syndrome coronarien aigu plus sévère, avec un score de GRACE moyen à l'admission de 112,2 ± 26,3 (versus 98,4 ± 19,2, $p < 0{,}001$). Dans le groupe OSA, nous avons mis en évidence une corrélation inverse entre l'index d'apnée-hypopnée et la fraction d'éjection du ventricule gauche à l'analyse de régression linéaire ($r = -0{,}26$; $p = 0{,}037$).

Conclusion. – Un dépistage systématique des apnées du sommeil chez les patients admis aux soins intensifs cardiologiques pour syndrome coronarien aigu est faisable. L'apnée obstructive du sommeil est fréquemment retrouvée dans la phase aiguë de la cardiopathie ischémique et sa présence est associée au syndrome coronarien aigu plus sévère avec une dysfonction systolique gauche significativement plus importante.
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Mots clés : Infarctus du myocarde ; Trouble respiratoire du sommeil ; Appareil de dépistage portable ; Insuffisance cardiaque

1. Abbreviations

ACS	acute coronary syndrome
AHI	Apnea-Hypopnea Index
AASM	American Academy of Sleep Medicine
BMI	body mass index
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CSA	central sleep apnea
CPAP	continuous positive air pressure
CVD	cardiovascular disease
ESS	Epworth Sleepiness Scale
ICCU	intensive cardiology care unit
IH	intermittent hypoxaemia
LVEF	left ventricle ejection fraction
LV	left ventricle
MI	myocardial infarction
NSTEMI	non ST-segment elevation myocardial infarction
OSA	obstructive sleep apnoea
PCI	percutaneous coronary intervention
PM	portable monitor
PSG	polysomnography
ROS	reactive oxygen species
SAS	sleep apnoea syndrome
SDB	sleep-disordered breathing
STEMI	ST-segment elevation myocardial infarction
UA	unstable angina

2. Introduction

In spite of the maximum care currently given to patients admitted with acute coronary syndrome (ACS), a residual risk remains with several clinical outcomes [1]. One of the underestimated pathophysiological factors could be obstructive sleep apnoea (OSA).

OSA is characterised by recurrent nocturnal respiratory interruptions, resulting from the total or partial collapse of the upper respiratory ways. The consequent breathing difficulties act against them and lead to sleep fragmentation, metabolic and biological disorders, thus impacting on the neuropsychological and cardiovascular systems.

Firstly, OSA is a frequent respiratory disorder with detrimental health effects. Its current high prevalence will supposedly increase in future years because of the obesity epidemic, the aging of the general population and the improvement in cardiovascular treatments. For instance, among people aged 30 to 60 years, the prevalence of asymptomatic and underdiagnosed sleep disorder breathing (SDB) is 24% among men and 9% among women [2].

Secondly, OSA is considered as a potential cardiovascular risk factor [3]. Even though no patent causal relationship between OSA and cardiovascular disease (CVD) has been clearly established until now, its pathophysiological mechanisms could make sense in supporting such a relationship. Intermittent hypoxaemia (IH), due to cycled upper airway collapse, is responsible for abnormal sympathetic activation [4], endothelial dysfunction [5], oxidative stress [6] and inflammation [7] all of which could pave the way for cardiovascular outcomes, especially hypertension [8], atherosclerosis [9], cardiac arrhythmias [10], heart failure [11] and coronary artery disease [12].

OSA is, likewise, positively correlated with an increased morbidity and mortality in the cardiovascular population [13,14] and seems to be an independent predictive factor in cardiovascular mortality after ACS [15].

However, the guidelines for the management of ACS do not provide any recommendation for systematic screening for OSA in the acute phase of ischaemic heart disease [16].

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The aims of our study are, firstly, to assess the estimated prevalence of OSA in patients admitted to the ICCU with ACS by a validated and user-friendly portable screening device; secondly, to determine the feasibility of this approach in this context and thirdly, to assess any negative impact of OSA on the severity of both the ACS, evaluated by the GRACE score at the admission, and the consequences of the myocardial infarction, expressed by the troponin-based infarct size and the left ventricular dysfunction.

3. Methods

3.1. Patients

We prospectively recruited 138 patients admitted to the ICCU with ACS but without clinical evidence of heart failure, from January to August 2015, in a tertiary care center. Inclusion criteria for participation in the study was the established diagnosis of ACS with an atherosclerotic etiology confirmed by coronary angiogram. Exclusion criteria included left ventricular ejection fraction (LVEF) < 40%, the use of continuous positive air pressure (CPAP) therapy and a non-atherosclerotic etiology of ACS. The presence of ACS was assessed by three main diagnostic tools: clinical history, ECG modifications and cardiac biomarker elevation. The ACS severity was evaluated using the following scores: the TIMI score for NSTEMI/UA, the TIMI score for STEMI and the GRACE score for all types of ACS.

After giving informed consent, all participants underwent an overnight sleep study using a 3-channel (nasal airflow, pulse and oxygen saturation) portable device (ApneaLink™ device, ResMed Corporation, Poway, Calif) within 24–72 hours following their admission to the ICCU. Estimated presence of OSA was considered where the apnoea-hypopnoea index (AHI) value was of at least 5 per hours, without taking into consideration symptoms. The ApneaLink AHI used for analysis was automatically analysed by the ApneaLink system.

The AHI was calculated as the average number of apnoeas and hypopnoeas per hour of sleep, in keeping with the recent update of the 2007 American Academy of Sleep Medicine (AASM) task force [17].

3.2. Device description

The ApneaLink™ device (ResMed Corporation, Poway, Calif) is a sleep monitoring device including nasal airflow, pulse and oxygen saturation. It is used as inexpensive screening tests for patients with type 2 diabetes mellitus [18] and in morbidly obese patients [19]. However, there are no studies providing information on the validity of this screening tool in ACS population in the ICCU context.

Limited-channel device analysing nasal airflow [20], or nasal pressure [21] as a surrogate of airflow, seems to provide accurate estimates of SDB indices with a high sensitivity and specificity. Such devices are promising as possible screening tools for OSA, since they are easy-to-use, inexpensive and well tolerated by the patient.

3.3. Statistical analysis

Data are presented as means ± SD when normally distributed and median and interquartile ranges otherwise. The normal-

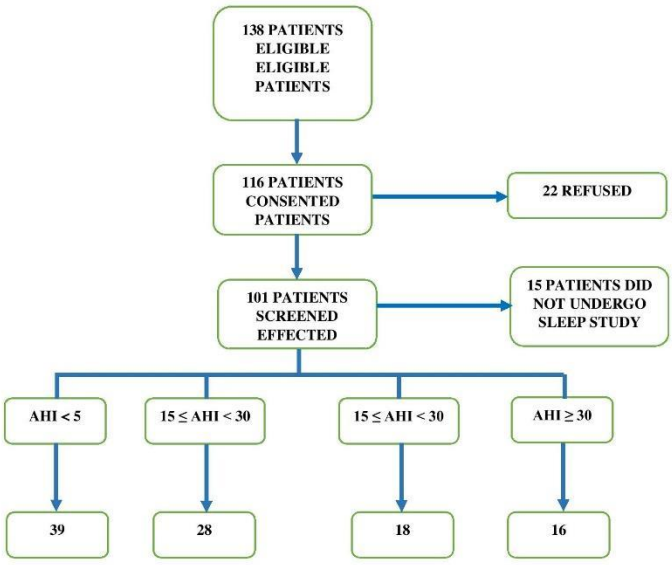

Fig. 1. Flow chart of patients through the study. AHI: apnoea-hypopnoea index.

