Effets cliniques, biologiques et aspects techniques de la ventilation non invasive

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RESUME :

L'hypoventilation alvéolaire chronique est considérée comme un marqueur d'évolution péjorative de différentes pathologies respiratoires. Cependant, son rôle physiopathologique dans différentes dysfonctions systémiques n'a pas été étudié de manière convaincante. Cette thèse avait pour but d'investiguer les conséquences de l'hypoventilation alvéolaire modérée au cours de l'insuffisance respiratoire chronique restrictive et les effets de son traitement par ventilation non-invasive.

Nous avons montré que des patients affectés d'un syndrome obésité-hypoventilation (SOH) avaient une fonction endothéliale plus sévèrement altérée et une inflammation systémique plus importante que les patients obèses simples. La $PaCO_2$ était corrélée à la dysfonction endothéliale (Borel et coll, manuscrit en préparation). Nous avons observé que la proportion d'hypoventilation en sommeil paradoxal, chez les sujets SOH, était associée à une réponse ventilatoire au CO_2 abaissée et une somnolence diurne excessive. Pour la première fois, nous avons constaté que la ventilation non invasive nocturne améliorait la vigilance diurne objective (Chouri-Pontarollo et coll, Chest 2007). Nous menons actuellement la première étude randomisée du traitement des patients porteurs d'un SOH par VNI versus observation pendant un mois. L'analyse intermédiaire montrait qu'un mois de VNI nocturne chez les patients SOH améliorait la $PaCO_2$ diurne, la capacité pulmonaire totale, la structure du sommeil, cependant aucun paramètre cardiovasculaire et métabolique n'était modifié.

Chez des patients insuffisants respiratoires chroniques pariéto-restrictifs, la VNI utilisée au cours d'un exercice aigu, augmentait la ventilation et améliorait la tolérance à l'effort (Borel et coll, Resp Med 2008). Chez ces mêmes patients, un réentrainement à l'effort sous VNI n'apportait pas de bénéfices additionnels par rapport à un réentrainement en ventilation spontanée sauf chez les patients les plus sévères. Ces derniers, amélioraient leur périmètre de marche et leur qualité de vie. Leur fatigue en particulier était améliorée s'ils s'étaient réentraînés sous VNI (Borel et coll, Am Journal of physical med and rehab, 2008, soumis).

Enfin, nous avons analysé l'impact des fuites intentionnelles des masques de VNI sur la performance des appareils de VNI bi-pressionnels. L'augmentation des fuites intentionnelles diminuait les capacités des appareils à atteindre et maintenir la pression de consigne. Ceci pouvait conduire à une diminution du volume délivré au patient, en particulier pour des fuites intentionnelles supérieures à 40 $L.min^{-1}$ à 14 cm H2O de pression (Borel et al, Chest, sous presse).

Conclusion : L'hypoventilation alvéolaire chronique peut-être considéré comme un déterminant physiopathologique de la dysfonction endothéliale, de l'inflammation, de la somnolence, et de l'intolérance à l'effort. La VNI, utilisée au cours des efforts, permet d'améliorer les capacités d'exercice et la qualité de vie des patients insuffisants respiratoires restrictifs les plus sévères. Malgré les limites technologiques des appareils de VNI bi-pressionnels utilisés actuellement, la VNI corrige l'hypoventilation alvéolaire des patients SOH, cependant les effets sur l'inflammation, la dysfonction endothéliale restent incertains à cours et long terme chez ces sujets obèses.

Mots clés :

insuffisance respiratoire chronique, ventilation non invasive, syndrome obésité hypoventilation, dysfonction endothéliale, Inflammation, exercice, réhabilitation.

ABSTRACT :

Chronic alveolar hypoventilation is considered as a pejorative factor of several respiratory diseases outcomes. However, its pathophysiological impact has not been studied in a convincing way. This thesis aimed to assess moderate alveolar hypoventilation consequences during restrictive chronic respiratory failure and the effects of its treatment by non-invasive ventilation (NIV).

We have shown that Obesity Hypoventilation Syndrome patients (OHS) had more severely impaired endothelial function and higher systemic low-grade inflammation than simple obese patients. Arterial $PaCO_2$ was correlated with endothelial dysfunction *(Borel et al, manuscript in preparation)*. We have also reported that in OHS, the proportion of REM-sleep time spent in hypoventilation was related to lowered CO_2 ventilatory response and to excessive diurnal sleepiness. Non-invasive ventilation improved objective diurnal vigilance *(Chouri-Pontarollo et al Chest 2007)*. Currently, we are conducting the first randomized NIV versus observation during one month study in OHS. The intermediate analysis showed that one month of nocturnal NIV led to a diurnal $PaCO_2$, an improvement of sleep structure and an increase of total lung capacity. However, neither cardiovascular nor metabolic parameters were modified.

When NIV was used during exercise, in patients with chronic thoracic restrictive respiratory failure, minute ventilation and exercise tolerance were improved (Borel et al, Resp Med 2008). In these patients, long term training with NIV had no additional benefits as to training in spontaneous breathing, except for the most severe of them. For those later patients, training with NIV lead to a larger improvement in six minutes walking distance and in quality of live, particularly in their fatigue.

We also focused on the impact of intentional leak levels of different masks on the performance of ventilators designed for bi-level positive pressure ventilation. Increase of intentional leaks significantly impaired the capacity of ventilators to attain and maintain preset inspiratory pressure and could decrease tidal volume. These significant effects occurred mainly for intentional leaks above 40 l/min (for an inspiratory pressure of 14 cmH_2O) *(Borel et al, Chest 2008 in press)*.

Conclusion: Chronic alveolar hypoventilation may be considered as one of the patho-physiological factors of endothelial dysfunction, inflammation, sleepiness and exercise intolerance. In spite of technological limitations of bi-level pressure machines currently used, nocturnal NIV corrects alveolar hypoventilation in OHS patients; however its short term and long term impacts on inflammation and endothelial dysfunction remain uncertain. During respiratory rehabilitation program, using NIV during exercise improves exercise capacities and quality of life for the most severe restrictive respiratory failure patients.

Keys words: chronic respiratory failure, non-invasive ventilation, obesity hypoventilation syndrome, endothelial dysfunction, inflammation, exercise, rehabilitation.

TABLE DES MATIERES :

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INTRODUCTION GÉNÉRALE

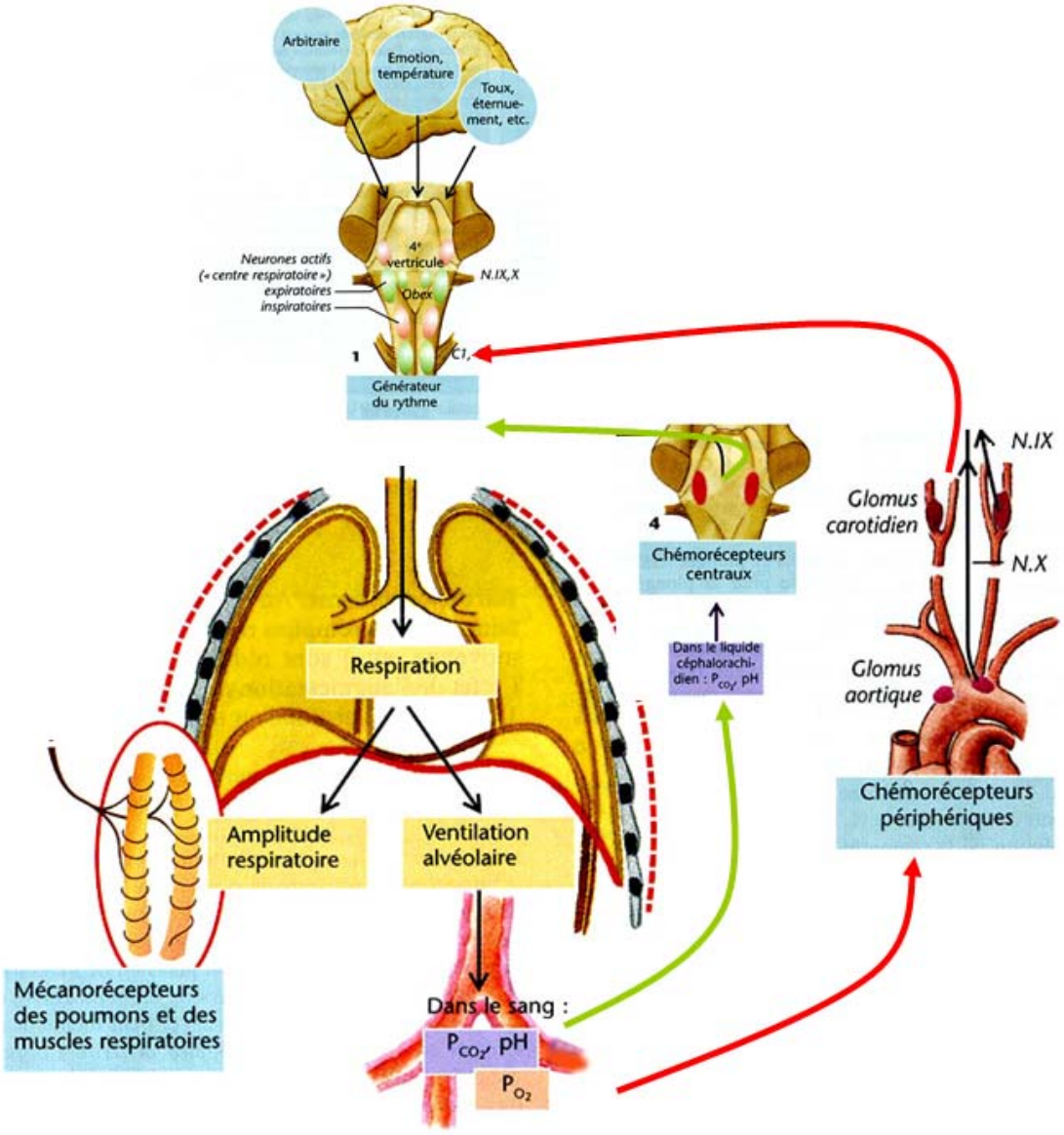
HYPOVENTILATION ALVEOLAIRE ET TRAITEMENT PAR VENTILATION NON INVASIVE

À l'état stable, la ventilation du sujet sain est adaptée à son métabolisme cellulaire; elle assure l'apport d'oxygène et l'élimination du CO_2. La pression partielle en CO_2 du sang artériel ($PaCO_2$) reflète l'équilibre entre la production de CO_2 et son élimination par la ventilation alvéolaire pour maintenir un pH stable. Le maintien de cette homéostasie nécessite que des chémo-récepteurs centraux sensibles aux altérations de pH (induites par les modifications de CO_2) renseignent les centres respiratoires, eux-mêmes en charge de la génération du rythme respiratoire. Ces centres vont ajuster la commande transmise aux muscles respiratoires, effecteurs de la mécanique thoraco-pulmonaire (Figure 1). Une déficience permanente d'une ou plusieurs de ces trois entités peut conduire à l'hypoventilation alvéolaire chronique, définie par une hypercapnie diurne ($PaCO_2$ > 45mmHg). Si pour certaines pathologies, comme les atteintes neuro-musculaires rapidement progressives (ex : la Sclérose Latérale Amyotrophique), la physiopathologie de l'hypoventilation alvéolaire est aisément identifiable, pour d'autres pathologies l'origine de l'hypoventilation est probablement multifactorielle et reste discutée dans la littérature (ex : le syndrome Obésité-Hypoventilation) (Martin and Sanders 1995).

Quelques que soient les mécanismes physiopathologiques à l'origine de l'hypoventilation alvéolaire chronique, la Ventilation Non Invasive (VNI) est actuellement le traitement de référence (Mehta and Hill 2001). Les mécanismes par lesquels la VNI agirait sur l'hypoventilation alvéolaire chronique sont : *(i)* l'amélioration de la sensibilité des centres respiratoires (McNicholas 1997; Annane, Quera-Salva et al. 1999); *(ii)* la mise au repos des muscles respiratoires au cours de l'utilisation de l'appareillage permettant une meilleure fonction musculaire au décours des séances d'utilisation (Cropp and DiMarco 1987;

Goldstein, De Rosie et al. 1991); (iii) l'amélioration de la compliance thoraco-pulmonaire permettant de diminuer le travail respiratoire.

Figure 1 : Schématisation des centres respiratoires et des chémorécepteurs périphériques et centraux.
D'après Silbernagl Atlas de physiologie.



Aucun de ces mécanismes n'est exclusif ; leur contribution respective pourrait être plus ou moins importante selon la pathologie à l'origine de l'insuffisance respiratoire (Estenne, Gevenois et al. 1993). Actuellement l'efficacité clinique de la VNI s'apprécie principalement sur les améliorations de la gazométrie artérielle diurne, la symptomatologie diurne, la qualité de vie, la tolérance à l'effort, la qualité du sommeil mais aussi sur la diminution de la morbi-mortalité.

L'intérêt clinique de la VNI dans les pathologies neuromusculaires et les déformations thoraciques est aujourd'hui parfaitement admis (Consensus 1999) et son efficacité dans ces pathologies n'est pas discutée même en l'absence d'études randomisées contrôlées (Annane, Orlikowski et al. 2007). Une $PaCO_2$ diurne supérieure ou égale à 6kPa (45 mmHg) pose l'indication formelle de mettre en place une assistance respiratoire nocturne chez les patients souffrant d'un syndrome pariéto-restrictif ou atteints d'une pathologie neuro-musculaire (Consensus 1999; Ward, Chatwin et al. 2005). Cela est également vrai pour le syndrome Obésité-Hypoventilation qui est aujourd'hui la cause la plus fréquente d'insuffisance respiratoire restrictive.

Le seuil d'hypoventilation alvéolaire à partir duquel des signes cliniques (somnolence, fatigue) apparaissent n'est pas connu tant ces signes sont bien tolérés dans des situations chroniques. De la même façon, les conséquences cardio-vasculaires, métaboliques, inflammatoires de l'hypoventilation alvéolaire chronique ont été peu étudiées. L'exemple du seuil de $PaCO_2$ indiquant de débuter une VNI chez les patients BPCO (55 mmHg) (Consensus 1999) illustre bien que l'hypoventilation est admise comme un mécanisme adaptatif ou un marqueur d'évolution péjorative plutôt qu'elle n'est envisagée comme un déterminant physiopathologique de dysfonctions ou complications systémiques.

ORGANISATION GENERALE DE LA THESE :

Cette thèse, intitulée « ***Effets cliniques, biologiques et aspects techniques de la ventilation non invasive*** » a pour objectif d'étudier les conséquences d'une hypoventilation alvéolaire au cours de l'insuffisance respiratoire chronique restrictive et l'impact de son traitement par ventilation non-invasive. Ce travail s'articule en trois chapitres. Le premier chapitre a pour objectif d'étudier les conséquences cardio-vasculaires d'une part, et sur la vigilance diurne d'autre part, du syndrome obésité hypoventilation, et d'évaluer l'effet du traitement par assistance ventilatoire non-invasive nocturne. Le deuxième chapitre a pour objectif d'étudier l'impact de la ventilation non-invasive utilisée pendant un effort aigu et à plus long terme, pendant les séances d'un programme de ré-entraînement à l'effort à domicile chez des patients insuffisants respiratoires chroniques pariéto-restrictifs. Le troisième chapitre concerne les aspects technologiques de la ventilation non-invasive.

CHAPITRE 1 :

CONSEQUENCES CARDIO-VASCULAIRES

ET SUR LA VIGILANCE

DU SYNDROME OBESITE HYPOVENTILATION

CHAPITRE 1 : CONSEQUENCES CARDIO-VASCULAIRES ET SUR LA VIGILANCE DU SYNDROME OBESITE HYPOVENTILATION

PREREQUIS :

Définition du syndrome obésité hypoventilation (SOH) :

Le syndrome Obésité hypoventilation est défini, chez un sujet en état stable, par la coexistence d'une obésité (indice de masse corporelle > 30 kg/m^2) et d'une hypercapanie ($PaCO_2$ > 45 mmHg) sans autre cause expliquant l'hypercapnie (BPCO, déformations thoraciques, pathologie neuro-musculaire, hypothyroïdie sévère et syndrome d'hypoventilation central congénital). La présence d'un syndrome d'apnée obstructif du sommeil (SAOS) n'exclut pas le diagnostic de SOH. En effet 70 à 90% des patients obèses qui sont en hypercapnie diurne ont un SAOS (Resta, Foschino-Barbaro et al. 2000; Kessler, Chaouat et al. 2001; Piper and Grunstein 2007) et 10 à 15 % des patients qui ont un SAOS ont une hypercapnie diurne (Laaban and Chailleux 2005).

Prévalence :

La prévalence du SOH n'a jamais été étudiée directement dans la population générale. Elle est actuellement estimée à partir de deux sources principales : (i) des cohortes de patients porteurs d'un SAOS (Leech, Onal et al. 1987; Resta, Foschino-Barbaro et al. 2000; Kessler, Chaouat et al. 2001; Verin, Tardif et al. 2001; Golpe, Jimenez et al. 2002; Laaban and Chailleux 2005; Akashiba, Akahoshi et al. 2006; Mokhlesi, Tulaimat et al. 2007); (ii) une cohorte de patients obèses hospitalisés (Nowbar, Burkart et al. 2004).

Dans les populations de patients SAOS, la prévalence du SOH est estimée entre 10 et 20%. Certaines études retrouvent des prévalences plus importantes (>30%) mais des patients avec une obstruction bronchique significative étaient alors inclus (Leech, Onal et al. 1987).

Dans l'étude de Leech et coll près de 10% des patients avaient une BPCO significative (VEMS/CVF<65%).

Dans une cohorte observationnelle d'obèses hospitalisés, Nowbar et coll (Nowbar, Burkart et al. 2004), retrouvaient une prévalence de patients obèses en hypoventilation de 30%. Cependant, les patients inclus avaient des BMI $\geq$ 35 kg/m^2, le critère d'exclusion d'obstruction bronchique retenu était peu restrictif (VEMS/CVF <50%), et les patients étaient hospitalisés donc potentiellement en état instable. Néanmoins, la prévalence augmentait avec l'augmentation de l'indice de masse corporelle (Resta, Foschino-Barbaro et al. 2000; Nowbar, Burkart et al. 2004; Laaban and Chailleux 2005) et pouvait être estimée à 10% pour un IMC $\leq$ 40 kg/m^2 et 25% pour un IMC $\geq$ 40 kg/m^2 (Resta, Foschino-Barbaro et al. 2000; Laaban and Chailleux 2005).

Ces études réalisées dans ces deux sources principales de recrutement mettent en évidence d'une part la surestimation potentielle du SOH par rapport à des patients obèses non hospitalisés en population générale et d'autre part le lien étroit entre SOH et SAOS. La prévalence pourrait être estimée entre 10% et 15% chez des patients obèses stables et sans décompensation cardio-respiratoire concomitante.