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ity of the distribution was estimated by the D'Agostino & Pearson omnibus normality test. The baseline sample characteristics were compared in the two groups. The Wilcoxon rank test was used to compare values of continuous variables and the Fisher's exact test was used for categorical variables. For GRACE score evaluation difference, the Student *t*-test was performed. Spearman rank correlation tests were used for the study of potential correlations. Differences were considered statistically significant at the 2-sided $P < 0.05$ level. All the statistical analyses were performed with the software GraphPad Prism (SAS Institute).

4. Results

As shown on Fig. 1, 138 consecutive patients admitted to our institution for ACS fulfilled the inclusion criteria; of these, 116 gave oral and written informed consent and 22 denied their participation. Fifteen consenting candidates withdrew from the overnight sleep study because of last minute refusal, device failure or technical problems; 101 successfully completed the examination. OSA was detected in 62 patients (61.4%): mild OSA ($5 \leq$ AHI < 15) was found in 28 cases, with a prevalence of 27.7%; moderate OSA ($15 \leq$ AHI < 30) was found in 18 cases (17.8%); severe OSA (AHI ≥ 30) was found in 16 cases (15.8%). Moderate-to-severe OSA was found in 33.6% of cases, which equates to more than one third of patients.

Table 1 summarizes the clinical and demographic characteristics of patients.

With the exception of age (61.3 ± 12.2 years in OSA group versus 54.5 ± 10.2 years in non-OSA group, $P < 0.001$) and BMI (27.7 ± 4.7 kg/m^2 in OSA group versus 25.5 ± 4.1 kg/m^2 in non-OSA group, $P < 0.005$), we found no statistically significant differences in the distribution of the variables pertaining to gender, cardiovascular risk factors (smoking, hypertension, dyslipidemia, diabetes), comorbidities (previous myocardial infarction, atrial fibrillation, stroke), LVEF, number of coronary artery lesions, type of ACS (STEMI/NSTEMI/UA) and relative treatments (PCI, CABG, medical treatment).

In the unadjusted analysis, the plasma peak of hs-cTnT tended to be higher in OSA patients, with a mean level of 3685 ± 3576 (ng/L) in OSA group and 2830 ± 3333 (ng/L) in non-OSA group ($P = 0.08$).

Table 1
Patients' demographic and clinical baseline characteristics.

	Overall ($n = 101$)	Non-OSA group ($n = 39$)	OSA group ($n = 62$)	*P*-value
Age	58.7 ± 11.9	54.5 ± 10.2	61.3 ± 12.2	< 0.001
Sex				
Men	74 (73.3%)	27 (69.2%)	47 (75.8%)	NS
Women	27 (26.7%)	12 (30.8%)	15 (24.2%)	NS
BMI	26.8 ± 4.6	25.5 ± 4.1	27.7 ± 4.7	< 0.005
CV risks factors				
Smoking	55 (54.5%)	21 (53.9%)	34 (54.8%)	NS
Hypertension	36 (35.6%)	12 (30.8%)	24 (38.7%)	NS
Diabetes mellitus	11 (10.9%)	2 (5.1%)	9 (14.5%)	NS
Dyslipidemia	31 (30.7%)	11 (28.2%)	20 (32.3%)	NS
Previous history of cardiovascular diseases				
Myocardial infarction	12 (11.9%)	6 (15.4%)	6 (9.7%)	NS
Stroke	2 (2.0%)	0 (0%)	2 (3.2%)	NS
Atrial fibrillation	3 (3.0%)	0 (0%)	3 (4.8%)	NS
Acute coronary syndrome				
STEMI	74 (73.3%)	28 (69.2%)	46 (75.8%)	NS
NSTEMI	25 (24.8%)	11 (28.2%)	14 (22.6%)	NS
UA	2 (2.0%)	1 (2.6%)	1 (1.6%)	NS
hs-cTnT (ng/L)	3355 ± 3492	2830 ± 3333	3685 ± 3576	0.08
LVEF (%)	51.9 ± 6.3	52.7 ± 6.4	51.5 ± 6.2	NS
Score of severity of the ACS				
GRACE	106.9 ± 24.8	98.4 ± 19.2	112.2 ± 26.3	< 0.001
TIMI STEMI	3.3 ± 1.7	2.9 ± 1.4	3.6 ± 1.7	NS
TIMI NSTEMI/UA	2.6 ± 1.4	2.8 ± 1.1	2.3 ± 1.5	NS
Number of vessels with CAD				
One	45 (44.6%)	19 (48.7%)	26 (41.9%)	NS
Two	32 (31.7%)	11 (28.2%)	21 (33.9%)	NS
Three	24 (23.8%)	9 (23.1%)	15 (24.2%)	NS
Treatments				
PCI	89 (88.1%)	35 (89.5%)	54 (87.1%)	NS
CABG	10 (9.9%)	4 (10.3%)	6 (9.7%)	NS
Medical	2 (2.0%)	0 (0%)	2 (3.2%)	NS

Dates are expressed as *n* (%), or mean ± SD. ACS: acute coronary syndromes; BMI: body-mass index; CABG: coronary artery bypass surgery; CAD: coronary artery disease; CV: cardiovascular; GRACE: global registry of acute coronary events; LVEF: left ventricle ejection fraction; NSTEMI: non ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction; UA: unstable angina; NS: non significantNS: non significant.

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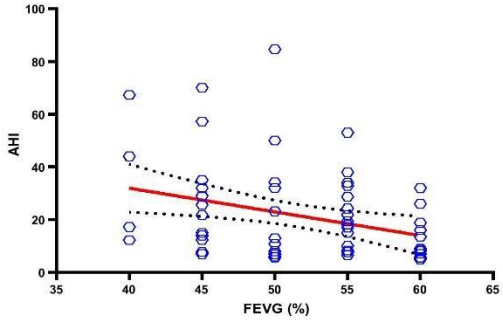

Fig. 2. Scatterplot of apnoea-hypopnoea index (AHI) and left ventricular ejection fraction (LVEF) in the obstructive sleep apnoea (OSA) group (AHI ≥ 5/h): the higher AHI, the lower LVEF is. Linear regression analysis revealed a significant negative correlation between the two variables ($r = -0.26$; $P = 0.037$).

Interestingly, OSA patients presented more severe clinical manifestation of coronary syndrome, with a greater mean GRACE score at admission of 112.2 ± 26.3 (versus 98.4 ± 19.2, $P < 0.001$).

No difference in the severity of ACS between the two groups was found when the TIMI score was performed.

In OSA patients, we also found an inverse relationship between the obstructive respiratory events and the systolic function of LV: the higher the AHI, the lower LVEF. As shown in Spearman rank correlation, these two variables exhibited a statistical inverse linear correlation in the unadjusted model (Fig. 2).

5. Discussion

In this study, we have shown that the presence of OSA in the acute phase of ischaemic heart disease without clinical evidence of LV systolic dysfunction was very high, with an estimated prevalence of 61.4% when considering AHI ≥ 5/h; a systematic screening in the ICCU setting was acceptable. Moreover, we found that the presence of OSA was associated with more severe clinical and biological manifestations of ACS and with a more impaired LV systolic function.

The prevalence of obstructive sleep apnoea in coronary patients is higher than in general population [22]. In the acute phase of ischaemic heart disease, OSA was frequently found in several previous studies [12,23,24], with a prevalence of moderate-to-severe class close to 69% [12].

As far as we are aware, there are other previous studies evaluating the interest in a very early screening of SDB in patients admitted for ACS in the ICCU setting [25,26], in both of which polysomnography (PSG) was performed.

We decided to use a 3-channel portable monitoring device screening tool; primarily because it is simple to use, an essential requirement when considering the context of an intensive care unit, and also because it is well tolerated by patient. Secondly, the simplicity of analysis, another important aspect, allows all physicians a correct interpretation of results. Thirdly, the rapidity of analysis avoids any prolongation of hospitalisation. In addition, increased evidence shows high sensitivity and specificity of this 3-channel monitoring device in comparison to full in-laboratory PSG, achieving the best result at an AHI ≥ 15/h (sensitivity of 91% and a specificity of 94%), with sensitivity greater than 80% for all AHI values; on the contrary, the specificity becomes lower as AHI values fall. However, these data are only applicable for diabetes patients [18].

Nevertheless, portable monitoring devices are not recommended by the task force of AASM, either for diagnosis of OSA in adult patients, mainly in those with significant medical comorbidities, or for general screening for asymptomatic population [27].

The significant negative relationship between the AHI and LVEF in apnoeic patients deserves to be investigated in both directions: the more severe the sleep apnoea, the more impaired the LVEF. Accordingly with previous studies [28,29], OSA is associated with a more impaired LV systolic function. A number of hypotheses, both haemodynamic and biological, could explain this relationship. First, the increased venous return due to the negative intrathoracic pressure is responsible for a reduction in LV pre-load (reduced LV end-diastolic volume secondary to a leftward shift of the interventricular septum); the increased afterload, secondary to the abnormal activation of the adrenergic system and the increased LV wall stress, contribute to a reduction of the cardiac output. Secondly, hypoxic-reoxygenation events, secondary to IH, could increase myocardial damage by ROS production, resulting in a more profound and prolonged post-ischaemic stunning condition. Thirdly, vascular damage resulting from inflammation, oxidative stress and endothelial dysfunction could be responsible for coronary microvascular dysfunction, and thus, myocardial hypo perfusion, regardless of the results of revascularization. As microvascular perfusion is a necessary condition to allow myocardial contractility, hypo perfusion results in a reduction in contractility, in order to achieve the metabolic balance between O_2 demand and O_2 supply, and thus, an impairment of LV systolic function. All these hypotheses could explain why a more severe OSA is associated with a more impaired LV systolic function. On the other hand, LV systolic dysfunction could be just as responsible for body fluid retention, as great as more impaired LV function that could result in an increased collapsibility of upper respiratory way. This could explain why a more impaired LV function is associated with more severe obstructive respiratory events.

Finally, we demonstrated that the severity of ACS evaluated by the GRACE score at the admission is significantly higher in OSA group than non-OSA group. Further evaluations are needed to investigate the specific involvement of confounding factors such as age, gender, BMI and haemodynamic parameters.

This study needs to be analysed in the light of some important limiting factors.

First, as discussed above, ApneaLink is not a reliable method of assessing SDB [27]. In addition, the automatic analysis used for calculating the ApneaLink AHI is not recommended by the French guidelines [30] and this could underestimate the real values of the AHI and thus, the true prevalence and severity of OSA. ApneaLink technology is not even able to discriminate betweencentral sleep apnoea (CSA) and OSA [31], owing to

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a lack of respiratory events, limiting a better interpretation of results.

Secondly, the screening device does not consider the total sleep time and the sleep disruption frequently observed in ICCU patients [32] has not been further considered: a sleep questionnaire should have been included to allow a more suitable interpretation of results.

Thirdly, the cutoff AHI ≥ 5/h chosen to discriminate between OSA and non-OSA patients is too low, as the most common threshold is 15/h [23,24], mainly because of the absence of daily symptoms in cardiovascular patients [33]. Moreover, above this threshold an increased mortality in heart failure patients is observed [34].

Finally, patients were not further investigated after their hospitalisation, limiting our conclusions on the real presence of SDB; its severity seems to change after the acute phase of myocardial infarction [23,24].

6. Conclusions

We found that more than half of patients admitted to the ICCU for ACS had evidence of SDB; this prevalence may be higher, the automatic analysis of the screening tool and sleep fragmentation underestimate the AHI values. The feasibility of such screening in the intensive care setting was acceptable and well tolerated by patients.

OSA seemed to be associated with more severe clinical manifestation of coronary syndromes, as shown by the greater mean GRACE score at admission and the more impaired LV systolic function. The inverse correlation between LVEF and the AHI suggests a potential role of myocardial ischaemia in the pathophysiology of obstructive sleep apnoea. Does a much more impaired LV systolic function increases the obstructive respiratory events, maybe secondary to greater body fluid retention?

However, further studies are necessary to answer several questions, such as the real interest of a very early screening of SDB in the acute phase of coronary syndromes, the natural course of SDB after the acute events and the usefulness of an appropriate treatment in decreasing the residual cardiovascular risk after a myocardial infarction.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements and findings

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Annexe 2 : Téléréhabilitation et obésité. Papier accepté dans JMIR mHealth uHealth en septembre 2021.

Original Paper

Impact of a mobile telerehabilitation solution on metabolic health outcomes and rehabilitation adherence in obese patients: a randomized controlled trial

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Abstract

Background: Obesity is a challenge for public health. Combining exercise training, nutrition and therapeutic education in a metabolic rehabilitation (MR) is recommended for obesity management. Yet, randomized controlled study-based evidences are lacking. In addition MR is associated with poor patient's adherence. Mobile Health (mHealth) devices improve the access to the MR components.

Objective: To compare the changes in body composition, anthropometric parameters, exercise capacity and QOL between 12 weeks of telerehabilitation program versus usual care in obese patients.

Methods: This was a randomised, controlled, parallel-design study. Fifty obese (body mass index BMI > 30 kg/m²) patients were included in a telerehabilitation group (TRG) or a usual care group (UCG) for 12 weeks. Patients underwent biometric impedance analyses, metabolic exercise tests, actimetry, quality of life (QOL) and satisfaction questionnaires. The primary outcome was the change in fat mass at 12 weeks from baseline. Secondary outcomes were changes in body weight (BW), metabolic parameters, exercise capacity, QOL, patient's adhesion and satisfaction.

Results: Forty-nine patients completed the study. No significant group*time interaction was found for FM (TRG:-1.7±2.6 kg; UCG :-1.2±2.4 kg; p=.48). Compared to UCG, TRG patients tended to significantly improve waist to hip ratio (TRG: -0.01±0.04 ; UCG :+0.01±0.06; p=.065) and improved QOL physical impact (TRG: +21.8 ± 43.6 ; UCG : -1.2 ± 15.4 ; p=.005). Significant time effects occurred for body composition, six-minute walk test (6MWT) distance, exercise metabolism, sedentary time and QOL. Adherence (95%) and satisfaction in the TRG were good.

Conclusions: In obese adults, TR program was not superior to usual care for improving body composition. However, TR was able to deliver a full multidisciplinary rehabilitation in obese patients and improved some health outcomes. Given the patient's adherence and satisfaction, pragmatic programs should consider mHealth devices to improve the access to MR. Further studies are warranted to establish the additional TR benefits versus usual care.

Trial Registration: Clinicaltrials.govNCT03396666,http://clinicaltrials.gov/ct2/show/NCT03396666

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KEYWORDS

Telerehabilitation; m-Health, Rehabilitation; Obesity

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Abstract

Background: Obesity is a challenge for public health. Combining exercise training, nutrition and therapeutic education in a metabolic rehabilitation (MR) is recommended for obesity management. Yet, randomized controlled study-based evidences are lacking. In addition MR is associated with poor patient's adherence. Mobile Health (mHealth) devices improve the access to the MR components.