Physiopathologie :

Mécanique thoraco-pulmonaire : Dans les études qui portent sur les mécanismes de l'hypoventilation alvéolaire associée à l'obésité, la réduction des volumes pulmonaires (capacité vitale forcée, capacité résiduelle fonctionnelle et capacité pulmonaire totale) est un des facteurs significatifs retrouvé (Leech, Onal et al. 1987; Resta, Foschino-Barbaro et al. 2000; Nowbar, Burkart et al. 2004; Laaban and Chailleux 2005; Akashiba, Akahoshi et al. 2006; Mokhlesi, Tulaimat et al. 2007). Ces réductions des volumes sont associées à une diminution de la compliance thoraco-pulmonaire et augmentent le travail respiratoire (Pankow, Hijjeh et al. 1997). L'origine de la diminution des volumes pulmonaires est le plus

souvent reliée à la charge mécanique induite par l'accumulation de la masse graisseuse intra-thoracique et abdominale (Babb, Wyrick et al. 2008). La production d'adipokines et l'inflammation systémique de bas-grade pourraient également participer à cette réduction des volumes. Lin et coll (Lin, Yao et al. 2006) ont mis en évidence, chez plus de 46 000 sujets sans pathologie respiratoire avérée, que la présence d'un syndrome métabolique était associé à un risque plus important d'avoir un syndrome restrictif à IMC, sexe et âge équivalent. Plusieurs autres études, sur des échantillons plus réduits, confortent l'hypothèse qu'une répartition androïde de la graisse, participant à la définition du syndrome métabolique, était associée à une restriction pulmonaire plus importante (Collins, Hoberty et al. 1995; Lazarus, Sparrow et al. 1997). L'inflammation de bas grade induisant une atteinte musculaire spécifique, pourrait participer à la diminution de la fonction respiratoire dans le SOH. Par ailleurs, l'augmentation du travail respiratoire, lié à la réduction des volumes pulmonaires pourrait aussi majorer cette inflammation induisant alors un cercle vicieux (Vassilakopoulos and Hussain 2007).

Si cette diminution de la fonction respiratoire est systématiquement évoquée pour expliquer l'hypercapnie au cours du SOH, les modèles de régression retrouvés dans la littérature montrent que les paramètres de la fonction respiratoire n'expliquent qu'une faible proportion de la variance de la $PaCO_2$ ($\approx$ 10%) (Leech, Onal et al. 1987; Resta, Foschino-Barbaro et al. 2000; Laaban and Chailleux 2005). Ceci suggère que d'autres facteurs prédisposent à l'hypoventilation chez ces patients obèses.

Capacités musculaires **:** La diminution de la force et de l'endurance des muscles inspirateurs a été rapportée dans le SOH (Kelly, Jensen et al. 1988; Weiner, Waizman et al. 1998). La perte de poids permet une amélioration de la force et de l'endurance des muscles respiratoires et, dans certains cas, la correction de l'hypoventilation (Kelly, Jensen et al. 1988; Weiner, Waizman et al. 1998). À l'encontre de cette perte de « capacité musculaire

respiratoire », Leech et coll (Leech, Onal et al. 1991) ont montré que les patients SOH peuvent corriger leur hypercapnie au cours d'une hyperventilation volontaire. Sampson et coll (Sampson and Grassino 1983) ont rapporté que les patients SOH pouvaient générer des pressions trans-diaphragmatiques identiques aux patients obèses normocapniques. Enfin, Pankow et coll (Pankow, Hijjeh et al. 1997) retrouvaient qu'au cours de la ventilation spontanée de repos, les pressions trans-diaphragmatiques générées étaient supérieures chez des patients SOH par rapport à des patients obèses contrôles, même si elles restaient insuffisantes pour permettre aux sujets de maintenir une $PaCO_2$ normale. La critique actuellement faite à ces études est que les capacités musculaires des sujets SOH n'ont pas été étudiées avec des techniques « non-coopération-dépendantes » (Mokhlesi and Tulaimat 2007) et ainsi le débat sur la déficience des muscles respiratoires du sujet SOH persiste.

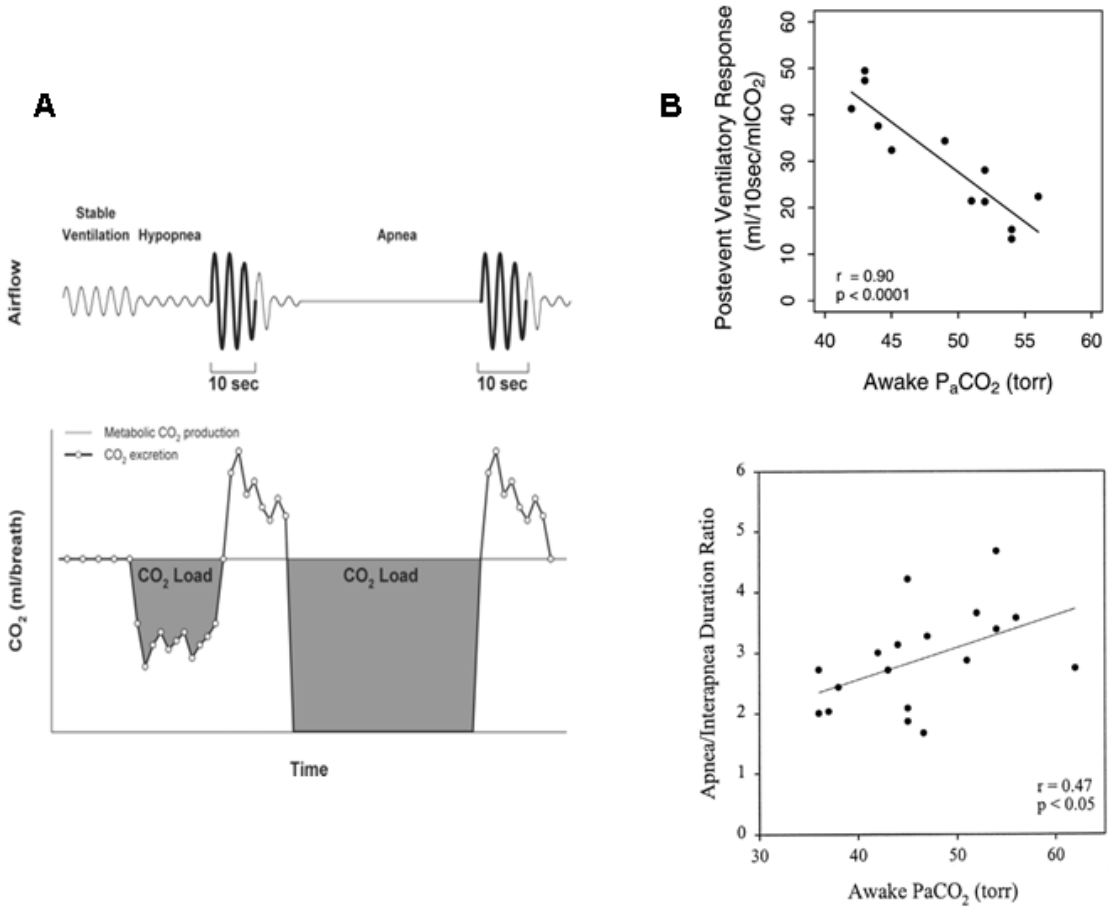
Anomalies respiratoires au cours du sommeil dans le SOH :

La forte prévalence du SAOS dans le SOH (Resta, Foschino-Barbaro et al. 2000; Kessler, Chaouat et al. 2001; Piper and Grunstein 2007) conduit à considérer le SAOS comme un des déterminants de l'hypercapnie diurne. En effet, Ayappa et coll ont montré que le ratio [durée évènement respiratoire obstructif / durée de la reprise ventilatoire] au cours du sommeil était corrélé à la $PaCO_2$ diurne (Ayappa, Berger et al. 2002) (figure 2). La même équipe a mis en évidence que l'intensité de la reprise ventilatoire après un évènement obstructif était inversement corrélé à la $PaCO_2$ diurne (Berger, Ayappa et al. 2002). La correction de l'hypercapnie après traitement par pression positive continue (Lin 1994; Han, Chen et al. 2001) renforce l'hypothèse de la participation du SAOS à l'hypoventilation. Cependant, les troubles du sommeil ne constituent pas la seule hypothèse puisque toutes les études ne mettent pas en évidence une amélioration de l'hypercapnie malgré une correction des obstructions pharyngées (Rapoport, Garay et al. 1986; Banerjee, Yee et al. 2007; Piper, Wang et al. 2008). Enfin, une minorité de patients SOH (15%) n'a pas de SAOS associé.

Contrôle ventilatoire **:** Le quatrième mécanisme impliqué dans l'hypoventilation du SOH est la modification du contrôle ventilatoire. En effet, plusieurs études montrent une diminution de la réponse ventilatoire à l'hypoxie et l'hypercapnie (Lin 1994; Han, Chen et al. 2001)

Figure 2 : Relation entre SAOS et hypercapnie diurne.

2A: D'après Berger et coll. Journal of Applied Physiology 2002 et 2B: D'après Ayappa et coll. Am J Resp Crit Care Med 2002.



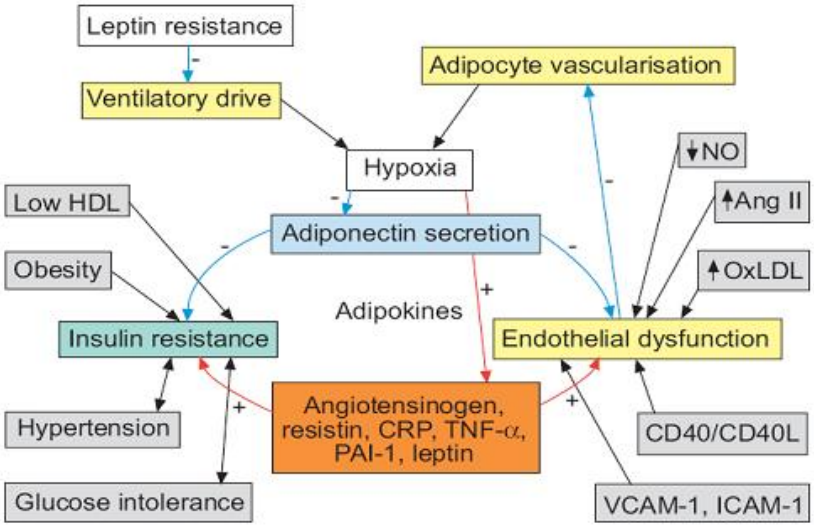
Ainsi, le patient SOH n'augmenterait pas suffisamment sa ventilation pour compenser la charge mécanique qui lui est imposée.

Les causes de cette hyposensibilité au CO_2 ne sont pas encore complètement connues. Les évènements obstructifs au cours du sommeil (décrits ci-dessus) pourraient participer à la diminution de la sensibilité des centres respiratoires. En effet, l'hypercapnie aigüe induite par les évènements obstructifs au cours du sommeil augmenterait la concentration en ion ($HCO3^-$) et altérerait la sensibilité des centres respiratoires (Heinemann and Goldring 1974; Javaheri, Colangelo et al. 1994; Norman, Goldring et al. 2006). Plusieurs études ont aussi montré que la privation de sommeil altérait la sensibilité des centres respiratoires (Cooper and Phillips 1982; White, Douglas et al. 1983). L'hypothèse de prédispositions innées au déficit des centres respiratoires a été évoquée. Cependant, Jokic et coll (Jokic, Zintel et al. 2000), en évaluant les réponses ventilatoires aux CO_2 et O_2 chez des descendants (première génération) de patients SOH, ne mettaient pas en évidence de différence par rapport à des sujets contrôles appariés pour l'âge et l'IMC. Ceci suggère que d'autres mécanismes acquis sont en jeu. La participation de la leptine pourrait jouer un rôle important dans le contrôle de la ventilation. O'Donnell et coll ont mis en évidence chez des souris déficientes pour le gène de la leptine (Ob/Ob) par comparaison à des souris non mutée (wild-type) une obésité, une diminution de la réponse ventilatoire au CO_2 et une hypercapnie (O'Donnell C, Schaub et al. 1999). L'apport exogène de leptine améliorait la ventilation, la réponse ventilatoire et corrigeait l'hypercapnie. Ces expérimentations mettent en évidence le rôle majeur de la leptine dans le contrôle ventilatoire. Chez la souris wild-type rendue obèse par un régime hypercalorique, O'Donnell démontrait également que l'augmentation du taux circulant de leptine était associé à une augmentation de la ventilation pendant le sommeil sans diminution de la réponse ventilatoire au CO_2 (O'Donnell C, Schaub et al. 1999); l'augmentation de la ventilation était adaptée à l'augmentation de la demande métabolique.

Chez l'homme obèse, le déficit congénital en leptine est connu mais rare (Montague, Farooqi et al. 1997) et au contraire les taux de leptine circulants sont le plus souvent élevés par rapport à des populations contrôles (Maffei, Halaas et al. 1995; Dagogo-Jack, Fanelli et al. 1996). Par contre, le taux de leptine dans le liquide cérébro-spinal est beaucoup moins important que le taux plasmatique et le rapport entre le taux de leptine dans le LCR / le taux de leptine plasmatique diminue lorsque le BMI augmente (Caro, Kolaczynski et al. 1996; Schwartz, Peskind et al. 1996). Ces résultats mettent en lumière l'hypothèse de *la résistance centrale à la leptine chez le sujet SOH* participant à une altération de la réponse ventilatoire au CO_2. Phipps and coll (Phipps, Starritt et al. 2002) retrouvent un taux sérique de leptine plus élevé chez des sujets SOH que chez des sujets appariés pour l'IMC et l'IAH ; ce taux était diminué après traitement par VNI. Ces résultats vont dans le sens de l'hypothèse d'une résistance *centrale à la leptine*. À l'opposé, des taux élevés de leptine circulante en périphérie auraient un rôle athérogène et participeraient à la dysfonction endothéliale (Beltowski 2006).

Inflammation de bas grade: L'obésité est associée à une inflammation chronique caractérisée par une production anormale de cytokines. Cette inflammation chronique participerait au développement ou à l'aggravation de la dysfonction métabolique (insulino-résistance) et aux pathologies qui en résultent (Diabète de type 2, syndrome métabolique) (Eckel, Grundy et al. 2005; Hotamisligil 2006). Plusieurs études ont mis en évidence que le SAOS était associé à un risque plus élevé d'avoir un syndrome métabolique indépendamment de l'IMC (Ip, Lam et al. 2002). Les mécanismes qui lient ces pathologies sont complexes, néanmoins toutes majorent le risque cardio-vasculaire en particulier en favorisant la dysfonction endothéliale et l'athérosclérose (Figure 3). Si la littérature est abondante sur l'inflammation de bas grade, le SAOS et le risque cardio-vasculaire (Gozal and Kheirandish-Gozal 2008), peu ou pas d'études à notre connaissance ont étudié l'impact du syndrome obésité hypoventilation sur

Figure 3 : Conséquences de l'hypoxie sur les adipokines, l'inflammation et leur rôle sur la dysfonction endothéliale.
D'après Levy et coll. Eur Resp J 2008 (adapté de Lau DC, Am J Physiol Heart Circ Physiol 2005).



Effect of hypoxia on adipokines and their interactions with insulin metabolism and endothelial function. The main factors involved are leptin, angiotensinogen (Ang), resistin, C-reactive protein (CRP), tumour necrosis factor (TNF)-α and plasminogen activator inhibitor-1 (PAI-1). Leptin promotes (red arrows) insulin resistance and endothelial dysfunction, whereas adiponectin is protective (blue arrows). Obesity, a state of leptin resistance and endothelial dysfunction, also exhibits hypoxia, which is known to activate (red arrow) promoting adipokines and inhibit (blue arrows) adiponectin production. In obesity hypoventilation syndrome, obesity and night-time hypoxia and hypercapnia might act synergistically in producing inflammation at the systemic and vascular level, and in promoting metabolic and cardiovascular dysfunction. HDL: high-density lipoprotein; OxLDL: oxidised low-density lipoprotein; CD40L: CD40 ligand; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; +: activation/ promotion; -: inhibition/protection; ↓ : decrease; ↑ : increase. Modified from [161] with permission from the publisher.

l'inflammation et le risque cardio-vasculaire. Or l'augmentation du travail respiratoire, le rôle athérogène d'un taux plasmatique de leptine élevé (Beltowski 2006), la sévérité des désaturations en oxygène nocturne et de l'hypercapnie pourraient être des facteurs aggravant l'inflammation de bas grade ou induisant une inflammation spécifique (figure 3).

Dysfonction endothéliale : L'athérosclérose est une pathologie inflammatoire chronique engendrée par l'altération de la biologie vasculaire. Elle est responsable d'une mortalité cardio-vasculaire importante et représente une des premières causes de décès dans le monde (Murray and Lopez 1997).

L'endothélium vasculaire est aujourd'hui considéré comme l'élément clé de la régulation de l'homéostasie vasculaire. Sous l'influence de facteurs chimiques circulants et/ou physiques, l'endothélium produit un ensemble de facteurs (Prostacyclines, Endothéline, Endothelium Derived Hyperpolarizing Factors (EDHF), Monoxyde d'azote (NO)) qui régulent la vasomotricité, l'adhésion cellulaire, la prolifération des cellules musculaires lisses péri-vasculaires, l'inflammation de la paroi vasculaire.

En situation non pathologique, le NO joue un rôle clé dans le maintien d'un état quiescent de la paroi vasculaire en inhibant l'inflammation, la prolifération cellulaire et la thrombose. Il agit par nitrosylation des résidus cystéine de certaines protéines (ex : le facteur de transcription NFkB). À l'état quiescent, la contrainte de cisaillement (shear-stress) de la surface des cellules endothéliales par le flux sanguin laminaire est le stimulus physiologique qui induit la production de NO à partir de L-arginine en présence de la NO-synthase-endothéliale (e-NOS) et de cofacteurs. Sur le plan vasomoteur, le NO diffuse à travers la cellule musculaire lisse et active la guanilate-cyclase qui induit une vasodilatation. L'activation endothéliale par des espèces réactives de l'oxygène (ROS) conduit à la production de peroxyde d'hydrogène en présence de superoxyde-dismutase. Ce gaz diffuse

comme le NO dans les cellules et induit la phosphorylation de facteurs de transcription et la production de cytokines conçues pour interagir avec les leucocytes et les plaquettes (figure 4).

L'étendue ou la durée de l'activation endothéliale, par l'inflammation chronique ou par la plupart des facteurs de risque cardio-vasculaire connus (hyperlipidémie, tabac, diabète), induit une dysrégulation de la production de NO et de ROS. La production de ROS peut alors dépasser les capacités anti-oxydantes. Au total, un cercle vicieux entre la production augmentée ROS et la biodisponibilité du NO diminuée s'engage et conduit à l'épuisement des processus anti-inflammatoires de la cellule endothéliale. La dysfonction endothéliale survient alors, et précède l'apparition des lésions visibles en angiographie (Deanfield, Halcox et al. 2007).

L'altération de la fonction endothéliale périphérique est un marqueur pronostic d'évènements cardio-vasculaires (Neunteufl, Heher et al. 2000; Gokce, Keaney et al. 2002; Gokce, Keaney et al. 2003). L'obésité est associée à une dysfonction endothéliale (Arkin, Alsdorf et al. 2008). Dans une cohorte de patients obèses, Apovian et coll ont montré que la dysfonction endothéliale était associée à l'infiltration des macrophages dans le tissu adipeux et à l'inflammation systémique (Apovian, Bigornia et al. 2008). Plusieurs études ont mis en évidence le rôle indépendant du SAOS dans la dysfonction endothéliale (Kato, Roberts-Thomson et al. 2000; Imadojemu, Gleeson et al. 2002; Ip, Tse et al. 2004). L'effet cumulatif du SAOS et de l'obésité suggère que les patients SOH pourraient avoir une dysfonction endothéliale plus altérée que les patients obèses sans hypoventilation. Cependant aucune étude n'a évalué spécifiquement l'impact de la $PaCO_2$ sur la dysfonction endothéliale.