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Registration:Clinicaltrials.govNCT03396666,http://clinicaltrials.gov/ct2/show/NCT03396666

Introduction

Obesity is a chronic disease defined by a body mass index (BMI) greater than 30 kg/m², in the context of an increased fat mass (FM). It is currently a highly prevalent disorder and is one of the major public health issues[1]. It is associated with increased morbidity and mortality[2], including metabolic comorbidities, disabilities and impaired quality of life (QOL). The metabolic risk is worst in case of fat mass (FM) increase and when abdominal visceral fat predominates[3]. Thus, the waist circumference (WC) – a marker of intra-abdominal fat[4] – as well as the voo (WHR) better predict the metabolic (i.e. insulin sensibility and lipid profile) and cardiovascular complications than the BMI[5].

Obesity results in an imbalance between energy intake and energy expenditure [6,7]. Creating a negative energy balance can induce or maintain weight loss in obese patients[10]. Thus, physical activity and nutrition interventions are the cornerstones of obesity treatment, improving weight, WC/FM and health outcomes[8]. Aerobic training alone induces significant weight loss in obese. Specifically, a light-to-moderate intensity corresponding to the intensity of the maximum lipid oxidation (LIPOXmax) individually determined in patient[9] has demonstrated significant weight loss and WC/FM reduction[10], as well as benefits on body composition and biological parameters (cholesterol and blood glucose)[11]. Yet, the most efficient strategy in obesity combines exercise training with nutrition interventions and therapeutic education [12,13] in a multidimensional metabolic rehabilitation (MR), for at least 12 weeks[14,15]. While scientific societies recommend MR for obese patients[16], the benefits of such intervention remain to be compared versus usual care alone.

However, the delivery of this MR in the clinical field is a complex issue, and population-based trials have shown a poor patient's the adherence (large drop-outs rates[17] and poor attendance [18]). This large underutilization of MR[19] is also due to the financial cost of such program [20]. In the pulmonary rehabilitation field, a widely developed domain, such kind of barriers limiting the access to and delivery of rehabilitation have well been described[21]. Thus, trials testing the effects of MR versus usual care – even if positive – would have a limited clinical relevance, because it is poorly applicable in obese patients.

The barriers of access to MR can be waived by the recent technology innovations in the field of mobile devices. Mobile health (mHealth) facilities (smartphones-based educational applications, web-based tools, text messaging, PDA physiological status monitoring, connected captors) improved the delivery of the components of rehabilitation when taken individually[22]. In obese patients, a 10 weeks' web-based exercise program has shown significant effect on the patient's FM[23]. Also, mHealth nutrition management or therapeutic education had significant effects on body weight (BW)and BMI in obesity[24,25]. Thus, because mHealth facilities would deliver a full metabolic rehabilitation, a telerehabilitation program could be more efficient than usual care in obese patients. In addition, this pragmatic research approach based on affordable tools could provide evidence for a real-world metabolic rehabilitation.

Therefore, we developed a mobile telerehabilitation solution for obese patients and used it in a blended multidisciplinary MR combining exercise training at the LIPOXmax intensity, nutritional intervention and educational tools. The aim of this randomized controlled study was to compare the changes in body composition, anthropometric parameters, exercise capacity and QOL between 12 weeks of TR program versus usual care in obese patients. In addition, the feasibility, patient's adherence satisfaction and effects of this telerehabilitation were assessed in the TRG.

Methods

Detailed information about the intervention and additional results are provided in the online supplementary material.

Study Population

Adult aged 25-65 years with body mass index (BMI) ≥30 kg/m² were eligible for participation. The main exclusion criteria were subjects with a contraindication for exercise training (like unstable cardiovascular disease or musculoskeletal problems).

Study design

This was a 12-weeks, , prospective, parallel group randomized controlled trial. Individuals were recruited from consultations of Physiology Department – University Hospital of Montpellier (France) and from the general population with media advertisements. After a screening period of 12 months, interested patients were contacted by email or phone and were registered on the Aviitam health platform. They were then scheduled for half-day baseline assessments. All participants gave their written informed consent. The study was conducted in accordance with the CONSORT ethical guidelines and CONSORT-EHEALTH checklist[26]. The study was approved by the ethics committee (CPP Nord Ouest IV - France). (ClinicalTrials.gov identifier NCT03396666).

Patients were admitted to the Physiology Department, University Hospital of Montpellier (France) between January 2018 and November 2018. Baseline assessments included physical examination, bioimpedance, blood test, effort calorimetry, 6-minute walk test (6MWT) and self-questionnaires. Once baseline assessments were completed, participants were randomized to either a 12-week telerehabilitation program or usual care. The randomization sequence was computer-generated using random blocks in an order unknown by the investigators. The list was established by a statistician and was only accessible by personnel in charge of

randomization. Although participants could not be blinded to their treatment, both programs were presented as active interventions.

All tests and evaluations of the study were performed at the same place for each group in the same conditions and with the same devices. All assessments made at baseline were realised at the end of follow-up by technicians blinded from group allocation.

Intervention and control groups

Patients from both groups had a specialized medical consultation with a cardiopulmonary exercise testing (CPET) and prescription of an adapted physical activity program at an intensity that elicits maximal lipid oxidation (called LIPOXmax). The patients in the usual care group (UCG) were advised to carry out their sessions independently, focusing on endurance physical activity sessions such as brisk walking, cycling or swimming. Moreover, these patients received a booklet with different exercises and tips on physical activity and nutrition management. All patients were registered on the Aviitam website before and during the trial. Aviitam® is a highly secure health record that allows to centralize, protect and share medical data with doctors. No restrictive diet was prescribed in both groups.

The TR program was a multicomponent intervention available on smartphone (Figure 1) and web site (Figure 2). Patients received a package containing a smartphone (Archos® with operating system Android®) on which TR Telemouv® application was installed. A pedometer (Care Trackfit®), and a heart rate monitor (Polar H7®) were connected to the smartphone via Bluetooth. Patients received secure access codes for the application and the website. They were trained in the use of the program and connected objects by a technician and received an instruction booklet to guide their first steps in the TR program. Telemouv® solution contained three components: physical activity (PA), nutritional and educational programs. After one week, a physical activity teacher went to the patients' homes to install a connected a bicycle ergometer (Care Fitness®) and perform a first supervised session. The exercise training

program included endurance sessions, muscle reinforcement, and posture and balance exercises. Regarding endurance exercises, patients were advised to increase the volume and intensity of the sessions to reach the weekly goal of 150 minutes, with a minimum of 3 sessions per week, which could combine sessions on the connected cycloergometer and walking sessions. Wearing a connected heart rate monitor was recommended during endurance sessions in order to reach the target heart rate (corresponding to LIPOXmax). For muscle strengthening, balance and posture exercises, patients had access to video sessions, sent to the mobile solution throughout the program. Moreover, patients could track their daily step count in order to reach their individualized goal. Nutrition management tools included hunger and satiety questionnaires and a 24-hour food intake questionnaire. Moreover, patients received daily educational content about illness, nutrition and the benefits of physical activity. Patients of TRG had two teleconsultations at one and two months. In addition, doctors also had access to a secure website with access to patient data of TRG.



Figure 1 Telerehabilitation mobile application



Figure 2 Telerehabilitation website

Outcomes

The primary outcome was the modification of the amount of fat mass, expressed in kilograms between baseline and 12-week follow-up in the TRG vs UCG.

Main secondary outcomes were changes from baseline in body composition indexes (fat free mass, muscular mass, mass muscular index), anthropometric parameters (weight, BMI, waist circumference and waist-to-hip ratio), and metabolism during exercise (Maximal Fat Oxidation, Power at LIPOXmax and at crossover). Other outcomes were changes from baseline in physical activity and sedentarity levels, exercise capacity, biological parameters and in self-assessment quality of life (QOL) questionnaires. Usability of the solution and satisfaction with the TR program were also assessed.

Measures

Body composition, weight, height, waist, hip and neck circumferences were measured after 12 h of fasting.

Bioelectrical impedance analyses

Subjects' body composition was assessed with bioimpedance analysis with a six terminal impedance plethysmograph BIACORPUS RX 4000 Biacorpus RX4000, (SoAGIL Developpement, France) with data analysis with the software BodyComp 8.4. This device measures total resistance of the body to an alternative electric current of 50 kHz[27,28]. Body fat mass, fat-free mass were calculated in each segment of the body according to manufacturer's database-derived disclosed equations, and total water with published equations using the classical cylindric model and Hanai's mixture theory[29]. Fat mass, fat-free mass and muscular mass were expressed in kilograms and as a percentage of total body mass. Muscle mass index was calculated as muscular mass/height² and expressed in kg/m².

Anthropometric parameters

Height was measured to the nearest 0.5 cm using a standardized height gauge. BMI was calculated as weight (kg)/height² (m). Neck, chest, waist, and hip circumference measurements (cm) were obtained using standardized procedures. Waist-to-hip ratio was calculated.

Metabolic exercise test

The subjects performed an exercise testing on an electromagnetically braked cycle ergometer (Ergoline Bosch 500) connected to a breath by breath device (COSMED Quark CPET) for gas exchange measurements. The theoretical maximal aerobic power (Wmax th) was calculated for all patients using Wasserman's equations[30] . After a fasting period of 12 hours, subjects underwent a standardized submaximal exercise-test[31] consisting of five 6-min submaximal steady-state work-loads (set at 30, 40, 50, and 60% of Wmax th), with calculation of carbohydrate and lipid oxidation rates from gas exchange measurements at steady state at the 5th-6th min of every step according to the nonprotein respiratory quotient technique[32]. Fat oxidation rates were calculated using the following equation: Fat (mg/min) = -1.7012×VCO 2 + 1.6946×VO 2 (gas volume expressed in ml/min). After smoothing of the curves, we calculated two parameters representative of the balance between fat and carbohydrate oxidation: the crossover point which is the point where carbohydrate becomes the predominant fuel representing more than 70% of the total energy[33] and the LIPOXmax point where lipid oxidation reaches a maximum. The maximal fat oxidation (MFO) rate is defined as the highest observed use of fat as an energy source during oxidative metabolism and is expressed in mg/min.

Six-minute walk test

The Six-minute walk test (6MWT) was performed at the hospital on a plane surface in a 30-m-long covered corridor marked every 2 m. The test was conducted according to the recommendations of the American Thoracic Society[34]. Heart rate and oxyhaemoglobin

saturation were recorded every minute and dyspnoea scores were measured on a Borg scale at the end of the test. Total distance was recorded.

Questionnaires

Quality of life was assessed with a questionnaire for the general population (SF-36) and one specific to the population of obese patients (EQVOD; Echelle Qualité de Vie, Obésité et Diététique). The physical activity level was assessed with the Voorrips questionnaire (modified Baecke's questionnaire). The questionnaire scored the past year's household activities, sports activities, and other physically active leisure-time activities and gave an overall PA score. The subjects were asked to describe the type of activity, hours per week spent on it, and period of the year in which the activity was normally performed. All activities were classified according to posture and movement. This questionnaire provides a reliable and valid method for classifying the activity level of older subjects as high, medium, or low. With this method, normal subjects with scores under 9.4 are classified as having low physical activity.

The SF-36 is a generic self-reported measure of health related QOL comprising 36 questions across eight domains (physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional, and mental health). Answers to each question are rated on a Likert-type scale and summed to produce a raw score which is transformed to a scale of 0–100, with higher scores indicating a better QOL[35]. SF-36 subscales are computed to generate 2 summary measures, the physical component summary (PCS) and the mental component summary (MCS). EQVOD is a French validated scale, specific to obesity, derived from the questionnaire Impact of Weight on Quality of Life (IWQOL) and its short version IWQOL-Lite[36]. The EQVOD questionnaire is adapted to socio-cultural factors of obesity and its dietetic treatment in France. It is easy to use in self-administration.

The usability was evaluated with the System Usability Scale (SUS)[37]. It consists of a 10 items questionnaire with five response options for respondents. A SUS score above a 68 would be considered above average and anything below 68 is below average.

Blood test

A venous blood sample was obtained in fasting state measure lipid profile, plasma glucose, insulinemia and CRP.

Actigraphy

Participants wore a GT3X accelerometer/inclinometer (ActiGraph, Pensacola, FL) on the non dominant wrist, programmed to collect data from the vertical axis in 15s epochs and initialized using the normal filter (AGNorm). Accelerometers were worn for 7 days during all waking hours and removed for sleeping and during water-based activities. The minimum wearing criteria was ≥ 4 days, with ≥ 8 h wearing time each day[38]. In addition, to the daily steps, daily sedentary time in minutes, and daily time spent in moderate to very vigorous activity (MVPA) were extracted from actimetry according to the manufacturer's specifications using the Freedson's cut off and the software (Actilife) provided by the company.

Power Calculations and Statistical analysis

The calculation of the NSN is based on a hypothesis supported by the literature[10] . We expect a difference between the two arms of 1kg of fat loss with a common standard deviation of 1kg. For an alpha threshold of 5% and a study power of 90%, the study should include 22 patients in each group. Taking in account a possible 10% of dropout the study will need to include 25 patients by randomized arm to demonstrate an effect.

The baseline characteristics of the two groups were compared with independent t-test or Mann-Whitney U according to the data distribution. The intra- and inter-group kinetics of changes for the variables under intervention were analyzed with linear mixed effects models including a

time effect, a group effect and the interaction between these both effects as fixed factor and a subject effect as random factor, using the nmle package on R. In case of significant interaction effect, FDR-adjusted post-hoc were performed. Linear mixed effect assumptions were tested before each test. Per group analysis of the effect of the intervention were performed in the TRG group with paired T-tests. The effect size was also calculated with Cohen's d. Spearman's rank order or Pearson correlations, depending on the data distribution, were used to determine associations between continuous variables. The data were analyzed with R software (R 4.0.3) and plotted with Prism Software. Statistical significance was set at $p<0.05$.

Results

Patients

Of the 140 screened patients, 50 were included in the study and underwent randomization. Forty-nine patients completed the study (Figure 3). One patient in the TRG discontinued the trial prior to endpoint without a post baseline assessment. Baseline characteristics of both groups were not statistically different for all the parameters assessed (Table 1.). All severities were represented, as class I, II, and III obesity represented 22 (44%), 18 (36%) and 10 (20%) patients, respectively. Forty-five (90%) patients had a low physical activity level, as defined by a Voorrips score <9.4. No patient was currently medically treated for obesity. Eight of them were diabetic and 7 were treated for dyslipidaemia.