Qualité de vie, vigilance **:** Les patients SOH souffriraient d'une moindre qualité de vie par rapport à des sujets obèses appariés pour l'âge et l'IMC (Hida 2003). Plusieurs études montrent que le SOH est associé à une somnolence diurne importante (Perez de Llano, Golpe et al. 2005) et majorée par rapport à des patients obèses sans hypercapnie

Figure 4 : Dysfonction endothéliale. A & B : D'après Danfield et coll, Circulation 2007.
C : D'après Davignon et coll, Circulation 2004

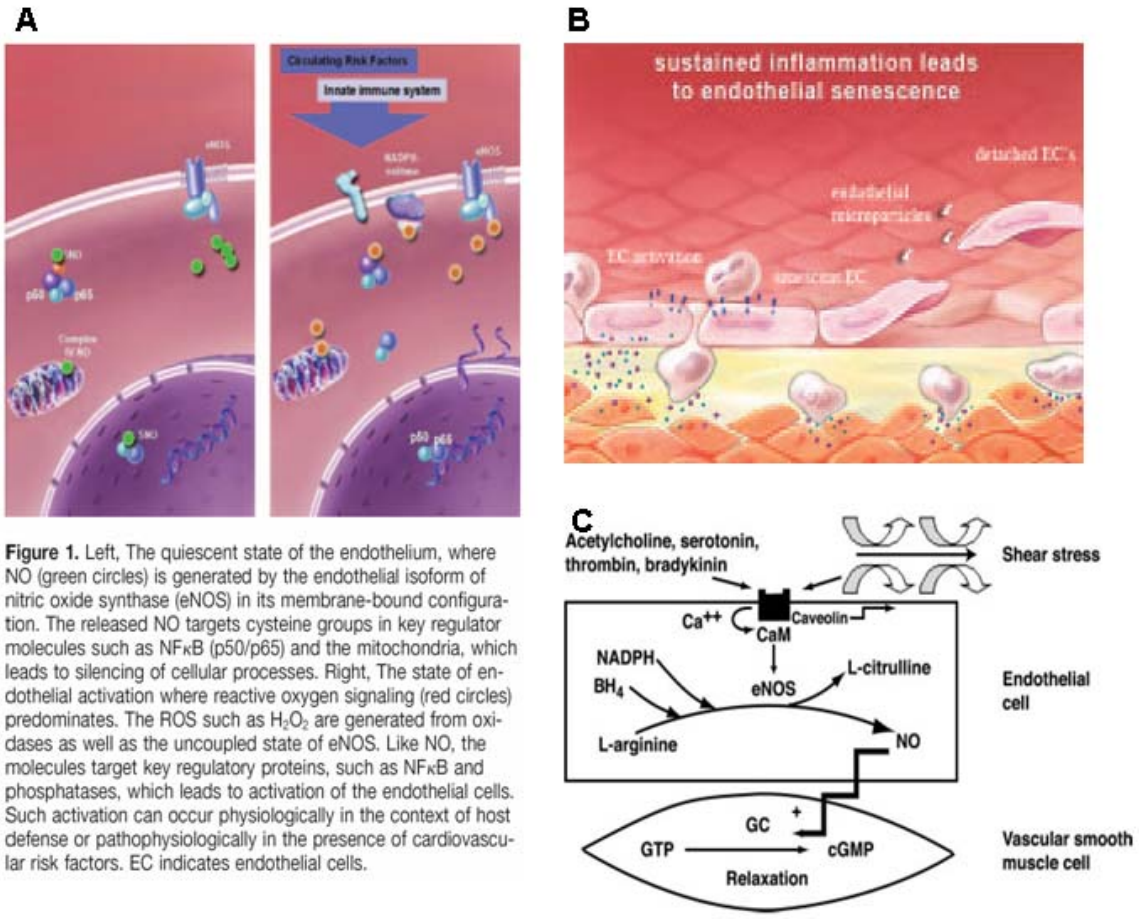


Figure 1. Left, The quiescent state of the endothelium, where NO (green circles) is generated by the endothelial isoform of nitric oxide synthase (eNOS) in its membrane-bound configuration. The released NO targets cysteine groups in key regulator molecules such as NFκB (p50/p65) and the mitochondria, which leads to silencing of cellular processes. Right, The state of endothelial activation where reactive oxygen signaling (red circles) predominates. The ROS such as H_2O_2 are generated from oxidases as well as the uncoupled state of eNOS. Like NO, the molecules target key regulatory proteins, such as NFκB and phosphatases, which leads to activation of the endothelial cells. Such activation can occur physiologically in the context of host defense or pathophysiologically in the presence of cardiovascular risk factors. EC indicates endothelial cells.

(Nowbar, Burkart et al. 2004) ou des patients SAOS appariés pour l'âge et l'IMC (Hida, Okabe et al. 2003). Toutefois, les études réalisées par Nowbar et Coll et Perez de Lano et coll incluaient des patients instables, ce qui limite l'interprétation pour des patients OHS stables. Seule l'étude de Hida et coll incluaient des patients OHS stables, mais aucune évaluation objective de la somnolence n'a été réalisée. La somnolence est un symptôme largement multifactoriel et les mécanismes restent partiellement méconnus (Vgontzas, Bixler et al. 2005); néanmoins plusieurs hypothèses étayent la possibilité d'une somnolence diurne plus importante chez ces patients OHS. L'obésité, le diabète, l'inflammation de bas grade (Vgontzas, Papanicolaou et al. 2000; Vgontzas, Bixler et al. 2005), les troubles respiratoires du sommeil et particulièrement ceux associés au sommeil paradoxal seraient des mécanismes possibles d'hypersomnolence (Kass, Akers et al. 1996; Haba-Rubio, Janssens et al. 2005). Au delà du handicap social et des risques pour la sécurité qu'elle occasionne, l'hypersomnolence par elle-même semble associée à une augmentation du risque cardio-vasculaire (Donadio, Liguori et al. 2007; Lindberg, Berne et al. 2007; Saletu, Sauter et al. 2008).

Co-morbidités: l'hypertension artérielle pulmonaire (prévalence estimée entre 30 et 88%), l'hypertension artérielle systémique (prévalence estimée entre 61 et 79%), l'insuffisance cardiaque congestive (prévalence estimée 20 à 30%), le diabète (prévalence estimée entre 30 et 32%) sont des comorbidités fréquemment associées au SOH (Mokhlesi and Tulaimat 2007). Les estimations de prévalence des co-morbidités sont souvent issues d'études initialement destinées au SAOS (Kessler, Chaouat et al. 1996), avec des petits effectifs (Kessler, Chaouat et al. 2001) ou encore incluant des patients en phase instable (Nowbar, Burkart et al. 2004; Perez de Llano, Golpe et al. 2005). Néanmoins, Berg et coll (Berg, Delaive et al. 2001) dans une étude rétrospective, montrent une utilisation du système de soins (hospitalisations, consultations médicales) plus importante chez des patients SOH par rapport à un groupe contrôle de patients obèses appariés pour l'âge et l'IMC et un groupe de

sujets non-obèses appariés pour l'âge. Ces éléments bibliographiques mettent donc en évidence une co-morbidité cardio-vasculaire importante au cours du SOH. Cependant, le rôle spécifique de l'hypoventilation alvéolaire sur la fonction cardio-vasculaire reste actuellement méconnu.

Mortalité : L'étude récente de Nowbar et coll (Nowbar, Burkart et al. 2004) montre une surmortalité à court terme (18 mois) des patients OHS au décours d'une hospitalisation par rapport à des sujets obèses sans hypoventilation après ajustement pour l'âge, le sexe, l'IMC, les antécédents d'hypothyroïdie, d'insuffisance rénale, de déséquilibre électrolytique et thrombo-embolique. Néanmoins, ces antécédents thrombo-emboliques étaient associées à un risque accrue de décès en analyse bivariée [RR = 4.6 ; 95% CI :1.6 to 13.7). Dans une série rétrospective (Sapala, Wood et al. 2003), le SOH était associé à un risque d'embolie fatale. Ces éléments suggèrent donc une morbi-mortalité d'origine cardio-vasculaire importante dans le SOH.

Traitement par assistance ventilatoire nocturne non-invasive :

Les études interventionnelles ayant pour objectif de traiter les troubles respiratoires nocturnes et diurnes associés au SOH soulèvent des incertitudes sur la méthode optimale d'assistance ventilatoire: S'agit-il de la pression positive continue nocturne (PPC) ou de la ventilation à deux niveaux de pressions (VNDP) ? En effet, la PPC (Han, Chen et al. 2001; Banerjee, Yee et al. 2007; Piper, Wang et al. 2008) et la VNDP avec ou sans oxygénothérapie associée (Masa, Celli et al. 2001; de Lucas-Ramos, de Miguel-Diez et al. 2004; Perez de Llano, Golpe et al. 2005; Piper, Wang et al. 2008) ont été utilisées dans ces études. La PPC, en corrigeant les phénomènes d'obstruction des voies aériennes supérieures pourrait permettre d'améliorer la chémo-sensibilité des centres respiratoires au CO_2 et corriger l'hypoventilation alvéolaire diurne (Han, Chen et al. 2001); Cependant, les troubles respiratoires dans le SOH ne se résument pas au SAOS. Une étude récente (Banerjee, Yee et al. 2007) met en évidence,

chez 43% des patients SOH, des déssaturations nocturnes en O2 persistantes malgré une PPC corrigeant les obstructions pharyngées. Ces patients avaient un IMC plus élevé que les autres (61.6 vs 56.5 kg/m^2). La même équipe a montré que l'efficacité de la PPC était identique à celle de la VNI après trois mois de traitement sur la correction de la $PaCO_2$ diurne et de la vigilance chez des sujets OHS (Piper, Wang et al. 2008). Dans cette étude, les patients qui présentaient des déssaturations en O_2 sous PPC « efficace » avaient été exclus ce qui représentait un biais majeur de recrutement. Plusieurs études ont mis en évidence à court terme et moyen terme l'efficacité de la VNI pour améliorer l'hypoventilation alvéolaire diurne (Masa, CHEST2001 ; De-Lucas-Ramos, Resp Med 2004 ; Perez de Llano, CHEST 2005). Cependant dans l'étude de Perez De Lano (Perez de Llano, CHEST 2005), après au moins un an de traitement par VNI, 54% des patients nécessitaient encore une oxygénothérapie associée à la VNI pour obtenir une SpO2 > 90% ce qui suggère que la VNI pouvait ne pas être parfaitement efficace pour corriger les évènements respiratoires nocturnes (Guo, Sforza et al. 2007) ou que l'indication était inappropriée. Si les modalités optimales du traitement des troubles respiratoires associés au SOH ne sont pas encore complètement définies, la prise en charge de ceux-ci semble essentielle pour diminuer la morbidité (Berg, Delaive et al. 2001) et la mortalité (Perez de Llano, Golpe et al. 2005) de ces patients. *Il faut souligner qu'aucune étude randomisée contre placébo n'est disponible dans le domaine*. Le niveau de preuve actuel des études disponibles reste donc limité sur plusieurs questions importantes.

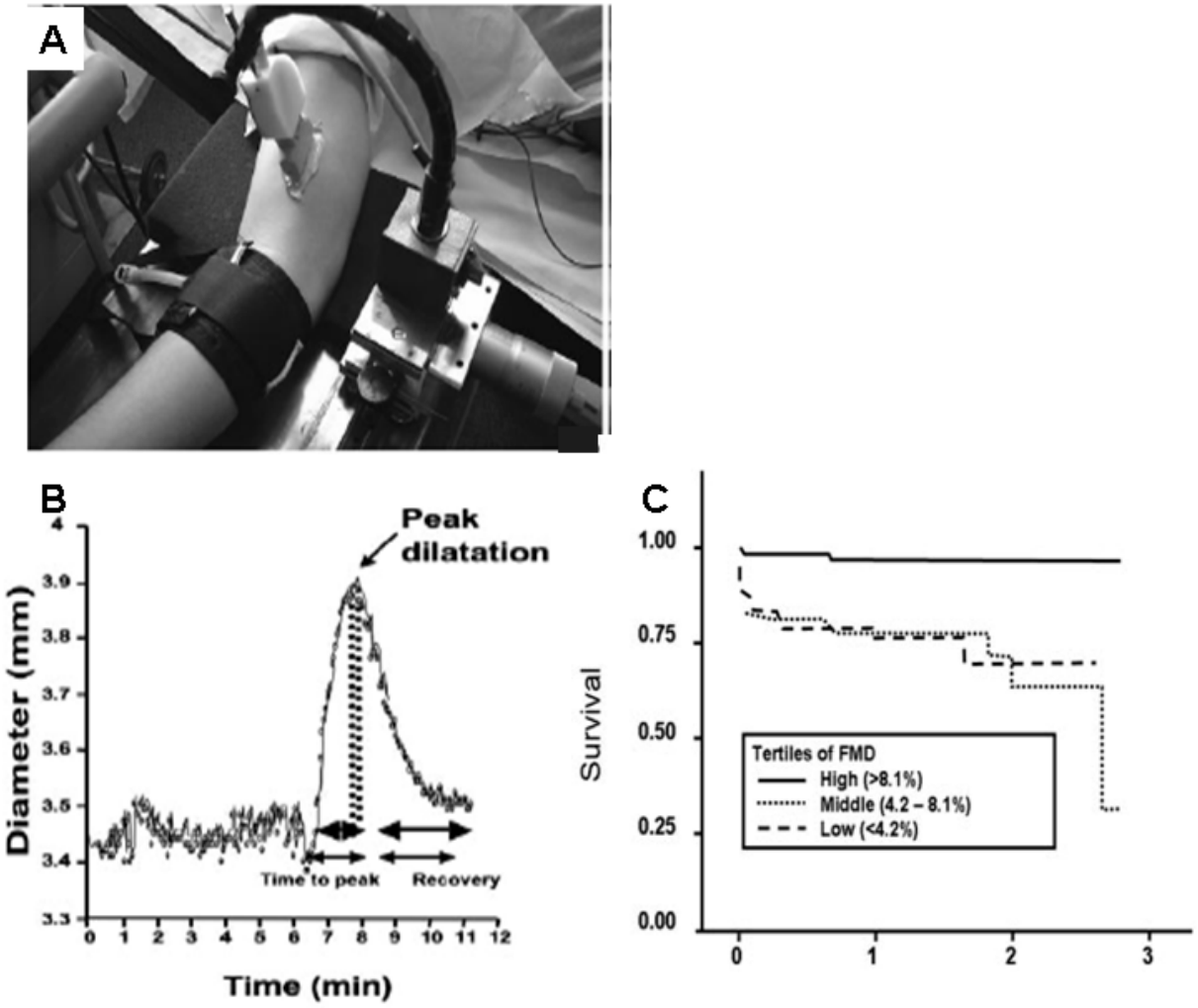
OBJECTIFS DE LA THESE ASSOCIÉS À LA PROBLEMATIQUE DU SYNDROME OBÉSITÉ HYPOVENTILATION (SOH):

La contribution de ce travail de thèse à la problématique du syndrome obésité hypoventilation était, premièrement, d'évaluer l'impact spécifique de l'hypoventilation du SOH sur l'inflammation et la dysfonction endothéliale (marqueurs majeurs du risque cardio-vasculaire (cf Etude N°1)). Deuxièmement, d'évaluer objectivement la vigilance des patients SOH et l'efficacité à court terme du traitement par VNI (étude ouverte) (cf Etude N°2). Enfin, d'évaluer au moyen d'une étude randomisée contrôlée l'effet d'un mois de traitement par VNI nocturne sur cette dysfonction endothéliale et la vigilance diurne. (cf Etude N°3)

MISE AU POINT METHODOLOGIQUE : EVALUATION DE LA FONCTION ENDOTHELIALE PAR LA MESURE DE LA PLETHYSMOGRAPHIQUE DE L'HYPERHEMIE REACTIONNELLE. (Reactive Hyperhemia-Peripheral Arterial Tonometry [RH-PAT]

L'endothélium vasculaire est aujourd'hui considéré comme l'élément clé de la régulation de l'homéostasie vasculaire et l'altération de sa fonction est un marqueur pronostic d'évènements cardio-vasculaires (Neunteufl, Heher et al. 2000; Gokce, Keaney et al. 2002; Gokce, Keaney et al. 2003). Le monoxyde d'azote (NO), produit par les cellules endothéliales, est un facteur prépondérant dans le maintien d'un état quiescent de la paroi vasculaire. Déterminer sa biodisponibilité permet d'estimer la fonction endothéliale. La dilatation artérielle induite par l'afflux brutal du flux sanguin (shear-stress) après une ischémie par occlusion est pour partie dépendante de la production de monoxyde d'azote (NO) et de l'effet relaxant du NO sur les cellules musculaires lisses adjacentes. La mise en évidence d'une diminution de la capacité de dilatation « flux-médiée » est un marqueur admis de la dysfonction endothéliale (Cox, Vita et al. 1989; Nabel, Selwyn et al. 1990). La vasodilatation « flux-médiée », post-ischémique, de l'artère brachiale mesurée par ultra-sons **(FMD : Flow mediated vasodilation)** est la technique de référence non-invasive pour mesurer la fonction endothéliale (Corretti, Anderson et al. 2002; Pyke and Tschakovsky 2005; Deanfield, Halcox et al. 2007). Joannides et coll. (Joannides, Haefeli et al. 1995) avaient montré l'implication prépondérante du NO dans cette réponse**.** Cette technique est opérateur dépendante et sa réalisation nécessite de respecter une procédure très standardisée (5 minutes d'occlusion et mesure faite en amont de l'occlusion) et d'avoir une expérience importante (Corretti, Anderson et al. 2002) pour limiter la variabilité inter-patient. Il existe une large gamme de valeur de FMD rapportée dans la littérature chez le sujet sain (de 2 à 19%) (Pyke and Tschakovsky 2005). Ceci rend difficile l'interprétation des valeurs de la FMD en situation clinique.

Figure 7 : Vasodilatation flux-médiée (FMD). A : Méthode . B : Vasodilatation post-ischémique (A et B d'après Danfield et coll Circulation 2007. C : Probabilité de survie en fonction du % de FMD (d'après Gocke N et coll. JACC 2003)



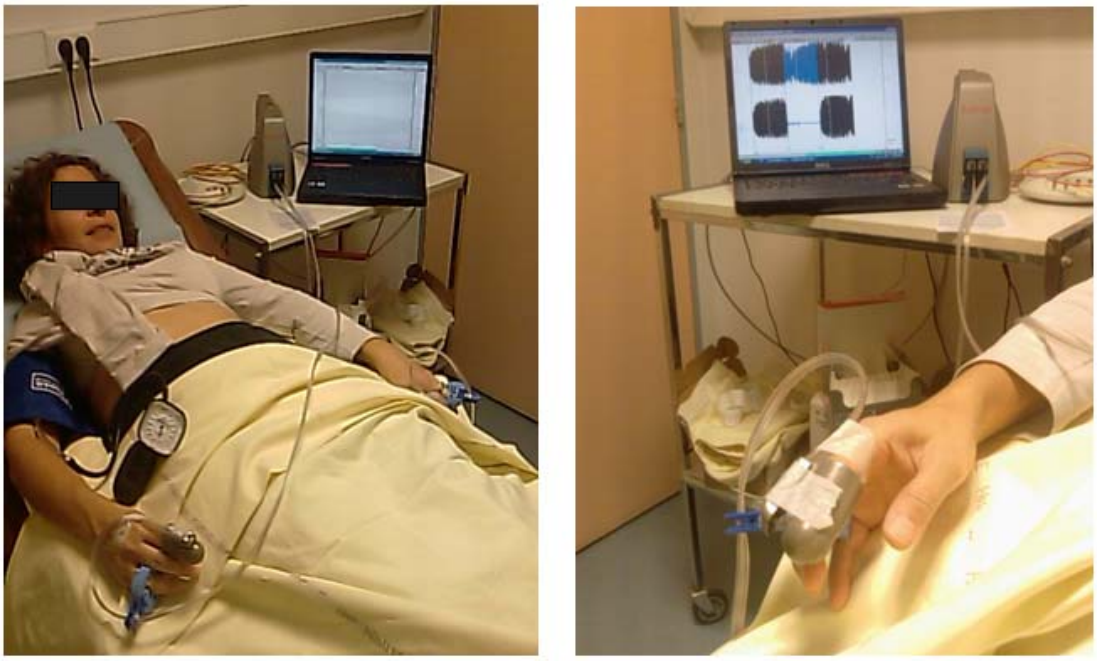
Néanmoins, une valeur de FMD de 10% est généralement admise comme normale. De plus, Gokce et coll ont montré qu'une vasodilatation flux-médiée inférieure à 8,1% était associée à un risque plus important d'évènements cardiovasculaires à court terme (OR=9.0 ; IC à 95% [1.2-68]) et long terme (OR=9.5, IC à 95% 2.3-40) (Gokce, Keaney et al. 2002; Gokce, Keaney et al. 2003). Malgré ces difficultés d'interprétation de la FMD, cette dernière est actuellement la mesure non-invasive la mieux validée pour prédire les évènements cardiovasculaires incidents (figure 7).