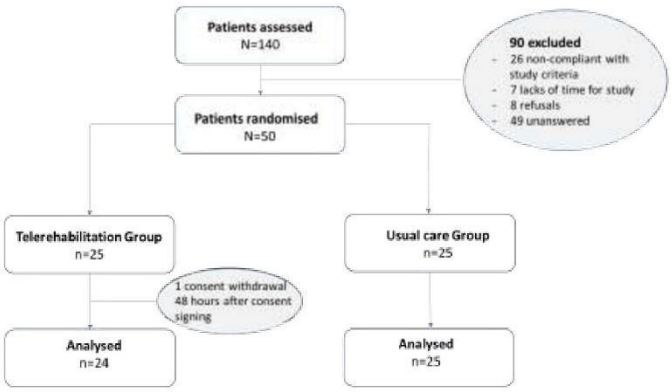

Figure 3. Flow Chart

	Intervention Group N= 25	Control Group N=25	P-value
Male (n, %)	11 (44)	12 (48)	.78
Age, years	51.2 ± 10.8	53.3 ± 11.3	.47
Active smoker, n (%)	5 (20)	1 (4)	.23
Voorrips score	5.7 ± 3.0	6.4 ±3.0	.37
Total blood cholesterol (mmol/L)	5.2 ± 1.1	5.1 ± 1.1	.16
Fasting blood glucose (mmol/L)	7.3 ± 3.0	5.9 ± 1.1	.26
Fat mass (kg)	44.8 ± 10.6)	43.6 ± 18.1	.51
Body weight (kg)	105.7 ± 18.1	104.4 ± 14.9	.78
BMI (kg/m²)	36.2 ± 4.2	36.82 ± 5.0	.74
Waist circumference (cm)	120.1 ± 11.5	120.4 ± 14.1	.21
Waist/hip ratio	0.96 ± 0.07	0.97 ± 0.10	.05
6MWT distance (m)	511 ± 69.6	514.8 ± 69.9	.77
Lipox Max (watts)	34.9 ± 11.6	36.04 ± 10.3	.87

Table 1. Characteristics of participants

BMI: body mass index, 6MWT: six-minute walk test

Effects of TR on primary and secondary outcomes

No significant group or group*time interaction were found for the FM (Figure 2 and Table 2). However, there was a significant time effect (p<.001), meaning that - although not different between groups - an improvement of the FM occurred in both study groups. A FM decrease was observed in the TRG (-1.7±2.6 kg and -4.0±6.2 %) and in the UCG (-1.2±2.4 kg and -3.0±6.6%), with 12 (50%) patients improving the FM of more than 5% of initial values (Figure 4). Similarly, significant time effects, with no group*time interactions were observed for the FFM (%), muscle mass, 6MWT distance, cross over point, and power at the LIPOXmax and psychosocial component of the EQVOD (Table 2). Significant differences for a group*time interaction were found for the waist-to-hip ratio (p=.065, Figure 5) and for the physical impact component of the EQVOD (p=.005, Figure 6), which was significantly increased in TRG.

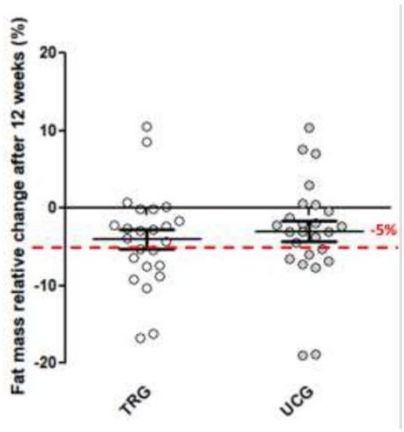

Figure 4. Relative change in fat mass after 12 weeks

	Intervention Group		Control Group		Between group
	Baseline	Follow-up	Baseline	Follow-up	P-value
Fat mass (kg)	44.80 ± 10.56	43.18 ± 10.79*	43.56 ± 12.19	43.18 ± 13.18*	Group : p = .94 Time : p < .001 Interaction : p = .48

Fat mass (%)	44.80 ± 10.56	41.11 ± 7.50*	41.88 ± 8.46	41 ± 8.78*	Group : p = .86 Time : p <.001 Interaction : p = .41
Fat free mass (kg)	60.92 ± 13.35	62.09 ± 14.08	60.85 ± 11.75	61.77 ± 12.03	Group : p = .95 Time : p = .052 Interaction: p = .45
Fat free mass (%)	57.52 ± 7.17	58.79 ± 7.52	58.12 ± 8.46	59 ± 8.78	Group : p = .84 Time : p < .001 Interaction : p = .52
Muscle mass (kg)	26.99 ± 7.78	28.23 ± 8.12	27.33 ± 7.07	27.98 ± 7.07	Group : p = .85 Time : p = .024 Interaction : p = .18
Muscle mass index (kg/m²)	9.10 ± 1.71	9.49 ± 1.70*	9.49 ± 1.83	9.75 ± 1.95	Group : p = .39 Time : p = .018 Interaction : p = .26
Body weight (kg)	105.72 ± 18.06	105.26 ± 19	104.41(± 14.86	104.89 ± 16.69	Group : p = .89 Time : p = .84 Interaction : p = .41
BMI (kg/m²)	36.22 ± 4.15	36.02 ± 4.40	36.82 ± 5.00	36.98 ± 5.72	Group : p = .54 Time : p = .82 Interaction : p = .41
Waist hip ratio	0.96 ± 0.07	0.95 ± 0.08	0.97 ± 0.10	0.99 ± 0.11	Group : p = .28 Time : p = .56 Interaction : p =.065
6 MWT distance (m)	511 ± 70	526 ± 71	515 ± 70	526 ± 67	Group : p = .90 Time : p = .030 Interaction : p = .75
Cross over point	56.00 (49;78)	69 (55.50;79)	62 (55;79)	74 (51;87)	Group : p = .91 Time : p = .002 Interaction : p = .33
Power at cross over (W)	42 (31;51)	48 (38.50;60.50)	50 (38;56)	48 (41;59)	Group : p = .67 Time : p < .001 Interaction : p = .64
Power at LIPOX Max (W)	32 (28;40)	33.50 (30;44.50)	36 (31;42)	37 (29;45)	Group : p = .75 Time : p = .019 Interaction : p = .90
MFO (mg/min)	270.5 ± 95.3	298.4 ± 81.5	301.5 ± 109.1	303.9 ± 102.0	Group : p = .46 Time : p = .14 Interaction : p = .20
MFO (mg/min/kg FFM)	10.61 ± 4.08	11.21 ± 3.11	11.23 ± 3.64	11.20 ± 3.45	Group : p = .70 Time : p = .52 Interaction : p = .47
SF 36 mental component	44.44 ± 12.43	48.29 ± 10.06	43.74 ± 11.97	43.71 ± 12.89	Group : p=.48 Time : p=.92 Interaction : p=.13
SF 36 Physical component	47.92 ± 7.31	45.90 ± 8.46	43.96 ± 9.23	45.49 ± 10.18	Group : p=.26 Time : p=.08 Interaction : p=.34
EQVOD Physical impact	64 ± 17	72 ± 0.16*	72 ± 0.16	72 ± 0.16	Group : p=.46 Time : p=.004 Interaction : p=.005
EQVOD Psychosocial	68 (± 19)	75 (± 21)	64 (± 21)	66 (± 22)	Group : p=.18 Time : p=.012 Interaction : p=.17

Table 2. Changes in primary and secondary outcomes between baseline and 12-week follow-up

BMI: body mass index; EQVOD: Echelle de Qualité de Vie, Obésité et Diététique ; MFO : maximal fat oxydation ; 6MWT: six-minute walk test

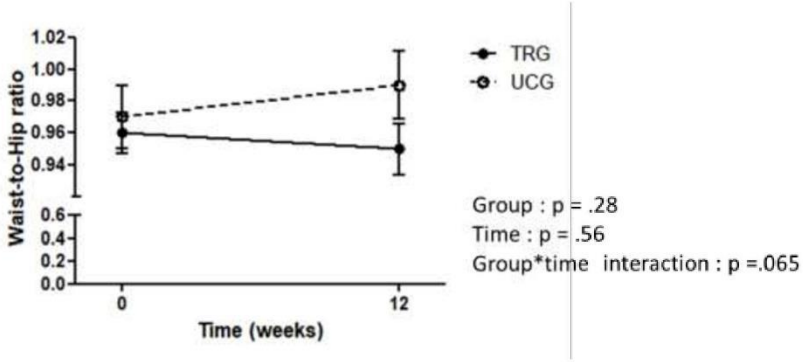

Figure 5. Waist-to-hip ratio change after 12 weeks (absolute)

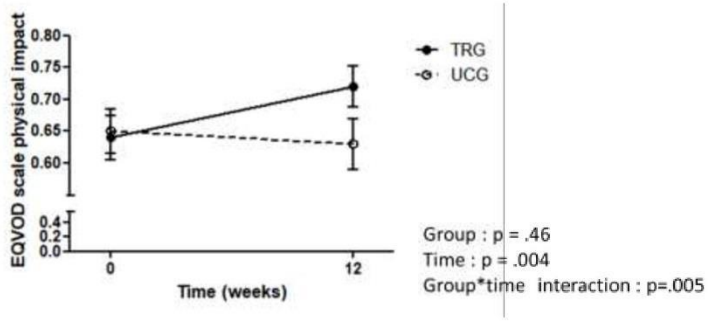

Figure 6. EQVOD scale physical impact change after 12 weeks (absolute)

Effect and feasibility of the telerehabilitation in users

TR patients who completed the 12-weeks intervention performed an average of 30,5±16.7 sessions of physical activity and connected 283.5±193.4 times to the application and the website throughout the study. SUS score averaged 65.3±15.02. A score greater than 68, indicating good usability of the system, was found in 11/24 patients. Only one patient found the program with a bad usability with a SUS score less than 39. In the TRG, per group analyses showed an improvement of body composition, exercise metabolism and health-related quality of life after the intervention. The FM (-1.7 ± 2.6 kg; p=.004), FFM (+1.2 ± 1.9 %; p=.005), muscle mass

+0.9 ± 2.0 kg; p= .028, cross over point +8.6 ± 14.0; p=.006, power at the cross over point and LIPOXmax (+5.8 ± 9.4 W; p=.006 and + 2.48 ± 5.2W; p=.034), SF 36 mental component (+3.53 ± 7.19; p=.041) and EQVOD Physical and psychosocial components (+9.4 ±14.1; p=.005 and +6.4 ± 11.7; p=.018) showed statistically significant improvements. Effects sizes ranged from small to moderate according to the Cohen's d (Table 3.).

	T0 (N=25)	T12 (N=25)	Difference (N=25)	P value	Effect size Cohen's d	Magnitude
Fat mass (kg)	44.80 (10.56)	43.17 (10.79)	-1.70 (2.60)	0.004	-0.65	small
Fat mass (%)	42.48 (7.17)	41.11 (7.50)	-1.31 (1.94)	0.003	-0.67	moderate
Fat free mass (kg)	60.92 (13.35)	62.09 (14.08)	0.86 (2.42)	0.096	0.35	moderate
Fat free mass (%)	57.52 (7.17)	58.79 (7.52)	1.21 (1.89)	0.005	0.64	moderate
Muscle mass (kg)	26.99 (7.78)	28.23 (8.12)	0.94 (1.97)	0.028	0.48	small
Muscle mass index (kg/m²)	9.10 (1.71)	9.49 (1.70)	0.30 (0.61)	0.025	0.49	small
Body weight (kg)	105.72 (18.06)	105.26 (19.00)	-0.85 (2.82)	0.155	-0.30	small
BMI (kg/m²)	36.22 (4.15)	36.02 (4.40)	-0.31 (1.02)	0.145	-0.31	small
Waist hip ratio	0.96 (0.07)	0.95 (0.08)	-0.01 (0.04)	0.248	-0.24	small
6 MWT distance (m)	511.00 (69.58)	526.46 (70.79)	13.88 (36.44)	0.075	0.38	small
Cross over point	63.96 (20.69)	72.96 (22.60)	8.58 (14.02)	0.006	0.61	moderate
Power at cross over point (W)	44.00 (17.16)	49.21 (16.52)	5.79 (9.43)	0.006	0.61	moderate
Power at LIPOX Max (W)	34.92 (11.59)	36.88 (11.51)	2.38 (5.15)	0.034	0.46	small
MFO (mg/min)	270.48 (95.25)	298.38 (81.45)	25.88 (73.12)	0.096	0.35	small
SF 36 mental component	44.44 (12.43)	48.29 (10.06)	3.53 (7.19)	0.041	0.49	small

SF 36 Physical component	47.92 (7.31)	45.90 (8.46)	-1.44 (6.76)	0.355	-0.21	small
EQVOD Physical impact	63.70 (17.45)	72.25 (16.11)	9.44 (14.11)	0.005	0.67	moderate
EQVOD Psychosocial	67.94 (19.32)	75.28 (21.30)	6.35 (11.66)	0.018	0.54	moderate

Table 3. Changes in parameters in the TRG group – paired t-test and Cohen's d

Baseline and intervention-induced changes correlations in parameters

At baseline, in all obese patients, we found univariate correlations between parameters. FM was correlated with the BMI (r=0.850; p<.001). FFM as well as the muscle mass were correlated with the cross-over point (r=0.509; p<.001 and r= 0,507; p<.001), LIPOXmax (r=0.495; p<.001 and r= 0.469; p<.001) and maximal fat oxidation (r= 0.365; p=.009 and r= 0.34; p=.02). 6MWT distance was correlated with muscle mass (r=0.316; p=.03), with the LIPOXmax (r=0.275; p=.05) and the SF36 physical impact (r=0.301; p=.05). EQVOD's psychosocial score was correlated with the FM (r=-0.338; p=.02) and WHR (r=0.281; p=.05). In addition, at the end of the 12 weeks trial, the change in BW was correlated with relative changes in FM (%) and FFM (%) in TRG and UCG (TRG: r=0.598; p<.001 and r=0.670; p<.001, respectively and UCG: (r=0.616; p=.01 and r=0.426; p=.04, respectively). In the whole population (n=49), BW change was inversely correlated with the 6MWT distance (r=-0.281; p=.05). In contrast, the number of training sessions and changes in WHR or FM (p=.56 and p=.26, respectively) as well as the number of connections and changes in WHR or FM (p=.86 and p=.69, respectively) were not significantly correlated.

Discussion

This study was one of the first to assess to propose the use of a mobile telerehabilitation programme using mHealth devices to deliver a full metabolic rehabilitation in obese patients. While our study didn't show significant additional benefits vs. usual care regarding the primary outcome (FM), there was a significant advantage regarding a domain of QOL and tendency for

the WHR. In addition, per group analysis indicates that the significant time effects on body composition, exercise capacity, PA behaviour and QOL were mainly due to the TRG. These effects occurred while the TR solution's adherence and usability were good during the 12 weeks trial duration.