La mesure pléthysmographique de la variation du volume sanguin digital secondaire à une ischémie de l'avant bras (**index Reactive Hyperhemia-Peripheral Arterial Tonometry : index RH-PAT**) est une technique récente, développée pour évaluer de façon moins opérateur dépendante la vasodilatation NO-médiée (Bonetti, Pumper et al. 2004; Nohria, Gerhard-Herman et al. 2006). Plusieurs études ont montré que l'index RH-Pat était corrélé au pourcentage de FMD (Kuvin, Patel et al. 2003; Dhindsa, Sommerlad et al. 2008). De plus, Bonnetti et coll avaient retrouvé un index RH-PAT abaissé chez des sujets présentant une dysfonction endothéliale coronaire mesurée par injection d'acétylcholine (Bonetti, Pumper et al. 2004). Enfin, dans une large cohorte de près de 2000 patients, l'index RH-PAT est significativement lié aux facteurs classiques de Framingham des risques cardio-vasculaires *(Hamburg, Keyes et al. 2008)*.

Principe de la mesure de l'index RH-PAT :

Cette mesure est faite par un appareil *Endo-PAT 2000* (Itamar Médical, Caesarea, Israel). Deux sondes de pléthysmographie sont placées sur les index des deux mains (figure 8). Chaque sonde est composée d'une membrane en latex placée dans un doigtier. La membrane est gonflée par un micro-compresseur intégré à l'appareil et maintenu à une pression proche de la pression artérielle diastolique. Les sondes sont ainsi parfaitement

Figure 8 : Mesure de l'hyperhémie digitale réactionnelle post ischémique acquise par l'appareil Endo-PAT 2000. Itamar Médical, Caesarea, Israel.



adaptées au volume des doigts et permettent de mesurer les variations de l'amplitude de l'onde de pouls (figure 9), qui sont un reflet des variations du volume sanguin capillaire.

Le protocole consiste à réaliser une épreuve de 5 minutes d'ischémie d'un des deux avant bras par occlusion complète de l'artère brachiale en gonflant un brassard 60 mmHg au-dessus de la pression artérielle systolique avec un minimum de 200 mmHg. L'amplitude de l'onde de pouls est enregistrée, en continu, des deux côtés, pendant 15 minutes : 5 minutes avant l'occlusion [état basal], pendant 5 minutes d'occlusion [ischémie] et durant 5 minutes en post occlusion [hyperhémie]) (figure 10A). Le calcul de l'index RH-PAT est fait automatiquement par le logiciel couplé à l'appareil. L'index RH-PAT est le rapport entre la moyenne de l'amplitude de l'onde de pouls calculée entre 90 et 120 secondes après le relâchement de l'occlusion et la moyenne de l'amplitude de pouls des 210 secondes qui précédent l'occlusion. Afin d'éliminer un effet vasomoteur neurovégétatif systémique confondant, cet index est normalisé par rapport au côté controlatéral (figure 10B). Ceci constitue une supériorité méthodologique considérable par rapport à l'échographie qui évalue un seul coté. Des études utilisaient directement ce rapport comme marqueur de la dysfonction endothéliale. Plus récemment, Naomi et coll (Hamburg, Keyes et al. 2008) ont montré que la transformation de cet index en son logarithme naturel était encore mieux corrélé aux risques cardiovasculaires traditionnels.

Intérêts et limites de la mesure de l'index RH-PAT :

Les principaux intérêts de la mesure de l'index RH-PAT est qu'elle est simple et opérateur-indépendante. De plus, elle permet contrairement à la **FMD** (technique de référence – *(Pyke and Tschakovsky 2005)*, de contrôler l'activité neurovégétative puisque l'index PAT est ajusté à la variation de l'amplitude de l'onde de pouls controlatérale.

Par contre, deux conditions essentielles distinguent l'évaluation de l'hyperhémie réactionnelle post-ischémique mesurée par FMD ou par pléthysmographie digitale (RH-PAT).

Figure 9 : Amplitude de l'onde de pouls acquise par l'appareil Endo-PAT 2000. Itamar Médical, Caesarea, Israel .

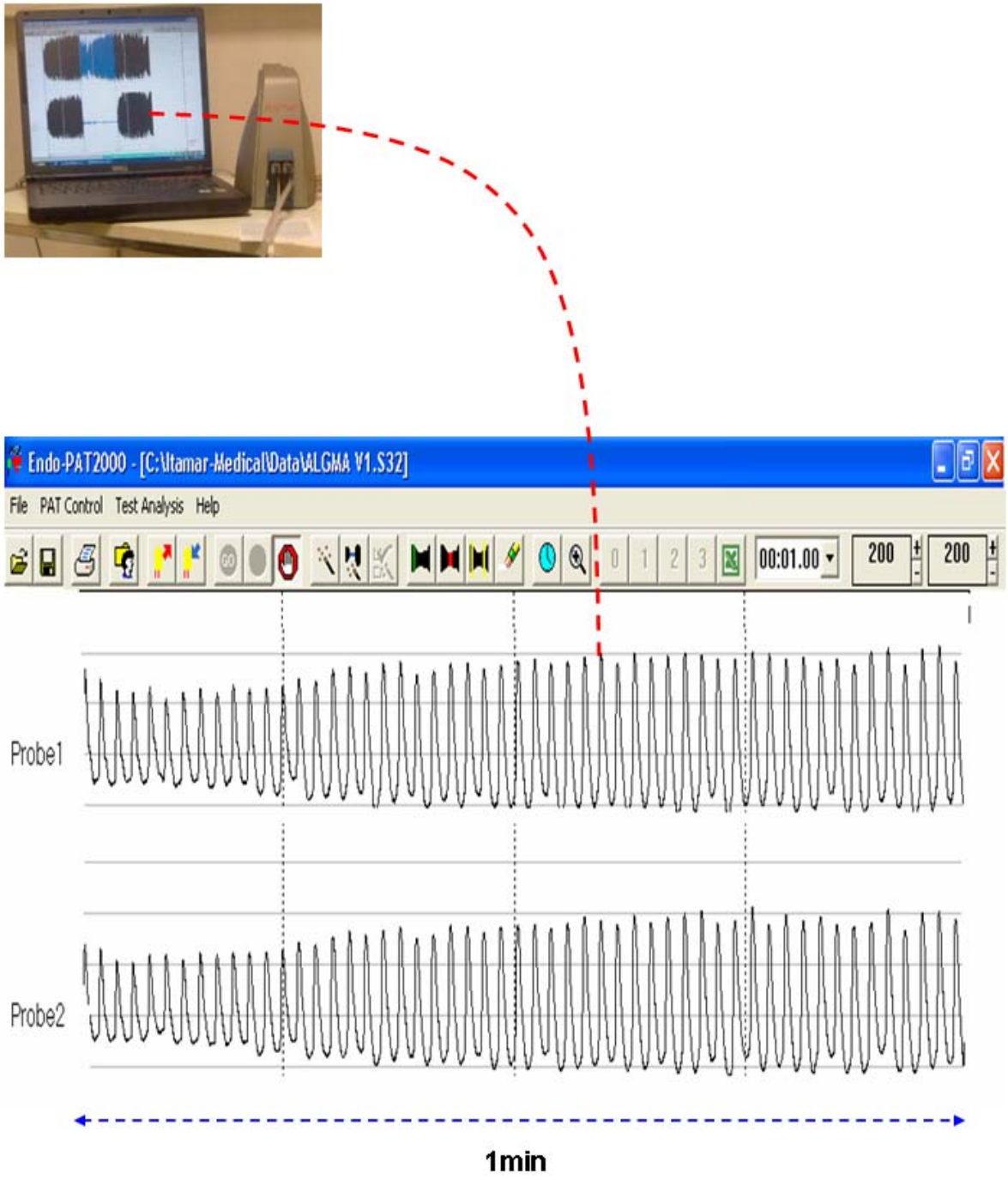
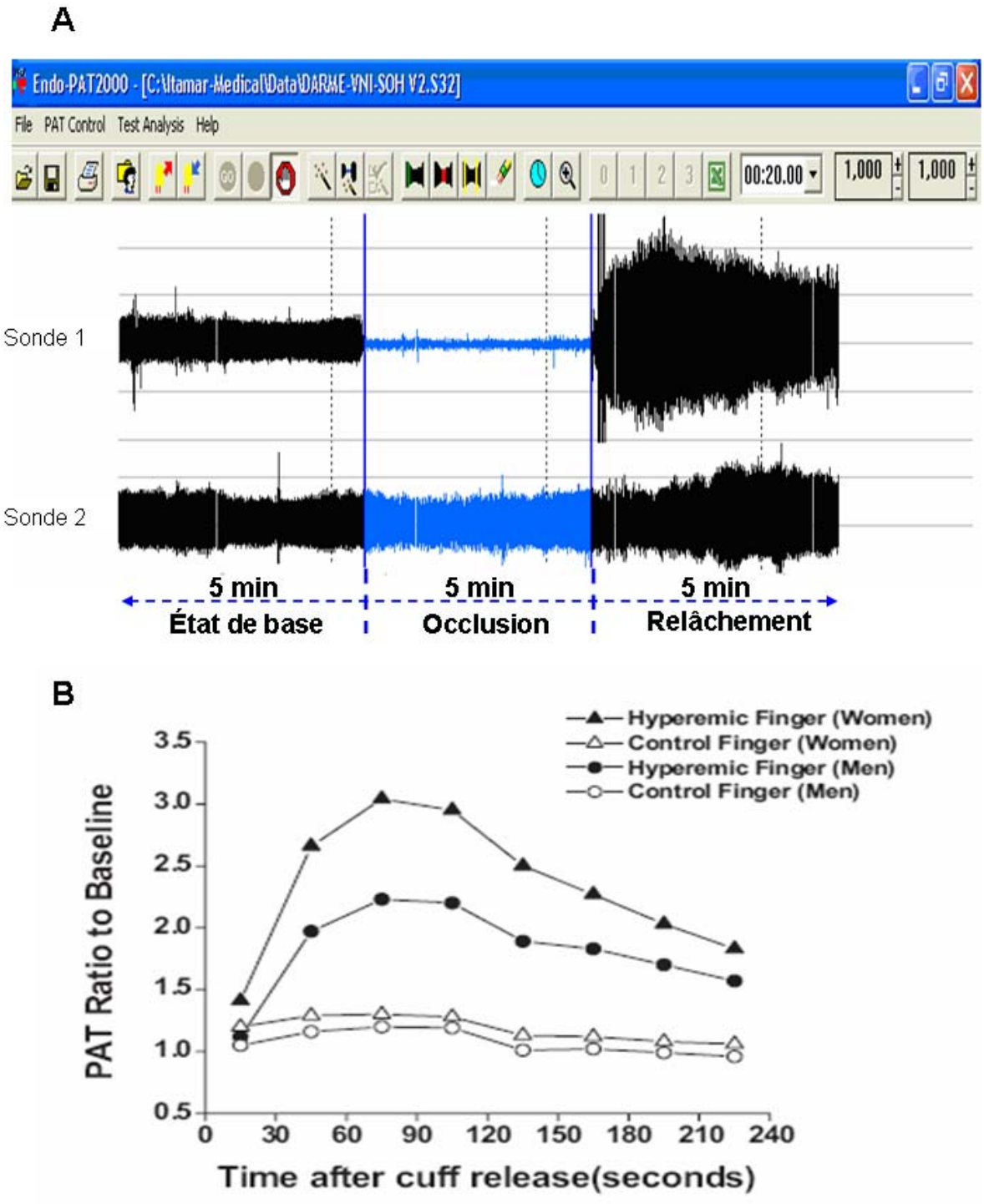


Figure 10 : A : Signal de l'onde de pouls acquis sur l'index du membre soumis à l'ischémie (sonde 1) et sur l'index du membre controlatéral sans ischémie (sonde 2). B : Analyse des deux signaux pour normaliser la dilatation post occlusion par rapport au « contrôle » (membre sans ischémie). D'après Naomi et coll. Circulation 2008.



Premièrement, la FMD mesure une vasodilatation des vaisseaux de conduction alors que la pléthysmographie digitale mesure la vasodilatation capillaire (Dhindsa, Sommerlad et al. 2008).

Deuxièmement, la mesure de la dilatation par FMD est faite en amont de la zone d'ischémie alors qu'elle est faite dans la zone ischémique par pléthysmographie. Des substances produites par le métabolisme des tissus ischémiés pourraient altérer la mesure spécifique de la dilatation NO-dépendante. Cependant, Nohria et coll ont montré que l'index RH-PAT était diminué de près de 50% après perfusion d'un inhibiteur de la NO-synthase (Nitro-L-Arginine Methyl Ester (L-NAME)), mettant en évidence qu'au niveau capillaire la vadodilation flux médiée est bien NO-dépendante et relativement peu influencée par l'ischémie préalable (Nohria, Gerhard-Herman et al. 2006).

Conclusion:

La mesure de l'hyperhémie digitale post-ischémique (RH-PAT) est une technique d'évaluation de la vasodilatation flux-médiée NO-dépendante. Cette technique permet donc une évaluation valide et non opérateur-dépendante de la fonction endothéliale.

ETUDE N°1 : DYSFONCTION ENDOTHÉLIALE ET INFLAMMATION SYSTEMIQUE SPÉCIFIQUE DANS LE SYNDROME OBÉSITÉ HYPOVENTILATION

ENDOTHELIAL DYSFUNCTION AND SPECIFIC SYSTEMIC INFLAMMATION IN OBESITY HYPOVENTILATION SYNDROME

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Prérequis : Le syndrome obésité-hypoventilation (SOH) est associé à une morbi-mortalité cardiovasculaire et métabolique démontrée. Ceci pourrait être expliqué par une inflammation spécifique et une dysfonction endothéliale majorant le risque cardiovasculaire.

Objectif : Comparer le statut inflammatoire et la fonction endothéliale chez des patients SOH et obèses appariés pour l'âge, le sexe et l'IMC.

Méthodes : Après une polysomnographie nocturne, la réalisation de gaz du sang diurnes, la fonction endothéliale était évaluée par tonométrie artérielle périphérique (index de vasodilatation post-ischémique (index-TAP)). Les paramètres inflammatoires (TNFα, IL-6, IL-8, IL-10, Leptine, MCP-1 *(monocyte chemotactic protein-1)*, RANTES (*Regulated upon Activation, Normal T-cell Expressed, and Secreted*) et anti-inflammatoires (adiponectine et IL1-RA) étaient dosés en multiplex.

Résultats : 14 patients SOH (IMC: 41± 5.2kgm^{-2}, PaCO2 : 6.5±0.4kPa, 57±10 ans) et 39 obèses simples (IMC: 40.9±5.1kgm^{-2}, PaCO2 : 5.3±0.4 kPa, 56±10 ans) étaient inclus. La $PaCO_2$ était significativement plus élevée chez les SOH ($p<0.001$). Le taux sérique de RANTES était significativement plus élevé chez les SOH que chez les obèses (55.9±55.3 *vs* 23.3±15.8 ng/ml, respectivement ; $p=0.003$), il était corrélé à la $PaCO_2$ ($r=0.53$, $p=0.0001$).

Le taux d'adiponectine était significativement plus bas chez les sujets SOH (7.6±2.9 *vs* 13.7±7.8µg/ml, p=0.004). La fonction endothéliale, évaluée par l'index-TAP, était significativement plus altérée chez les sujets SOH (p=0.006). L'index-TAP était corrélé à la PaO_2 (r=0.36 p=0.01) et inversement corrélé à la $PaCO_2$ (r=-0.37 p=0.009).

Conclusion: Par rapport à l'obésité simple, le SOH est associé à une augmentation de RANTES, une diminution de l'adiponectine et une dysfonction endothéliale plus importante. Ces trois facteurs sont classiquement liés à un risque cardiovasculaire plus important.

Endothelial dysfunction and specific systemic inflammation in Obesity Hypoventilation Syndrome

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At a Glance Commentary:

Scientific knowledge: Obesity hypoventilation syndrome is associated with an increased cardiovascular morbidity and mortality. Little is known on what moderate chronic hypoventilation adds to obesity as regard systemic inflammation, adipokines production and endothelial dysfunction.

What does the study add in the field: This study showed a much more severe endothelial dysfunction and a specific pattern of systemic inflammation in obesity hypoventilation compared to usual obese patients matched for age, sex and BMI.

Running Head: Obesity Hypoventilation syndrome

Running Title: Endothelial dysfunction in obesity hypoventilation

Word count for the body of the manuscript:

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This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org"

ABSTRACT (246 words)

Background: Obesity hypoventilation syndrome (OHS) is associated with increased cardiovascular morbidity and mortality. Little is known on what daytime moderate chronic hypoventilation adds to obesity on systemic inflammation, adipokines production and endothelial dysfunction. **Aim:** To compare inflammatory status and endothelial function in OHS *versus* "uncomplicated obese" patients (UO), matched for BMI, age and sex. **Methods:** Diurnal blood gazes, respiratory function, CO_2 ventilatory response, overnight polysomnography and endothelial function, measured by reactive hyperemia peripheral arterial tonometry (RH-PAT), were assessed. Inflammatory (Leptin, RANTES, MCP1, IL6, IL8, TNFα, Resistin) and anti-inflammatory (adiponectin and IL1-RA) cytokines were measured by commercially available multiplex beads immunoassays. **Results:** 14 OHS (BMI: 41±5.2 kgm^{-2}, PaCO2: 6.5±0.4 kPa, age: 57±10 years) and 39 UO patients (BMI: 40.9±5.1 kgm^{-2}, PaCO2: 5.3±0.4 kPa, 56±10 years) were included. $PaCO_2$ was significantly higher in OHS ($p<0.0001$) whereas vital capacity and CO_2 chemoresponsiveness were lowered ($p<0.02$). Serum RANTES levels were significantly higher in OHS (55.9±55.3 *vs* 23.3±15.8 ng/ml; $p=0.003$) and correlated with daytime $PaCO_2$ ($r=0.53$ $p=0.0001$). Serum adiponectin was lower in OHS (7.6±2.9 *vs* 13.7±7.8µg/ml, $p=0.004$). Endothelial function was significantly more impaired in OHS ($p=0.006$) compared to UO and negatively correlated with $PaCO_2$ ($r=-0.37$ $p=0.009$) and positively with PaO2 ($r=0.36$ $p=0.01$). **Conclusion:** Compared to "uncomplicated obesity", OHS is associated with a specific increase in the pro-atherosclerotic RANTES chemokine, a decrease in the anti-inflammatory adipokine adiponectin and impaired endothelial function. These three conditions are known as being strongly associated with an increased cardiovascular risk. *[The clinical trial registration number is NCT00603096]*

INTRODUCTION

The obesity-hypoventilation syndrome (OHS) is defined by obesity (BMI≥30 kg/m^2), and chronic alveolar hypoventilation resulting in daytime hypercapnia ($PaCO_2$ >45 mmHg), after exclusion of all other causes of alveolar hypoventilation (severe obstructive or restrictive diseases, chest wall disorders, neuromuscular diseases) (1, 2). Patients suffering from OHS are considered as much more severely ill than those with "simple obesity". The use of health-care resources is increased compared to usual obese patients (3) and OHS is carrying a momentous cardiovascular morbidity (1, 4). Compared with obese control subjects, patients with OHS are statistically much more likely to have been diagnosed with congestive heart failure (OR 9; 95% CI, 2.3–35), angina pectoris (OR, 9; 95% CI, 1.4–57.1) and cor pulmonale (OR, 9; 95% CI, 1.4–57.1) (3). In obese, prospectively followed during 18 months after hospital discharge, OHS patients had a higher rate of death compared to simple obesity (23% versus 9%) (5).

Uncomplicated obesity is a disease state characterized by chronic systemic low grade inflammation and associated inflammatory changes in the adipose tissue (6-9). OHS adds up on obesity several extra stimuli that might increase the burden of chronic inflammation and as a consequence its proatherogenic effects. Work of breathing is higher in OHS compared to obese without the disease (10). It has been demonstrated that adding a load to the respiratory system is resulting in proinflammatory cytokines release (11, 12). Up to 85% percent of OHS patients are exhibiting sleep apnea, a disease condition, linked with cardiovascular diseases (13). Furthermore, mild hypoxaemia during daytime and extreme oxygen desaturations during REM sleep with concomitant repeated acute increases in PaCO2 are OHS landmarks. In

animal models, hypoxia of the adipose tissue, resulting from adiposity per se, has been shown as associated with local fat inflammation (14). Such an aggravation of inflammatory state in adipose tissues is then conceivable in OHS. Finally, the pivotal mechanism underlying daytime hypercapnia in OHS is the reduction in ventilatory drive owing to central leptin resistance (15, 16). Central leptin resistance results in high plasmatic levels of leptin and preservation of peripheral actions of leptin such as increased sympathetic outflow and cytokine production (17).

Thus, it seemed reasonable to anticipate that OHS compared to simple obesity should be associated with more systemic inflammation and with an increased production of proinflammatory adipocytokines. Apovian et al. have recently demonstrated that local adipose tissue inflammation is linked with endothelial dysfunction (6). Our working hypothesis was that OHS patients would exhibit a specific profile of inflammation and a more severe endothelial dysfunction than simple obesity. Thus, we aimed to compare inflammatory status and endothelial function in OHS *versus* "uncomplicated obese" patients (UO), matched for BMI, age and gender.

MATERIALS AND METHODS

See the one line supplement for additional information on the methods.

Patients:

Patients with obesity hypoventilation syndrome (OHS) were eligible when aged between 20 and 75 years, in stable state for more than one month and non-hospitalized at the entrance in the study. Body mass index (BMI) had to be more than 30kg/m^2, $PaCO_2$ more than 6kPa, without any significant airway obstruction (FEV1/FVC <70%), history of heart failure or progressive neuromuscular disease. Control subjects, (uncomplicated obesity group: UO), were recruited by advertisement in newspaper or addressed to the sleep laboratory for suspicion of OSAS. The study was approved by the university hospital ethics committee. All patients signed a written informed consent. *[The clinical trial registration number was NCT00603096]*

Study design:

Patients underwent an overnight polysomnography. After waking up, in fasting state, a peripheral blood sample was drawn and endothelial dysfunction was assessed by reactive hyperhemia with finger plethysmographic methodology (RH-PAT). After breakfast, Epworth sleepiness scale, pulmonary function tests, arterial blood gases analysis, and ventilatory response to CO_2 were performed.

Study procedures:

Polysomnography (PSG):

An overnight PSG was performed during spontaneous breathing in order to characterize abnormal respiratory events during sleep according to standard criteria (18, 19) as previously described (20, 21).

Biomarkers dosages:

After peripheral blood sampling, plasma glucose and serum triglycerides levels were measured on automat (Modular 700, Roche, Meylan, France). Serum insulin was measured using a radio-immunometric sandwich assay (CIS bio international, Gif-Sur-Yvette, France). Serum HS-CRP level was measured using automated immunonephelometry (Behring Nephelometer II Analyzer, Dade Behring, Germany).

Leptin, RANTES, MCP1, IL6, IL8, TNFα, Resistin, Adiponectin and IL1-RA were measured by commercially available multiplex beads immunoassays (Fluorokine MAP Multiplex Human Cytokine Panel and Obesity Panel, R&D Systems, Minneapolis, USA) and read by the Bioplex 200 array reader (Bio-Rad Laboratories, Hercules, CA, U.S.A.) which uses Luminex xMAP™ Technology (Luminex Corporation, Austin, TX, U.S.A.).

Respiratory function and ventilatory responses to CO_2:

Spirometry and plethysmography were measured according to the European Respiratory Society recommendations (22). CO_2 chemo-sensitivity was assessed using Read's method (23).

Endothelial Dysfunction:

Endothelial dysfunction was assessed by reactive hyperhemia with finger plethysmographic methodology (RH-PAT) using Endo-PAT device (Itamar Medical Ltd, Caesarea, Israel) as previously described (24, 25). RH-PAT index was calculated as the natural logarithm of the average amplitude of PAT signal after 90 to 120 second deflation divided by average amplitude of the PAT signal during 210 second prior the cuff inflation (26).

Statistical analysis:

Results are expressed as mean ± SD. NCSS 97 (Kaysville, Utah, USA) software was used for the statistical analysis. Comparison between OHS and "uncomplicated obesity" groups used unpaired parametric (T-test) or non parametric (Mann-Withney) tests according to variables normality of distribution. Qualitative variables were compared using Chi-squared test. Correlations were performed using non parametric correlation Spearman test or parametric correlation Pearson test.

RESULTS

Patients characteristics (Table 1-3):

Fourteen obesity hypoventilation syndrome patients (OHS) matched for sex, age, BMI with 39 "uncomplicated obese" (UO) were included. Anthropometrics, blood pressure and lung function characteristics are reported in Table 1. OHS had significantly impaired lung volumes, blood gases and CO_2 ventilatory responses. Compared to UO (Table 2), OHS had comparable severity in obstructive sleep apnea syndrome as expressed by AHI (40 ± 28 for UO vs. 57 ± 54 for OHS) but they spent more time during sleep with SpO_2 less than 90% and had lower mean and nadir nocturnal SpO_2. As shown in table 3, OHS were more frequently treated for hypertension and had higher glycated hemoglobin. HOMA index reflecting insulin resistance was three fold higher in OHS. Low density lipoprotein levels were also significantly lower in OHS. Finally, there was a trend for a higher percentage of patients treated with glucose lowering medications and statins in OHS compared to UO.

Inflammatory and anti-inflammatory status (figures 1,2):

$_{HS}$-CRP tend to be elevated in OHS compared to UO (11.1 ± 10.9 vs. 5.7 ± 5.5 $mg.l^{-1}$, p=0.09). Serum level of RANTES, a pro-atherosclerotic chemokine, was also significantly higher in OHS (55.9± 55.3 vs 23.3 ± 15.8 ng/ml, p=0.003). Others pro-inflammatory cytokines, chemokines and leptin levels were not different between the two groups. Adiponectin, an anti-inflammatory adipokine was significantly lower in OHS compared to UO (7606 ± 2977 vs 13660 ± 7854, ng/ml p=0.004).

Predictive factors of endothelial dysfunction in OHS (figures 3):

As shown in figure 3A, endothelial function was significantly more impaired in OHS patients than in UO patients (RH-PAT index: 0.22 ± 0.06 versus 0.51 ± 0.11 respectively, p= 0.006). RH-PAT index was significantly correlated with $PaCO_2$ (r=-0.37 p=0.009, figure 3B) and PaO2 (r=0.36 p=0.01, figure 3D). Moreover, RH-PAT index was correlated with FVC (expressed as % predicted value) (r=0.43, p=0.003) and TLC (expressed as % predicted value) (r=0.34, p=0.03). RANTES was also significantly correlated with $PaCO_2$ (r=0.53 p=0.0001, figure 3C) whereas PaO2 was not.

DISCUSSION

In this controlled study, the first comparing inflammatory status and endothelial function in obesity hypoventilation syndrome and simple obesity, proatherogenic cytokine RANTES increased significantly whereas insulin sensitizing and antiatherogenic adipokine adiponectin was significantly reduced in OHS patients. Consistently, endothelial function was significantly more impaired in obesity hypoventilation syndrome than in uncomplicated obesity. Daytime PaO_2 and $PaCO_2$ were significantly related to endothelial dysfunction.

Not only obesity but many other systemic diseases like diabetes, COPD, cardiovascular diseases or sleep apnea are associated with an underlying pro-inflammatory state (7, 27, 28). Although sharing what is generally called 'low-grade' or 'chronic' inflammation, all these diseases have a different time course evolution and prognosis. Moreover, obesity per se, is not a homogeneous condition. It would be useful to distinguish subclasses of inflammation among obese populations reflecting different risks and allowing tailoring specific anti-inflammatory treatments. The present study is the first to compare the serum profiling of an extensive panel of 9 chemokines and adipokines by multiplex assay in OHS and obese non OHS patients. Of all chemokines tested, only RANTES was seen to be elevated in OHS. RANTES is involved in atherogenesis (29), has been demonstrated as related to coronary heart disease risk in middle age subjects (30), is elevated in symptomatic coronary artery disease (31) and is acutely increased in unstable angina pectoris during severe ischemic symptoms (32). RANTES is expressed by activated platelets, lymphocytes and adipocytes. As a result circulating RANTES concentrations are elevated in obese rats (33), during human obesity, impaired glucose tolerance (IGT) and type 2 diabetes (34). Our study design did not allow identifying the main source of plasmatic RANTES but we can speculate on more visceral fat inflammation and/or significantly more activated platelets as landmark characteristics of OHS metabolic and cardiovascular profile. Hosegai et al. (14) have shown

that local adipose tissue hypoxia dysregulates adipocytokines production. In the present study, OHS patients exhibited significantly more severe daytime hypoxaemia and nocturnal oxygen desaturations compared to matched obeses. Thus, mild hypoxaemia during daytime and during sleep, the later representing an additional hypoxic insult, might favor RANTES production by adipose tissue. On the other hand, the relative risk of thromboembolism is 4-fold higher in OHS compared to uncomplicated obesity (5), suggesting a pro-coagulant state in OHS potentially linked to platelet activation. Platelets are the main source of RANTES and the interplay between RANTES and platelets allow triggering monocytes arrest, a determinant pathway in atherosclerosis initiation (35). Further studies directly addressing local fat inflammation and platelets activation in the specific population of OHS are required for elucidating the respective part of these two mechanisms.

Whereas proatherogenic RANTES increased significantly, insulin sensitizing and antiatherogenic adipokine adiponectin was significantly reduced in our OHS patients. Obesity-related cardiovascular diseases are associated with decreased plasma levels of adiponectin (36, 37). Hypoadiponectinemia correlates significantly and independently with coronary artery disease (38) and more generally plasma adiponectin levels are an inverse predictor of cardiovascular outcome (36). In our study, as for RANTES, the severity of sleep apnea and REM sleep related desaturations together with moderate daytime hypoxaemia, may play a major role as it has been demonstrated that local hypoxia at the abdominal fat level reduced adiponectin release by the adipocytes (14). Evidencing for the first time that hypoadiponectinemia is further reduced in OHS compared to non OHS obese subjects is in accordance with the OHS observational cohorts data, with cardiovascular diseases being more prevalent and participating to increased mortality of OHS patients (1, 5). We also found in our study that OHS patients used more antihypertensive agents, had higher insulin resistance and were more frequently treated by glucose lowering medications. However, strong evidence

base medicine is lacking in this field and epidemiological studies in different subclasses of obesity are desirable to more clearly delineate the respective metabolic and cardiovascular risk of different subgroups of obese subjects with and without daytime hypoventilation (39).

Having demonstrated a specific pattern of inflammation and a decrease in adiponectin levels, aggravated endothelial dysfunction in OHS patients appeared as expected (40). This is supporting a particular cardiovascular risk associated with OHS as endothelial dysfunction is the early key event of atherosclerosis and a strong predictor of incident cardiovascular events (41-43). Arkin et al. (39) have recently suggested that endothelial dysfunction aggravates with higher degrees of obesity being more severe in super obese (>50kg/m^2) than in morbidly obese (>40kg/m^2). They assumed that more visceral fat in super obese patients can be an explanation for their results. As the expected prevalence of OHS is more than 50% in super obese patients (5) versus only 30% in morbidly obese, we suggest that inflammation specifically associated with OHS may be a complementary explanation. This is leading to propose a systematic measurement of blood gazes both in clinical practice and in research protocols in obese. In our study, even supra normal values of $PaCO_2$ were significantly linked with RANTES elevation and endothelial dysfunction. To our knowledge, no experimental data are available regarding effects of chronic moderate elevation of $PaCO_2$ on cardiovascular system and metabolic disorders. Further studies are desirable in this field.

Clinical implications, research and therapeutic perspectives

Our study demonstrated that obesity hypoventilation syndrome is a specific cluster in obesity with associated specific inflammation and aggravated endothelial dysfunction. Whether RANTES elevation will allow delineating suitable specific therapeutic targets in this particular subgroup of obese needs to be addressed in future studies (33, 44). However, this already have clinical implications as individuals with higher RANTES levels have higher risk

to develop diabetes mellitus despite intensive lifestyle intervention than individuals with lower RANTES levels (45). Moreover, non invasive ventilation the current first line therapy of OHS should now be evaluated, in randomized controlled trials, not only regarding its effects on $PaCO_2$, sleep and quality of life but also should be questioned on its cardiovascular and metabolic impact.

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lifestyle changes in the prevention of type 2 diabetes: results from the Finnish Diabetes Prevention Study. *Diabetes* 55(8):2340-6.

Table 1: Anthropometric characteristics and respiratory function

	OHS (14)	UO (39)	p-value
Sex F/ M	9/5	26/13	ns
Age (years)	57 ± 10	56 ± 10	ns
BMI (kg/m2)	41.0 ± 5.2	40.9 ± 5.1	ns
Waist/Hip ratio	0.98 ± 0.06	0.94 ± 0.1	ns
SBP (mmHg)	133 ± 23	132 ± 12	ns
DBP (mmHg)	75 ± 9	80 ± 10	ns
FVC L; (% predicted value)	2.2± 0.8 (72±24)	3.1± 1.0 (92±17)	0.003 (0.002)
TLC L; (% predicted value)	4.7± 1.3 (90±17)	5.8± 1.3 (99±12)	0.01 (0.06)
FEV1/ FVC	84 ± 8	79 ± 8	ns
PaO_2 (kPa)	9.78 ±1.73	10.71 ±1.44	0.02
$PaCO_2$ (kPa)	6.45 ± 0.39	5.31 ± 0.44	< 0.0001
HCO_3- (mmol/l)	29.2 ± 2.69	25.2 ± 1.83	<0.0001
CO_2 sensitivity (l/m/mmHg)	1.4 ± 0.9	2.4 ± 1.5	0.02

Table 2: Sleep structure and sleep associated disorders breathing

	OHS (14)	UO (39)	p-value
Total Sleep Time (min)	341 ± 66	338 ± 83	ns
Sleep 1-2 (% of total sleep time)	75 ± 9	72 ± 10	ns
Sleep 3-4 (% of total sleep time)	5 ± 8	7 ± 8	ns
REM Sleep (% of total sleep time)	19 ± 7	21 ± 8	ns
AHI (n/h)	57 ± 54	40 ± 28	ns
Respiratory-related μ-arousals(n/h)	50 ± 36	36 ± 20	ns
Mean nocturnal SpO2	89 ± 5	91 ± 4	0.04
Nadir nocturnal SpO2	65 ± 15	76 ± 10	0.009
Sleep time spent with SpO2<90%	44 ± 35	19 ± 21	0.007

Table 3: Cardiovascular, metabolic history, treatment and biomarkers

	OHS (14)	UO (39)	p-value
Treated hypertension , *%*	86	54	0.03
Myocardial Infarction ,*%*	0	3	ns
Diabetes, *%* (Treated for diabetes, *%*)	54 (43)	29 (21)	ns
Statins, *%*	43	23	ns
Fast blood insulin level, $\mu u.mL^{-1}$	22.7 ± 21.1	11.2 ± 7.9	ns
Fast blood glucose level *mmol/l*	7.5 ± 3.8	6.5 ± 2.7	ns
HOMA – IR *(G*I/22.5)*	9.8 ± 13.0	3.2 ± 2.4	ns
HbA1c, %	7.3 ± 4.3	6.1 ± 1.7	0.003
Triglycerids, *g/l*	1.69 ± 0.8	1.4 ± 0.7	ns
HDL, *g/l*	0.41 ± 0.13	0.40 ± 0.1	ns
LDL, *g/l*	1.0 ± 0.4	1.3 ± 0.5	0.05
Total Cholesterol, *g/l*	1.8 ± 0.5	2.0 ± 0.6	ns

Legends of the tables

Table 1: Anthropometric data, blood pressure and respiratory function

BMI: Body Mass index; SBP: Systolic Blood pressure; DBP: Diastolic Blood Pressure; FVC: Forced Vital capacity, expressed as liter and percentage of predicted value; TLC: Total Lung Capacity; FEV1/ FVC: forced expiratory volume in 1 second on forced vital capacity ratio; CO_2 sensitivity: Central CO_2 chemo-sensitivity was assessed using Read's method (23).

Table 2: Sleep structure and sleep associated breathing disorders

REM: Rapid Eye Movement sleep; AHI: Apnea-hypopnea index.

Table 3: Cardiovascular and metabolic status: history, biological parameters and medications

HOMA-IR was calculated with the formula: Fast blood glucose level*Fast blood insulin level/22.5; HbA1c: Glycated haemoglobin; HDL: High density lipoprotein; LDL: Low density lipoprotein

Legends of the figures

Figure 1: Serum levels of 7 pro-inflammatory cytokines in Obesity Hypoventilation Syndrome (OHS) compared to uncomplicated obese (UO) patients.

Figure 2: Serum levels of 2 anti-inflammatory cytokines in Obesity Hypoventilation Syndrome (OHS) compared to uncomplicated obese (UO) patients.

Figure 3: A: Endothelial function, assessed by Reactive Hyperhemia-Peripheral Arterial Tonometry index (RH-PAT index), in Obesity Hypoventilation Syndrome (OHS) compared to uncomplicated obese (UO) patients. B: Correlation between RH-PAT index and $PaCO_2$. C: Correlation between Serum level of RANTES and PaCO2. D: Correlation between RH-PAT

index and PaO_2. For figures 3B, 3C and 3D: open circles represented OHS and black circles UO.