Comparison of the effects of telerehabilitation versus usual care in obese patients

Scientific societies have recommended that obese patients should beneficiate of a multidisciplinary program including exercise, diet and cognitive behavioral therapy[16]. However, except for one study[39], this recommendation was not based on RCT evidence. In obese patients rehabilitation improvements in BW, exercise capacity and comorbidities have not been compared to a control group[40–42]. Thus, our randomized controlled trial fulfils a gap in the scientific knowledge regarding obesity treatment. Although our study didn't show significant improvement of the FM – the primary outcome of the study – with telerehabilitation versus usual care, numerous observations have to be underlined. Among the secondary outcomes, we observed a significant time*group effect for the physical impact domain of the EQVOD. This result is in line with the improvement of SF36-assessed QOL previously reported in obese patients by metabolic rehabilitation[43], after 12 weeks in particular[44]. There was also a tendency for the WHR in favour of the TRG versus UCG ($p=0.065$), which is consistent with previous reports of effect on waist circumference induced by multidisciplinary rehabilitation[45] or 12 weeks exercise training[46]. This effect of the telerehabilitation would be clinically relevant, given the critical role of the visceral fat accumulation in the patient's comorbidities[3,47]. As power calculation were performed on the basis of expected change in FM, further studies are required to confirm the effect of the telerehabilitation on these secondary outcomes. Nonetheless, the mixed model showed significant time effects for most of the secondary outcomes (FM (kg, %), FFM (%), muscle mass (kg), muscle mass index, 6MWT

distance (m), crossover point, intensity at the LIPOXmax, sedentary time (%), SF36 and EQVOD), which requires per group analyses to complete the interpretation.

Effects in the Usual Care Group

A detailed structured physical activity counselling in the daily life was provided to the UCG patients in line with guidelines in obesity[48]. The intensity of the endurance exercises were set at the LIPOXmax, an individually intensity determined on the metabolic exercise test, but there was no supervision. Therefore, UC patients did not beneficiate from the metabolic effects reported after 8 to 12 weeks of supervised training at the LIPOXmax intensity[10,49]. Similarly, patients also beneficiated of a nutrition counselling through the Aviitam platform registration, but, again, the nutritional intervention was not supervised. Thus, the metabolic effects were logically not significant, and close to the one reported in previous usual care groups in obesity[50]. Altogether, this means that although an optimized standard care with specific assessments, prescription and counselling was provided to the UCG patients, its short-term impact on the patient's metabolism was limited.

Effects in the telerehabilitation group

In contrast, patients of the TRG showed significant improvements in body composition (FM), exercise capacity (6MWT distance), exercise metabolism (intensity at the cross over point and LIPOXmax), health-related QOL (SF36 and EQVOD) ,biological parameter (total and LDL cholesterol) and sedentary time in per group analysis (supplementary tables1-2). All these parameters constitute classical outcomes improved by a multidisciplinary metabolic rehabilitation. Results showed an internal validity because physiological correlations were found between study's parameters at baseline [FFM and exercise metabolism , 6MWT distance and muscle mass, LIPOXmax, SF36], and after 12 weeks. The magnitude of the BW loss after 3 months in TRG (-2.82±2.81 %) could appear as limited. However, it is in line with the 6% BW loss after 12 months of non-surgical clinical obesity services[17,39]. In addition, clinical

benefits have been reported in randomized control trial reporting weight loss of ≤ 3%, when mediated by physical exercise[51], in particular regarding the body composition[52]. Training combined with diet induced a 5.1% reduction of FM[53], and the 4±6% FM decrease in our TRG was thus consistent with previous studies. The effect size for the FM loss was medium (Cohen's d>0.50), and reached 5% or more in 48% of patients in the TRG. These effects appear as particularly relevant, as FM loss has appeared as the best predictor of the physical functioning improvement during weight loss in obese patients[13]. In addition, FM loss has been associated with improvement of systemic inflammation and lipid profile[47,54] . The decrease of the total and LDL cholesterol (supplementary data) in the TRG supports a clinical relevance of the FM loss in the TRG. Absolute and relative increase intensity at the crossover point was +17±27 %, less than previously reported[49], but Cohen's d was 0.644, which indicates a medium improvement exercise metabolism in obese patients. In addition, given that the MCID has been estimated from 2 to 4 points of the SF36 PCS/MCS[55,56], 25 to 35% and 5 to 10% of the obese patients in the TRG experienced clinically a significant improvement of their physical and mental component of QOL, respectively. Altogether, results in obese patients of the TRG support mild to medium effects of the multidisciplinary telerehabilitation, with benefits being clinically in a significant a relevant proportion of patients.

mHealth for to foster adherence to metabolic rehabilitation in obese patients

Telerehabilitation has been studied in several conditions like stroke[57], chronic obstructive pulmonary disease [58], cardiac diseases[59,60], diabetes[61] or neurodegenerative diseases[62]. To the author's best knowledge, this study is the first to test a telerehabilitation solution in a population of obese patients. Indeed, current mHealth interventions for obesity have been limited to self-management, or self-monitoring, or physical activity, or nutrition or education alone[63]. Metaanalysis of mHealth in obesity has shown heterogeneous evidence on health outcomes[25]. Yet, establishing the impact of mHealth-based on the metabolic

rehabilitation was not the aim of our study. In accordance with previous studies, our strategy was rather to develop a mHealth device to improve the access to the metabolic rehabilitation in obese patients. Indeed, attendance and dropout represent a critical issue in rehabilitation, because previous studies have shown that the highest clinical benefits were seen in subjects or obese patients with the highest attendance[64,65]. Accordingly, we found that the adherence of the 12 week program reached 95% in the TRG with only 1 dropout. This is largely above dropout rate reported in mHealth studies[66]. Dropout rates usually ranged from 43 to 62% over 6–24 months during multidisciplinary rehabilitation for obese patients[17]. This high attendance in the TRG was in line with the SUS score usability showing that the solution was acceptable for the patients. Thus, our study showed that our telerehabilitation solution succeeded to waive some of the barriers to face-to-face rehabilitation, and appeared a relevant tool to deliver metabolic rehabilitation in obese patients.

Study limitations

One limitation of the study was the lack of sufficient objective monitoring of the intervention in the TRG. Indeed, patients experienced difficulties, mainly secondary to connectivity defects with the Bluetooth, to use heart rate monitor, pedometer, and cycle ergometer. Therefore, too few data have been collected to correctly monitor the intervention. However, our study was a pragmatic trial and analyses were performed in intention-to-treat, which means that the impact of this missing data on the results was limited. Nonetheless, monitoring the intervention would have allow a better understanding of the effects of the TRG in obese patients, in particular in terms of patient's phenotype of response to the intervention. Also, the IT firm who co-developed with our team the telerehabilitation solution had not the possibility to push notifications and pertinent feedback to the patients. Finally, it is probable that patients need a longer and a more stimulant intervention. Therefore, longer-term intervention and the addition of human support, for example via videoconferencing, could address these limitations and

improve the outcomes of telerehabilitation programs. Altogether, the development of telerehabilitation solution remains an issue that will have to address in the global perspective of our mHealth project.

Conclusion

In obese adults, our telerehabilitation program was able to deliver a full metabolic rehabilitation but did not demonstrate superiority to the usual care on body composition. Over a period of 12 weeks, it induced effects on most rehabilitation outcomes in obese patients (body composition, total cholesterol, and lipid oxidation during exercise …). These effects were not significantly superior to those induced in our "usual care" group. However, the excellent patient's adherence to the telerehabilitation constitutes an answer to the challenge of patient's adherence to face-to-face rehabilitation programs. Pragmatic metabolic rehabilitation programs should consider mHealth devices to deliver their interventions. In parallel to the continuous development of technological solutions, larger-scale and longer-term studies are needed to translate these technological promises into fully efficient intervention in the clinical field.

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Author's contributions

FB: design of the work, investigation, data curation, funding acquisition, writing. GB : investigation, Data Curation. BA : investigation, data curation. LB: formal analysis. DS : data curation. NM: methodology, formal analysis. FG: data curation, formal analysis, writing. MH: design of the work, investigation, data curation, funding acquisition, writing. All authors contributed and reviewed the final version of the paper.

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