Figure 1:

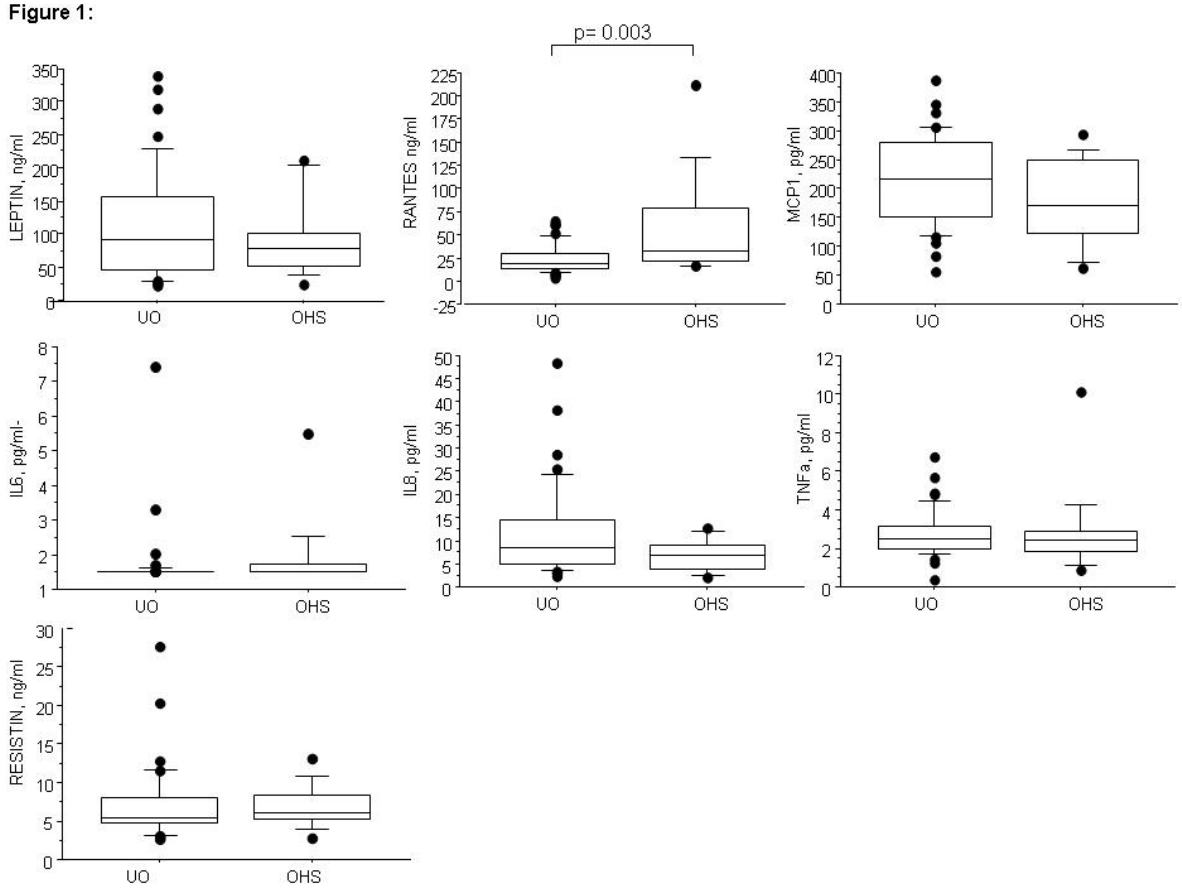

p= 0.003
LEPTIN, ng/ml
RANTES ng/ml
MCP1, pg/ml
IL6, pg/ml-
IL8, pg/ml
TNFa, pg/ml
RESISTIN, ng/ml
UO
OHS

Figure 2:

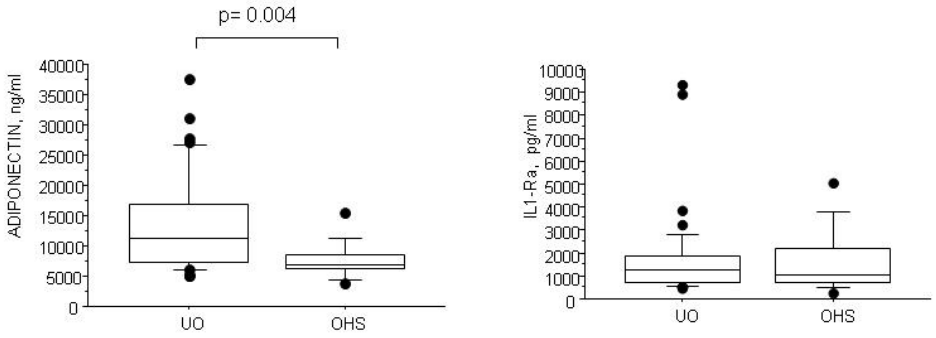
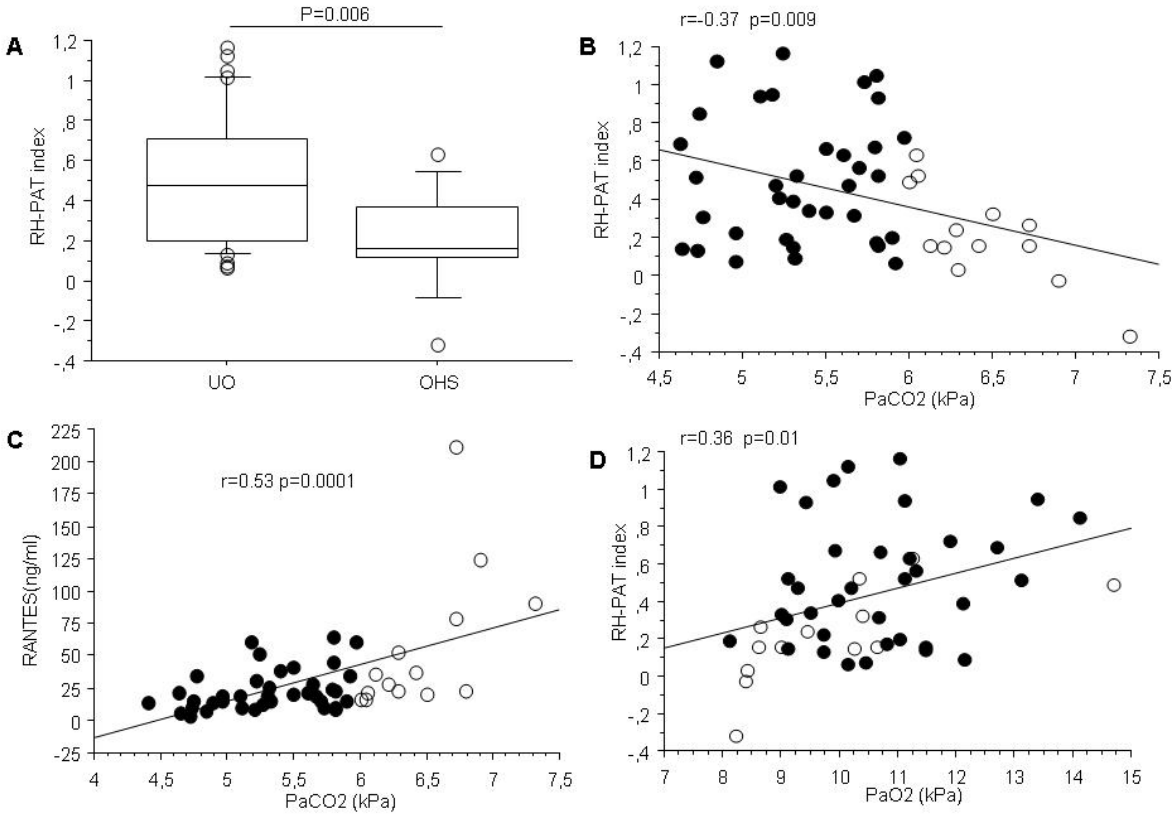

p= 0.004
ADIPONECTIN, ng/ml
40000
35000
30000
25000
20000
15000
10000
5000
0
UO
OHS
IL1-Ra, pg/ml
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
UO
OHS

Figure 3:


A
P=0.006
RH-PAT index
UO
OHS
B
r=-0.37 p=0.009
RH-PAT index
PaCO2 (kPa)
C
r=0.53 p=0.0001
RANTES(ng/ml)
PaCO2 (kPa)
D
r=0.36 p=0.01
RH-PAT index
PaO2 (kPa)

ETUDE N° 2 : ALTERATION DE LA VIGILANCE CHEZ LES PATIENTS SOUFFRANT D'UN SYNDROME OBESITE HYPOVENTILATION : IMPACT DE LA VNI.

IMPAIRED OBJECTIVE DAYTIME VIGILANCE IN OBESITY HYPOVENTILATION SYNDROME.

N. Chouri-Pontarollo, JC. Borel, R. Tamisier, B. Wuyam, P. Levy, JL Pépin

CHEST 2007; 131:148-155

Editorial associé: A.Cuvelier, J-F.Muir. Chest 2007;131:7-8

Prérequis : La somnolence diurne des patients porteurs d'un SOH serait plus importante que celle des obèses sans hypercapnie (Nowbar, Burkart et al. 2004) ou des patients présentant un SAOS appariés pour l'âge et l'IMC (Hida, Okabe et al. 2003). Aucune évaluation objective de la somnolence n'avait été réalisée. La somnolence est un symptôme largement multifactoriel et ses mécanismes restent partiellement méconnus (Vgontzas, Bixler et al. 2005) ; néanmoins plusieurs hypothèses étayent la possibilité d'une somnolence diurne plus importante chez ces patients SOH. L'obésité, le diabète, l'inflammation de bas grade (Vgontzas, Papanicolaou et al. 2000; Vgontzas, Bixler et al. 2005), les troubles respiratoires du sommeil et particulièrement ceux associés au sommeil paradoxal (SP) seraient des mécanismes possibles d'hypersomnolence (Kass, Akers et al. 1996; Haba-Rubio, Janssens et al. 2005). En effet, Kass et coll ont mis en évidence que la latence d'endormissement était inversement corrélée à la quantité d'évènements respiratoires en SP malgré un index apnée-hypopnée inférieur à 10 sur une nuit entière. Haba-rubio et coll retrouvaient que des patients dont les évènements respiratoires étaient prédominants en SP, avaient une somnolence diurne objective identique à celle de patients dont les évènements étaient répartis sur toutes les phases de sommeil, malgré un index d'évènements totaux sur la nuit trois fois moins important *(Tableau 1)*.

Tableau 1 : Impact sur la vigilance des obstructions pharyngées en sommeil paradoxal.
D'après Habba-Rubio et coll. Chest 2005.

Table 2—*Polysomnographic Data of the Total SDB Patients, REM SDB Patients, and Non-REM SDB Patients

Variables	Total (n = 415)	REM SDB (n = 151)	Non-REM SDB (n = 264
TST, min	415.3 (70.2)	421.3 (70)	413.1 (69.4)
Wake after sleep onset, min	98.5 (57.4)	91 (53.4)	101.4 (58.7)
Stage 1, min	74.5 (31.9)	61.5 (22.1)	81.4 (34)†
Stage 2, min	221 (58.4)	218 (53.1)	223.1 (60.2)
Stage 3–4, min	51.8 (40.1)	66.3 (40)	44.5 (38.2)†
Stage REM, min	67.9 (28.8)	75.4 (29.1)	64 (27.4)†
Sleep latency, min	10.4 (14.1)	10.3 (12.8)	10.6 (15.1)
Sleep efficiency, %	78.1 (10.9)	79.3 (10.8)	77.5 (10.8)
SFI, No./h	139.8 (77.2)	104.4 (38.3)	158.1 (84.6)†
Sleep time in dorsal position, min	183.5 (128.4)	186 (131.6)	181.3 (126.8)
Sleep time in lateral position, min	230.8 (130.3)	229.7 (134.9)	230.5 (128.3)
Periodic leg movement index, No./h	11.6 (16.2)	9 (12.7)	13.2 (17.6)
AHI, No./h	34.1 (25.5)	15.7 (9.2)	43.3 (25.9)
REM AHI, No./h	37.9 (23.4)	40.2 (20.9)	37.2 (24.5)
Non-REM AHI, No./h	30.3 (25.1)	9.6 (7.9)	40.7 (24.3)†
Apnea duration, s	18.1 (5.9)	16.3 (5.7)	19.1 (5.8)†
Hypopnea duration, s	15 (2.6)	14.3 (2.2)	15.4 (2.8)†
Wake Sao_2, %	93.1 (4.9)	93.1 (7.7)	93.1 (1.9)
Mean minimal Sao_2, %	88.4 (3.9)	89.3 (3.2)	87.9 (4.2)†
Minimal Sao_2, %	77.8 (8.6)	79.9 (6.8)	76.7 (9)†
ODI, No./h	21.9 (20.3)	9.7 (7.7)	27.9 (21.8)†
MWT, min	21.8 (12.1)‡	23.7 (10.7)	21.3 (12.5)
ESS score	9.4 (4.9)	9.3 (4.7)	9.3 (5)

*Data are presented as mean (SD).
†$p < 0.001$, REM SDB vs non-REM SDB.
‡Total patients, n = 228; REM SDB patients, n = 67; non-REM SDB patients, n = 169.

Objectifs : Le premier objectif de cette étude était de caractériser précisément les troubles respiratoires du sommeil notamment l'hypoventilation en sommeil paradoxal dans un groupe de patients SOH. Le deuxième objectif était d'évaluer le lien entre la diminution de la chémo-sensibilité au CO_2 et la vigilance diurne (objective et subjective) ; enfin le troisième objectif était d'évaluer l'efficacité de la VNI nocturne à court terme sur ces paramètres.

Méthodes : 15 patients OHS étaient inclus. L'évaluation initiale consistait en des explorations fonctionnelles respiratoires, des gaz du sang en ventilation spontanée, un test de sensibilité au CO_2, une polysomnographie diagnostic. La vigilance était évaluée subjectivement par l'échelle d'Epworth et objectivement par le test d'OSLER (Oxford Sleep resistance test). Après cinq à sept jours de VNI nocturne, l'évaluation finale était identique à l'évaluation initiale.

Résultats : La diminution de la sensibilité des centres respiratoires était corrélée à la quantité d'hypoventilation en sommeil paradoxal. Les patients qui avaient une hypo-sensibilité des centres respiratoires étaient objectivement plus somnolents. À court terme, la VNI améliorait significativement cette somnolence diurne excessive.

Discussion-Conclusion : La sévérité de l'hypoventilation en sommeil paradoxal pourrait être un des déterminants de la somnolence diurne excessive. Les patients qui présentaient une diminution de la sensibilité au CO_2 et une proportion de sommeil paradoxal passé en hypoventilation plus importante n'avaient pas une $PaCO_2$ diurne plus élevée, ni un indice de masse corporelle supérieur. De même la fragmentation du sommeil était identique dans les deux groupes. Aussi d'autres mécanismes liés à ces phénomènes d'hypoventilation en sommeil paradoxal pourraient être impliqués. L'inflammation, les troubles métaboliques potentiellement plus sévères chez ces patients hypoventilateurs seraient sont des hypothèses plausibles.

CHEST

Original Research

NONINVASIVE MECHANICAL VENTILATION

Impaired Objective Daytime Vigilance in Obesity-Hypoventilation Syndrome*

Impact of Noninvasive Ventilation

Nathalie Chouri-Pontarollo, MD; Jean-Christian Borel, PT; Renaud Tamisier, MD, PhD; Bernard Wuyam, MD, PhD; Patrick Levy, MD, PhD; and Jean-Louis Pépin, MD, PhD

Background: **Obesity-hypoventilation syndrome (OHS) is efficiently treated by noninvasive ventilation (NIV). Sleep respiratory disturbances, reduced ventilatory drive, and excessive daytime sleepiness (EDS) are commonly reported, but their relationships remain unclear.**
Objectives: **To characterize sleep breathing disorders encountered in patients with OHS, to compare low and normal CO_2 responders in terms of sleep abnormalities, subjective and objective measures of EDS, and to measure the changes induced by NIV on these parameters.**
Methods: **At baseline and after 5 nights of NIV, 15 consecutive patients (mean [± SD] age, 55 ± 9 years; mean body mass index, 38.7 ± 6.1 kg/m^2; $Paco_2$, 47.3 ± 2.3 mm Hg) prospectively underwent polysomnography, CO_2 ventilatory response testing, Epworth sleepiness scale scoring, and the Oxford Sleep Resistance (OSLER) test, which is an objective vigilance test.**
Results: **OHS patients exhibited obstructive sleep apnea syndrome (mean apnea-hypopnea index, 62 ± 32 events per hour) and rapid eye movement (REM) sleep hypoventilation (mean REM sleep time, 35 ± 33%). Baseline CO_2 sensitivity was significantly related to the proportion of hypoventilation during REM sleep ($r = 0.54$; $p = 0.037$). Six patients showed abnormal sleep latencies during the OSLER test (71% of the low CO_2 responders vs 14% of the normal CO_2 responders). Low CO_2 responders exhibited significantly shorter sleep latencies during the OSLER test (23 ± 14 vs 37 ± 8 min, respectively; $p = 0.05$). Using NIV, diurnal blood gas levels were improved and REM sleep hypoventilation were suppressed. Objective sleepiness was improved in low CO_2 responders ($p = 0.04$).**
Conclusion: **In OHS patients, the lower the daytime CO_2 response, the higher the proportion of REM sleep hypoventilation and daytime sleepiness. Short-term therapy with NIV improves all of these parameters.** ***(CHEST 2007; 131:148–155)***

Keywords: noninvasive ventilation; obesity hypoventilation syndrome; ventilatory response; vigilance test

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; EDS = excessive daytime sleepiness; NIV = noninvasive ventilation; OHS = obesity-hypoventilation syndrome; OSAS = obstructive sleep apnea syndrome; OSLER = Oxford Sleep Resistance; PSG = polysomnography; REM = rapid eye movement

Obesity-hypoventilation syndrome (OHS) is defined as a combination of obesity and awake chronic hypoventilation occurring in the absence of other known causes of hypoventilation.[1] The disease remains underrecognized as > 30% of obese hospitalized patients, whatever the cause of hospitalization, actually exhibit an undiagnosed daytime hypercapnia.[2] Use of health-care resources,[3] and rates of hospitalization and early mortality are increased in OHS patients.[2] Noninvasive ventilation (NIV) is the first-line therapy for patients with OHS.[4] Patients have good compliance rates with NIV,[5] and the therapy is effective in terms of clinical status and improvement in blood gas levels.[4–6]

The pathophysiology of OHS results from complex interactions, among which are increased work of breathing related to obesity, normal or diminished ventilatory drive, various associated sleep breathing disorders (*ie*, obstructive sleep apnea and rapid eye movement [REM] sleep hypoventilation), and neurohormonal changes such as leptin resistance.[1] There have been no studies as to whether low responders to

CO_2 hypoventilate more significantly during REM sleep compared to OHS patients with normal ventilatory responses and whether this can influence their daytime vigilance.

Among the classical symptoms associated with OHS, daytime sleepiness has been systematically reported.[2] Surprisingly, to date no objective measurements of sleepiness have been performed in a well-characterized population of OHS patients. However, it is generally accepted that impairment in daytime functioning does exist and is related to breathing abnormalities occurring during sleep. During sleep, obstructive sleep apnea syndrome (OSAS), sleep hypoventilation syndrome, or a combination of both can be observed in polysomnography (PSG) findings. The respective consequences of these different sleep breathing abnormalities in terms of subjective and objective alteration in vigilance are still unknown.

For editorial comment see page 7

Therefore, the objectives of this investigation were threefold. First, we sought to characterize the different sleep-related breathing disorders encountered in OHS patients. Second, we wished to compare low and normal CO_2 responders in terms of sleep abnormalities, and subjective and objective daytime sleepiness as measured by the Oxford Sleep Resistance (OSLER) test.[7,8] Our last objective was to look at the short-term effects of NIV therapy on all these parameters.

Materials and Methods

Patients

Women or men, between 20 and 65 years of age, presenting with a body mass index (BMI) of >32 kg/m^2 and daytime hypoventilation (*ie*, $Paco_2$, >45 mm Hg) in the absence of other known causes of chronic hypoventilation (*eg*, COPD [FEV_1/vital capacity ratio, $<65\%$] or hypothyroidism) were eligible for the study. The study was approved by the hospital Ethics Committee, and patients gave written informed consent.

Study Design

A diagnosis of OHS was established according to the diurnal $Paco_2$ and pulmonary function test results. At baseline, patients also underwent overnight PSG testing. On the following morning, OSLER test and central CO_2 chemosensitivity test were performed. Afterward, patients were referred to the pulmonary ward for 5 to 7 days in order to initiate therapy with NIV and to make adjustments to it. The same measurements were then performed with PSG recorded under NIV conditions.

Measurements

PSG: At baseline, PSG was performed during spontaneous breathing in order to characterize the abnormal respiratory events associated with OHS. Sleep and respiratory events were recorded and scored manually according to standard criteria,[9–11] as previously described.[12]

REM hypoventilation was scored when progressive oxygen desaturation occurred that was associated with a sustained reduction in both flow and thoracic components of ventilation. During the same period, a constant or reduced respiratory drive (assessed by a reduction in respiratory effort as demonstrated by pulse transit time) should be observed without characteristic apneic or hypopneic episodes (Fig 1). Pulse transit time is a validated measure of respiratory effort. It has been validated against esophageal pressure. Thus, by semiquantitatively measuring respiratory effort, pulse transit time is a valuable measurement of the changes in respiratory drive occurring during REM sleep.[11] In the definition proposed by Olson and Zwillich,[1] hypercapnia is assumed to be present or to aggravate even the unmeasured transcutaneous Pco_2.

Respiratory Function and Ventilatory Responses to CO_2: Spirometry and plethysmography were measured according to the European Respiratory Society recommendations.[13] CO_2 chemosensitivity was assessed using Read's method.[14,15] The threshold of 1.5 L/min/mm Hg was used to separate low responders to CO_2 from normal responders to CO_2.[14]

Subjective and Objective Sleepiness Assessment (Epworth Sleepiness Scale and OSLER Test): The epworth sleepiness scale is a validated eight-item, self-completion questionnaire.[16] The OSLER test consisted of a 40-min sleep-resistance challenge that was conducted in a dark and quiet room. The subject was asked to remain awake and to react to a visual stimulus, which appeared for 1 s of every 3 s, by hitting a button. *Sleep latency* was the term used to describe the delay between the onset of the test and the moment corresponding to seven consecutive flashes (*ie*, 21 s) without response. Error profile 3–6 represented the number of three to six consecutive errors (*ie*, 9 to 18 s without a response from the patient), which is assumed to represent fluctuations in vigilance and microsleep episodes.[17] Patients underwent an OSLER test at 9:00 AM as we have previously described that this test has the most sensitive and specific criteria with which to detect sleepiness and impairment in attentional capabilities.[8] Both in the study by Bennett et al[7] and in our study,[8] all of the control subjects were able to finish the 40-min test without falling asleep.

NIV Treatment

Patients were treated with bilevel positive-pressure ventilation (SERENA; SAIME; Savigny le Temple, France) in pressure

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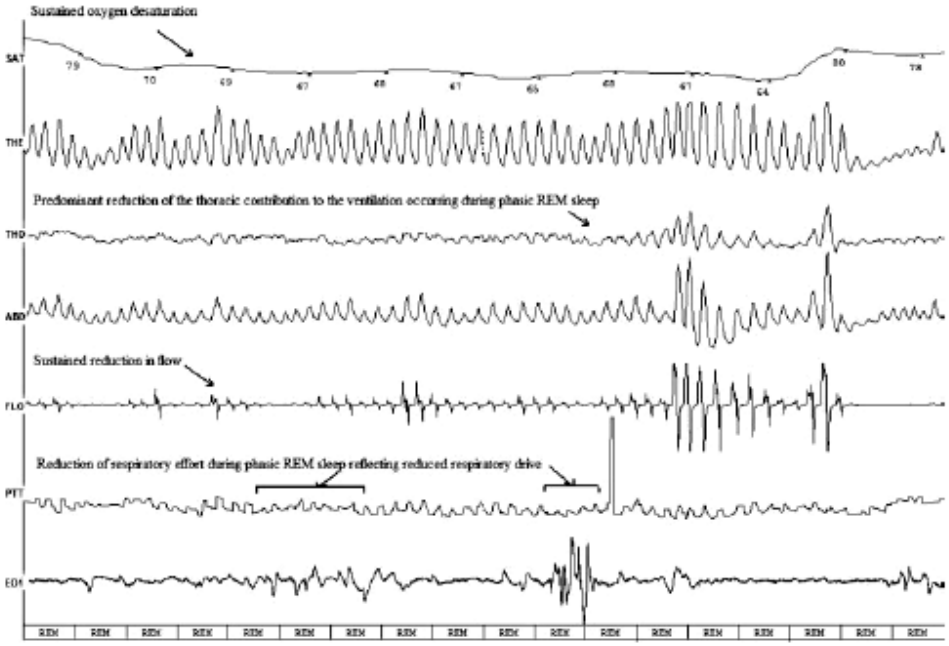

FIGURE 1. REM Sleep hypoventilation (a 5-min epoch is presented). SAT = arterial oxygen saturation; THE = buconasal thermistor; THO = thoracic movements; ABD = abdominal movements; FLO = nasal pressure; PTT = pulse transit time; EO1 = eye movements.

support mode with a minimal respiratory rate setting. Inspiratory pressure was increased in order to achieve a maximal reduction in daytime P_{CO_2} and optimal correction of nocturnal oxygen desaturation. Moreover, the control of nocturnal hypoventilation was assessed by measuring blood gas levels at the end of the night just before stopping NIV. Expiratory pressure was increased to eliminate obstructive sleep apnea.

Statistical Analysis

A statistical software package (NCSS 97; NCSS; Kaysville, UT) was used for the statistical analysis. Results are expressed as the mean ± SD. A Wilcoxon test was used to compare measurements at baseline and when using NIV. We hypothesized that patients who had a low CO_2 chemosensitivity would exhibit more REM sleep hypoventilation. OHS patients were then separated into groups of low and normal responders using a threshold of < 1.5 L/min/mm Hg. Variables between these two groups were compared using a Mann-Whitney test. The correlation between the proportion of time spent hypoventilating during REM sleep and CO_2 sensitivity was assessed by a logarithmic best-fit analysis. For all tests, a significance level of 0.05 was used.

RESULTS

Baseline Anthropometric, Functional, Sleep, and Vigilance Data

Fifteen consecutive patients (10 men), with a mean age of 55 ± 9 years were prospectively included (Tables 1–3). They were morbidly obese, had moderate-to-severe daytime hypercapnia without abnormal ventilatory function. They presented with a combination of OSAS (*ie*, apnea-hypopnea index [AHI], 62 ± 32 events per hour of sleep) and REM hypoventilation. The average sleep time spent in hypoventilation exceeded one third of REM sleep (mean duration, 35 ± 33% [corresponding to a mean duration of 19.2 ± 17.4 min per night]). Subjective daytime sleepiness was impaired, with a mean Epworth sleepiness scale score of 11 ± 4. An objective

Table 1—*Anthropometric Parameters and Functional Data Before and After NIV Treatment (n = 15)

Variables	Before NIV	After NIV	p Value
Patients			
Female	5		
Male	10		
Age, yr	55 ± 9		
BMI, kg/m^2	38.7 ± 6.1		
$Paco_2$, mm Hg	47.3 ± 2.3	41.3 ± 3	< 0.0001
Pao_2, mm Hg	77.3 ± 6.8	74.3 ± 6.8	NS
VC			NS
L	3.6 ± 1.0	3.5 ± 1.1	
% predicted	90	89	
TLC			NS
L	6.0 ± 1.5	5.8 ± 1.7	
% predicted	99	97	
CO_2 sensitivity, L/min/mm Hg	2.0 ± 1.3	2.4 ± 1.9	NS

*Values are given as the mean ± SD, unless otherwise indicated. VC = vital capacity; TLC = total lung capacity; NS = not significant.

Table 2—*Sleep Parameters Before and During NIV (n = 15)

Variables	Without NIV	With NIV	p Value
Sleep architecture			
TST, min	343 ± 68	312 ± 66	NS
Sleep latency, min	20 ± 19	21 ± 18	NS
Stage 1, % TST	26 ± 15	15 ± 7	0.005
Stage 2, % TST	50 ± 13	50 ± 7	NS
Stage 3–4, % TST	3 ± 3	7 ± 5	0.007
REM sleep, % TST	20 ± 9	27 ± 4	0.02
RMAI, No. events/h of sleep	61 ± 24	11 ± 12	< 0.001
Respiratory events			
Non-RMAI, No. events/h of sleep	4 ± 6	14 ± 11	0.006
AHI, No. events/h of sleep	62 ± 32	11 ± 13	< 0.0001
REM HypoVA, % REM sleep	35 ± 33		
Mean sleep SaO_2, %	89 ± 3	93 ± 1	< 0.001
Nadir sleep SaO_2, %	65 ± 14	87 ± 6	< 0.001
Time spent with SaO_2 < 90%, % TST	38 ± 32	5 ± 10	0.002

*Values are given as the mean ± SD, unless otherwise indicated. TST = total sleep time; RMAI = respiratory-related microarousals index; REM HypoVA = time spent in alveolar hypoventilation during REM sleep. See Table 1 for abbreviations not used in the text.

Table 4—*Patients With Normal CO_2 Sensitivity Compared to Those With Low CO_2 Sensitivity (n = 15)

Variables	Low CO_2 Sensitivity (n = 7)	Normal CO_2 Sensitivity (n = 8)	p Value
CO_2 sensitivity, L/min/mm Hg	1.1 ± 0.3	2.8 ± 1.3	0.001
BMI, kg/m^2	38.5 ± 7	38.8 ± 6	NS
$PaCO_2$, mm Hg	47.3 ± 2.3	47.3 ± 2.3	NS
PaO_2, mm Hg	78.0 ± 8.3	75.0 ± 6.0	NS
Sleep parameters			
RMAI, No. events/h of sleep	54 ± 27	67 ± 20	NS
Non RMAI, No. events/h of sleep	6 ± 9	3 ± 2	NS
AHI, No. events/h of sleep	50 ± 38	73 ± 24	0.16
REM HypoVA, %REM sleep	46 ± 37	25 ± 29	0.16
Mean sleep SaO_2, %	89 ± 3	89 ± 3	NS
Nadir sleep SaO_2, %	63 ± 14	67 ± 15	NS
Time spent with SaO_2 <90%, % TST	35 ± 30	39 ± 34	NS
Epworth scale	12 ± 2	11 ± 4	NS
OSLER test	23 ± 14	37 ± 8	0.05
Sleep latency, min			
EP 3–6, n	2.7 ± 5.1	2.7 ± 4.7	NS

*Values are given as the mean ± SD, unless otherwise indicated. See Tables 1–3 for abbreviations not used in the text.

sleepiness assessment showed reduced sleep latency during the OSLER test in six patients.

CO_2 Ventilatory Response Status, Sleep Abnormalities, and Daytime Vigilance

Seven patients were included in the low CO_2 responder group (< 1.5 L/min/mm Hg), whereas eight patients had a normal CO_2 sensitivity (Table 4). There was a significant relationship between CO_2 sensitivity and the amount of hypoventilation in REM sleep ($r = 0.54$; $p = 0.037$) [Fig 2]. Patients who were low responders had higher objective daytime sleepiness, which was measured in terms of shorter mean sleep latency periods during the OSLER test (23 ± 14 min vs 37 ± 8 min, respectively; $p = 0.05$), although they exhibited the same amount of sleep fragmentation.

Table 3—*Daytime Sleepiness Before and After 5 Nights of Efficient NIV (n = 14)

Variables	Before Treatment	After Treatment	p Value
Epworth sleepiness scale score			
Whole group	11 ± 4	8 ± 3	0.05
Low CO_2 sensitivity	12 ± 2	7 ± 2	0.02
Normal CO_2 sensitivity	11 ± 5	8 ± 5	NS
OSLER test			
Sleep latency, min	30 ± 14	35 ± 10	0.08
Total errors, No.	11 ± 15	8 ± 3	NS
EP 3–6, No.	2.0 ± 3.9	0.7 ± 1.7	0.14

*Values are given as the mean ± SD, unless otherwise indicated. EP 3–6 = error profile 3–6. See Table 1 for abbreviation not used in the text. Only 14 patients have been considered for this table. One patient has been excluded owing to technical problems occurring during the final OSLER test. His baseline sleep latency was 39.7 min.

NIV Efficacy Assessment

NIV settings were 12 to 22 millibars for inspiratory pressure and 6 to 12 millibars for expiratory pressure

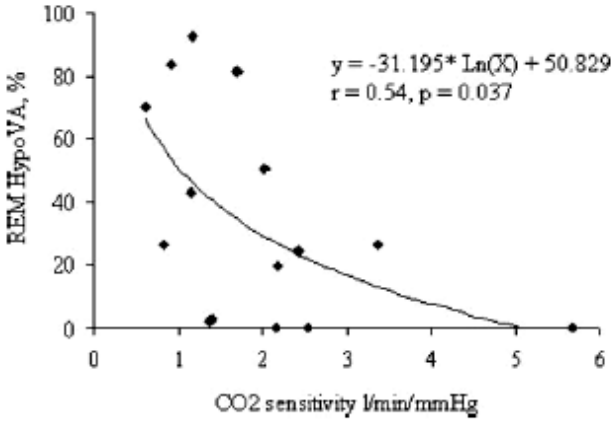

FIGURE 2. Correlation between the percentage of REM sleep spent in hypoventilation and initial CO_2 sensitivity (n = 15). REM HypoVA = time spent in hypoventilation during REM sleep, expressed as a percentage of REM sleep time.

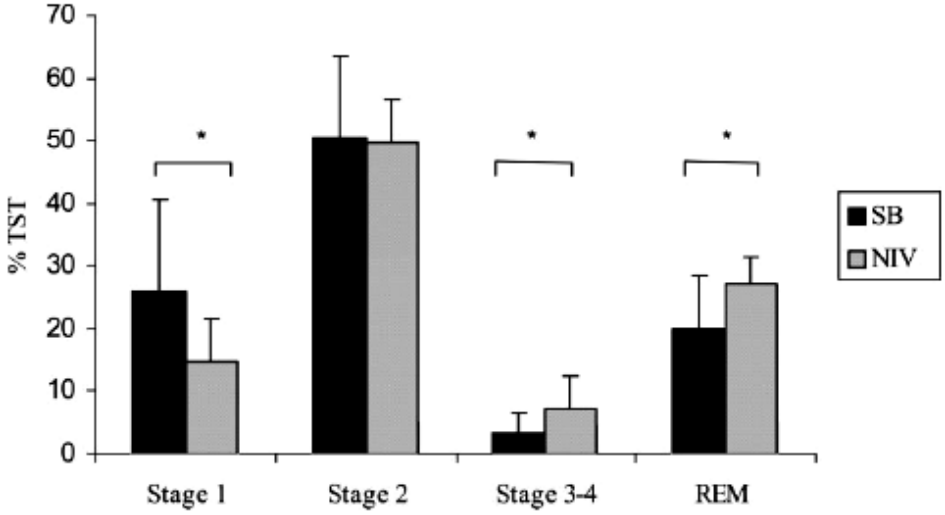

FIGURE 3. Sleep architecture before and after NIV for the whole group (n = 15). % TST = percentage of total sleep time; SB = spontaneous breathing. * = statistical significance with $p < 0.05$.

(Tables 2, 3). Short-term NIV use improved diurnal $Paco_2$ significantly (from 47.3 ± 2.3 to 41.3 ± 3 mm Hg; $p < 0.0001$).

AHI decreased significantly from 62 ± 32 to 11 ± 13 events per hour ($p < 0.0001$). We did not find any residual hypoventilation with the use of NIV during REM sleep. Sleep architecture changed significantly. Stage 1 decreased ($p = 0.005$), while stages 3 and 4 and REM sleep significantly improved ($p = 0.007$ and 0.02, respectively) [Fig 3]. Whereas the AHI normalization was associated with a major reduction in the number of respiratory-related microarousals, the number of non-respiratory-related microarousals increased significantly.

For the whole group, there was a nonsignificant increase in ventilatory responses to CO_2 (Table 1). Low responders at baseline increased their ventilatory responses by 47%, but the mean value remained close to 1.5 L/min/mm Hg, which is the lower limit for normal values (Table 5). The values of only two patients returned to the normal range.

Using NIV, the vigilance assessed by the Epworth sleepiness scale score was significantly improved by the treatment ($p = 0.05$) for the whole group. The Epworth sleepiness scale score was significantly improved in low CO_2 responders ($p = 0.02$), whereas it did not improve in normal CO_2 responders (Table 3). Moreover, only low CO_2 responders who significantly improved their vigilance, according to the number of sleep latency periods during the OSLER test, reached an average level that was comparable to the values of the normal CO_2 responders ($p = 0.04$) [Fig 4].

DISCUSSION

Our study is the first to have assessed in the same OHS individuals different types of sleep respiratory abnormalities, ventilatory responses to CO_2, and both subjective and objective measures of sleepiness at baseline and when using NIV. Awake ventilatory responses to CO_2 were significantly related to the proportion of hypoventilation during REM sleep. The lower the CO_2 ventilatory responses, the higher the percentage of REM sleep spent in hypoventila-

Table 5—*O_2 Sensitivity Before and After 5 Nights of Efficient NIV (n = 15)*

Variables	Low CO_2 Sensitivity (n = 7)	Normal CO_2 Sensitivity (n = 8)	p Value
Baseline CO_2 sensitivity, L/min/mm Hg	1.1 ± 0.3	2.8 ± 1.3	0.001
Post-NIV CO_2 sensitivity, L/min/mm Hg	1.5 ± 0.97	3.2 ± 2.2	0.09-NS
ΔCO_2 sensitivity, L/min/mm Hg	0.44 ± 1.1 (47)	0.47 ± 1.9 (18)	NS

*Values are given as the mean ± SD (% of variation compared to baseline), unless otherwise indicated. ΔCO_2 sensitivity = variation of CO_2 sensitivity between baseline and after 5 days of NIV. See Table 1 for abbreviation not used in the text.

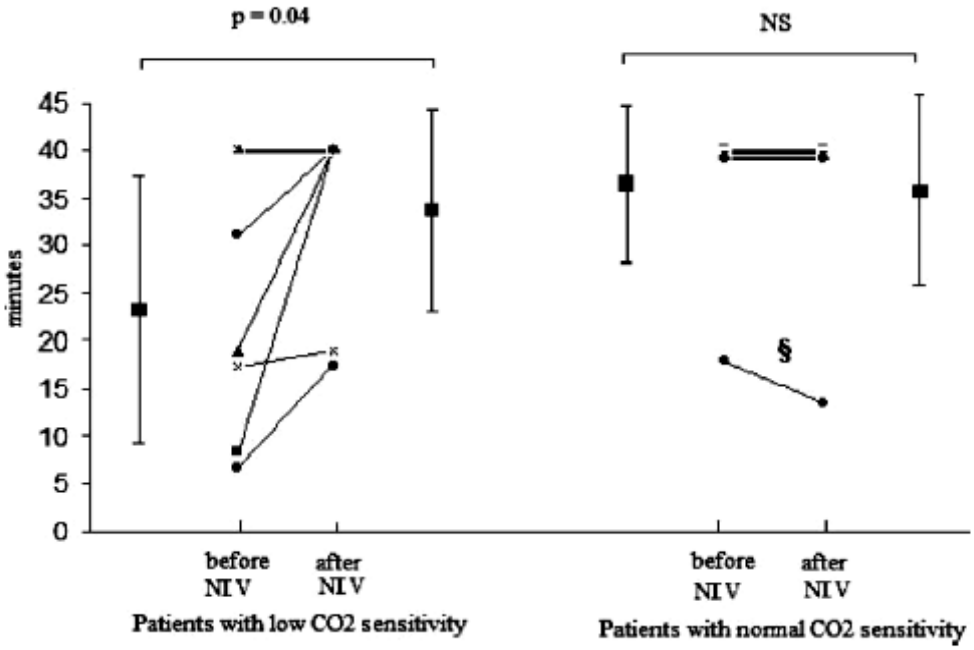

FIGURE 4. Sleep latency during the Osler test before and after NIV for patients with low CO_2 sensitivity (n = 7) and normal CO_2 sensitivity (n = 7). NS = no statistical significance; § = this patient decreased his sleep latency after NIV; an analysis of his individual data showed that his total sleep time spent using NIV was 30% less than during the first PSG session. Only seven patients with normal sensitivity had been considered in this figure because one patient was excluded from the study owing to technical problems occurring during the final OSLER test. His baseline latency period was 39.7 min.

tion. Those patients with lower responses to CO_2 and marked REM hypoventilation were the sleepiest and demonstrated more significant improvement in objective daytime sleepiness after receiving short-term therapy with NIV.

Sleep Respiratory Disturbances, Daytime Hypercapnia, and OHS

OSAS, REM sleep hypoventilation, and sustained episodes of flow limitation are commonly reported when studying OHS patients by PSG.[10,18] OSAS is present in most cases[19] and can contribute to the occurrence of daytime hypercapnia. The maintenance of eucapnia during sleep in OSAS patients requires a balance between CO_2 loading during apnea and CO_2 elimination in the interevent period.[20,21] Berger et al[21] found an inverse relationship between the postevent ventilatory response slope and the chronic awake arterial $Paco_2$ in OSAS patients, suggesting that this mechanism might be impaired in OHS patients who were predominantly exhibiting OSAS during the night. The ventilatory response to CO_2 measured during wakefulness and the postevent ventilatory responses measured during sleep were only poorly correlated. Thus, awake ventilatory responses are unable to predict the postevent ventilatory response slope. This may explain why, in the current study, patients with normal ventilatory responses and prominent sleep apnea still exhibit chronic hypercapnia. Similarly, chronic hypercapnia has been demonstrated to be directly related to the apnea/interapnea duration ratio. With increasing chronic hypercapnia, the interapnea duration shortens relative to the apnea duration.[20] In this subgroup of OHS patients principally exhibiting OSAS, one may ask whether a similar positive result would have been obtained by simply treating the obstructive apneas with continuous positive airway pressure, instead of using the more complex ventilatory support approach. This requires further studies comparing therapy with NIV to therapy with continuous positive airway pressure in patients with this specific condition.

The second typical respiratory abnormality taking place during sleep in OHS patients is REM sleep hypoventilation. During REM sleep, rib-cage and accessory breathing muscle activity is suppressed, particularly during bursts of eye movements, and breathing is more irregular, rapid, and shallow, with a significant fall in ventilation.[22] REM sleep hypoventilation is central in nature and is related to a reduction in respiratory drive that is associated with phasic REM sleep. The impaired respiratory system mechanics that are associated with obesity and the REM-related drive reduction support the absence of compensatory increases in work of breathing and

thus aggravate hypoventilation. Our study demonstrates that this mechanism is more pronounced when the awake ventilatory response is already significantly reduced.

Ventilatory Responses to CO_2 and OHS

In OHS patients, whatever the associated sleep respiratory disturbances, the common final pathway seems to be the reduced respiratory drive. Whether a genetic impairment in ventilatory chemoresponsiveness also underlies the development of OHS has been questioned. Jokic et al[23] have studied first-degree relatives of OHS patients and did not find impaired ventilatory responses. Thus, reduced chemosensitivity in OHS patients is probably at least partially acquired, and this conclusion is reinforced by treatment efficacy since NIV improves but incompletely normalizes ventilatory responses to CO_2 (Table 5). A potential mechanism associating the obesity-related decrease in ventilatory responses and OHS is leptin resistance.[24–26] Leptin acts on the central respiratory centers to stimulate ventilation. Obese patients generally have a high plasma concentration of leptin and present with a resistance against leptin that could operate like a relative deficiency.[25,27–29] Both animal studies[30] and human studies[24,26] have demonstrated that leptin resistance is associated with an impaired hypercapnic ventilatory drive, particularly during sleep.

Daytime Subjective and Objective Sleepiness Associated With OHS

Sleepiness and attentional deficits are classic clinical symptoms associated with OHS.[1] For the first time, we have provided data regarding objective vigilance in OHS patients. The OSLER test, in which the occurrence of sleep is assessed behaviorally rather than by EEG recording, reproduces many of the characteristics of the maintenance-of-wakefulness test, with the advantage of being a simpler and less expensive tool that does not require the presence of a trained technician.[7,8,17,31] Using this technique, we found that 40% of the patients demonstrated abnormal objective vigilance (Fig 4). The patients with excessive daytime sleepiness (EDS) were actually those with prominent REM sleep hypoventilation. The different mechanisms underlying EDS are complex and not at all limited to sleep deprivation or sleep fragmentation. There is published evidence[32,33] that chronic inflammatory status leading to the increased secretion of inflammatory cytokines is associated with sleepiness. Obesity *per se* is a cause of inflammation and increased levels of cytokines, and can contribute to daytime hypersomnia.[32,33] In our study, daytime $PaCO_2$ and BMI values were not significantly different when comparing low CO_2 responders to normal CO_2 responders. With EDS being more significantly correlated with inflammatory cytokines than with BMI, this subgroup of patients may have presented with more significant numbers of plasma inflammatory cytokines, although this needs to be demonstrated in further studies. Finally, our data are in accordance with a report by Haba-Rubio et al.[34] They showed that OSAS patients with sleep respiratory disturbances limited to REM sleep (mean AHI for the whole night, 9.7 events per hour) were as sleepy as classic OSAS patients exhibiting a threefold greater AHI. The hypothesis is that hypoxemia occurring during REM sleep may affect daytime vigilance as much as a generalized disruption of sleep continuity.

NIV as a Treatment for OHS

NIV has been shown to be effective in improving blood gas levels[4–6,35] and in reducing the use of health-care resources by OHS patients.[3] Regarding the mechanisms associated with OHS occurrence, ventilatory responses to CO_2 are systematically improved after NIV.[35,36] This may be mediated by improving leptin resistance. A recent study[37] demonstrated that regular NIV users had significantly reduced leptin levels. During the same time period, they normalized their daytime $PaCO_2$. Improvements in daytime sleepiness have been previously reported[6] as a fall in the mean Epworth sleepiness scale score from 16 to 6 in very severe OHS patients, with some of those patients having been included in the study while experiencing an episode of acute respiratory failure. In our study, the rate of improvement in Epworth sleepiness scale score was greater in the low CO_2 responders, demonstrating the strength of the association between ventilatory responses and sleepiness. Moreover, for the first time we have been able to demonstrate an objective improvement in sleepiness for patients with OHS and low CO_2 responses. This is an important finding regarding the prevention of driving and occupation-related risks in obese patients who have chronic respiratory failure. The mechanisms by which NIV acts on daytime sleepiness are probably the reduction of sleep fragmentation (Table 2) and the improvement in OHS-related metabolic disorders. A decrease in leptin resistance has been demonstrated,[37] and a reduction of proinflammatory cytokine production is likely when using NIV.

Conclusion

In OHS patients, impairment in daytime ventilatory responses to CO_2 was associated with the

amount of REM sleep hypoventilation and the occurrence of daytime sleepiness. We have now demonstrated that therapy with NIV also improves objective vigilance in the subgroup of OHS patients who demonstrate a high proportion of REM hypoventilation and low CO_2 responses during the daytime.

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ETUDE N°3 : IMPACT D'UN MOIS DE VNI NOCTURNE SUR L'HYPOVENTILATION DIURNE, LA STRUCTURE DU SOMMEIL, LE STATUT LIPIDIQUE ET GLYCEMIQUE, LA FONCTION ENDOTHELIALE ET LA VIGILANCE DANS LE SYNDROME OBÉSITÉ HYPOVENTILATION : ÉTUDE RANDOMISEE CONTRÔLÉE.

Préambule :

L'étude présentée ci-dessous est en cours. Il s'agit d'une analyse intermédiaire. Le calcul d'effectif était basé sur l'amélioration de la $PaCO_2$ diurne. En estimant une amélioration de la $PaCO_2$ de 0.5 kPa après 1 mois de VNI, 32 patients devaient être inclus pour mettre en évidence cette amélioration avec une puissance de 80% et un risque α à 5%. Compte tenu du risque d'inobservance de la VNI l'effectif était estimé à 45 sujets à inclure.

Prérequis :

Plusieurs études ont montré que dans le Syndrome Obésité Hypoventilation (SOH), la VNI améliorait l'hypoventilation alvéolaire diurne(Masa, Celli et al. 2001; de Lucas-Ramos, de Miguel-Diez et al. 2004; Perez de Llano, Golpe et al. 2005), la vigilance subjective (Hida, Okabe et al. 2003; Piper, Wang et al. 2008) et objective (Chouri-Pontarollo, Borel et al. 2007), réduisait l'utilisation du système de soin et la mortalité (Berg, Delaive et al. 2001; Perez de Llano, Golpe et al. 2005). Cependant aucune de ces études n'était contrôlée ni randomisée. De plus, aucune étude n'a évalué l'impact de la VNI sur des paramètres cardio-vasculaires et métaboliques chez des patients SOH stables.

Objectifs :

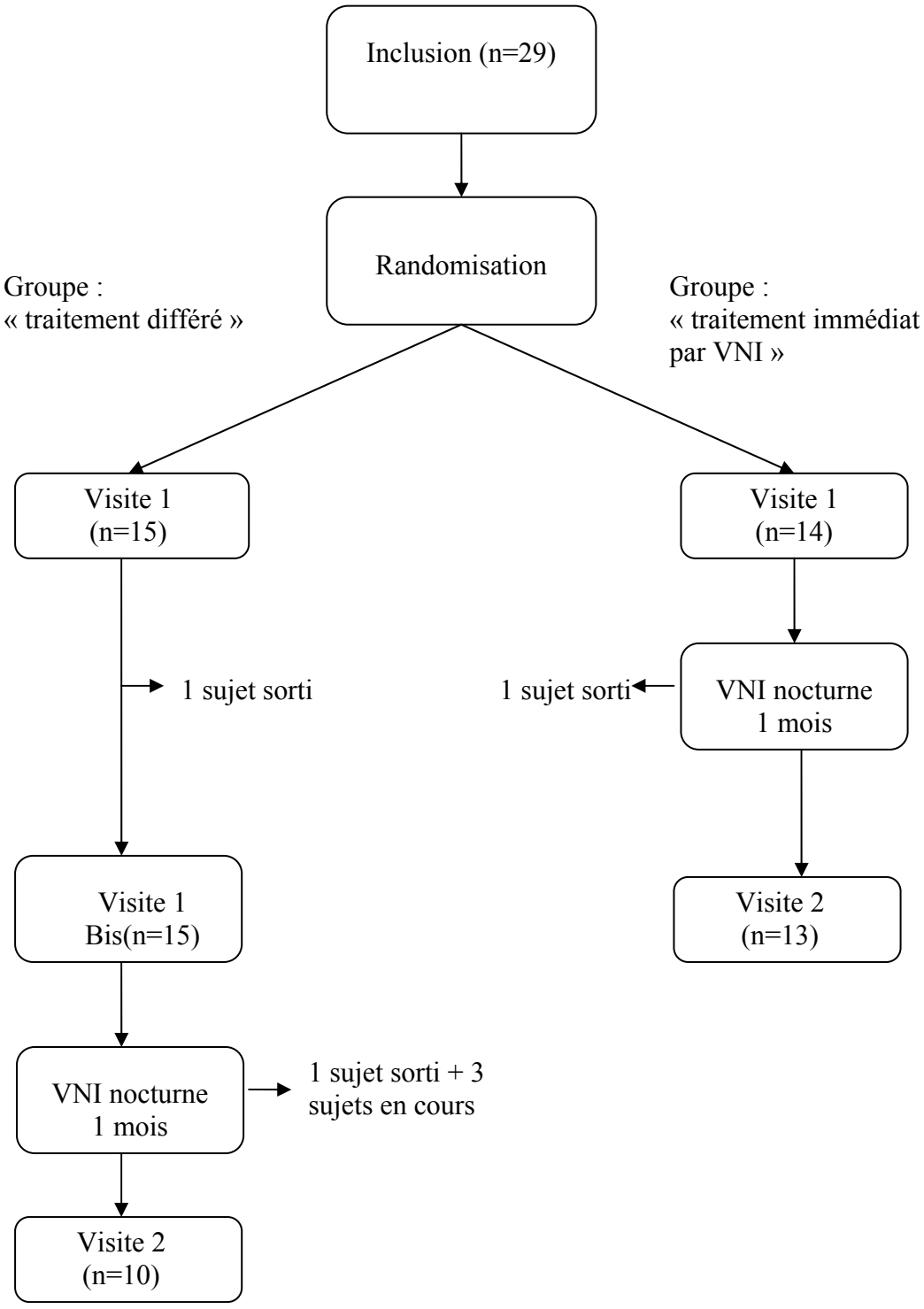
L'objectif de cette étude contrôlée randomisée était d'évaluer les effets de la VNI sur la $PaCO_2$ diurne, la vigilance diurne, la structure du sommeil, les paramètres métaboliques (glycémie, insulinémie, HbA1C, triglycérides, HDL, LDL) et la fonction endothéliale.

Méthodes :

Les patients OHS inclus étaient randomisés en deux groupes : un groupe *« traitement immédiat par VNI »* et un groupe *« traitement par VNI différé »* (groupe contrôle). Dans le groupe *« traitement par VNI immédiat »*, les patients étaient traités par VNI nocturne pendant un mois dès l'inclusion ; dans le groupe *« traitement par VNI différé »*, les patients poursuivaient pendant 1 mois leur traitement médical habituel, puis étaient traités par VNI nocturne pendant 1 mois (figure 1).

Toutes les évaluations étaient identiques et comprenaient une polysomnographie nocturne, un prélèvement de sang veineux à jeun, un test de OSLER, une évaluation de la fonction endothéliale par hyperhémie réactionnelle post-ischémique (RH-PAT, cf annexe 1), des explorations fonctionnelles respiratoires, une évaluation de la réponse ventilatoire au CO_2 et des gaz du sang diurnes. Les explorations fonctionnelles respiratoires de quatre patients, n'étaient pas incluses dans l'analyse des résultats à cause de problèmes techniques ou de réalisation des manœuvres.

Figure 1 : Schéma de l'étude.



Résultats :

Vingt neuf patients ont été inclus, 15 dans le groupe « traitement par VNI différé », 14 dans le groupe « traitement par VNI immédiat ». Dans ce dernier groupe, 1 patient est sorti de l'étude à cause d'un trouble du rythme nécessitant la mise en place d'un stimulateur implantable. Dans le groupe « traitement par VNI différé » 1 patient est sorti de l'étude pour un événement cardiaque intercurrent au cours du mois sans VNI, un patient est sorti car il a été perdu de vue, 3 sujets sont en cours de protocole.

Les caractéristiques anthropométriques et respiratoires initiales sont présentées dans le tableau 1. Les patients des deux groupes étaient comparables pour le sexe, l'âge, l'indice de masse corporelle. Les patients du groupe «traitement par VNI immédiat » avaient une concentration en ion [HCO_3^-] significativement plus élevée, une capacité pulmonaire totale et une capacité résiduelle fonctionnelle plus basse que le groupe «traitement par VNI différé » (contrôle). Les patients des deux groupes avaient un SAOS sévères. Les patients inclus dans le groupe «traitement par VNI immédiat» avaient une proportion de sommeil paradoxal inférieure aux patients du groupe «traitement par VNI différé» (Tableau 2). Le taux plasmatique de triglycérides était significativement plus élevé dans le groupe «traitement par VNI immédiat» (Tableau 3). Les autres paramètres métaboliques et cardiovasculaires étaient comparables dans les deux groupes.

Tableau 1 : Caractéristiques anthropométriques et fonction respiratoire, et évolution sous VNI pendant 1 mois par rapport au groupe contrôle

	Traitement différé (n=14)			Traitement immédiat par VNI (n=13)			
	Initial	J30	Variation	Initial	J30	Variation	***p-value***
Sexe ♀, %	64	-	-	69	-	-	-
Age, ans	55.0 ± 5.5	-	-	58.2 ± 9.7	-	-	-
IMC, kg/m^2	38.9 ± 4.3	38.9 ± 4.5	-0.1 ± 0.7	40.0 ± 6.6	40.1 ± 6.7	0.1 ± 0.4	ns
$PaCO_2$, kPa	5.7 ± 0.5	5.8 ± 0.6	0.1 ± 0.4	6.1 ± 0.7	5.7 ± 0.4	-0.4 ± 0.6	0.04
PaO_2, kPa	11.0 ± 1.7	10.65 ± 1.68	-0.3 ± 2.0	10.0 ± 1.3	10.2 ± 1.4	0.2 ± 1.3	ns
HCO_3^- *mmol.L*$^{-1}$	26.3 ± 1.5	26.8 ± 2.3	0.5 ± 2.0	28.2 ± 2.0*	26.2 ± 2.3	-2.0 ± 1.5	0.001
RV-CO2, *l.min*$^{-1}$*.mmHg*$^{-1}$	1.48 ± 0.90	1.70 ± 1.44	0.2 ± 1.2	1.48 ± 0.98	1.55 ± 0.71	0.1 ± 0.7	ns
CVF L, *(% pred)*	3.0 ± 0.8 *(93 ± 11)*	3.2 ± 0.8 (97± 12)	0.1 ± 0.2 (5 ± 5)	2.4 ± 0.8 *(78 ± 25)*	2.5 ± 0.8 *(82±18)*	0.1 ± 0.3 (4 ± 11)	ns
CPT L, *(% pred)*	5.9 ± 1.2 *(107 ± 7)*	5.8 ± 1.3 (106± 11)	-0.09 ± 0.5 (-0.3± 7)	4.8 ± 1.1* *(90 ± 16)**	5.1± 1.2 *(95 ± 17)*	0.3 ± 0.3 (5 ± 5)	0.03 0.04
VEMS/ CVF, %	81 ± 8	78 ± 8	-2 ± 5	82 ± 7	80 ± 7	-2 ± 6	ns
CRF, L, *(% pred)*	3.3 ± 0.6 110 ± 10	3.0 ± 0.8 101 ± 16	-0.26 ± 0.25 -9 ± 9	2.65 ± 0.57§ 92 ± 19§	2.71 ± 0.53 94 ± 16	0.06 ± 0.4 2 ± 14	0.036 0.045
SNIP, *mmHg*	65 ± 26	64 ± 21	-0.7 ± 19	63.8 ± 18.9	68.7 ± 18.7	4.9 ± 14.1	ns

* signifie $p<0.05$ et § signifie $p<0.01$ entre groupe différé vs. groupe traité pour les valeurs initiales.

p-value : p-valeur de la comparaison des variations (J30-initial) entre groupe différé et groupe traité.

Tableau 2 : Architecture du sommeil et vigilance diurne et évolution avec VNI pendant 1 mois par rapport au groupe contrôle

	Traitement différé (n=14)			Traitement immédiat (n=13)			
	Initial	J30	Variation	Initial	J30	Variation	***p-value***
TST, *min*	334 ± 68	354 ± 60	20 ± 59	371 ± 52	320 ± 74	-51 ± 81	0.02
SL1-2, *%TST*	73 ± 8	73.2 ± 9.6	0.6 ± 10	76 ± 9	65 ± 11	-11 ± 12	0.01
SP3-4, *%TST*	4 ± 5	4 ± 4	-0.5 ± 4	8 ± 9	10 ± 7	1 ± 7	ns
SP, *%TST*	23 ± 7	23 ± 8	-0.1 ± 10	15 ± 6 §	24 ± 11	10 ± 9	0.02
µ eveil respi, *n/h*	48 ± 31	51.3 ± 31.3	3.3 ± 24.0	36 ± 30	4.2 ± 4.5	-32 ± 29	0.003
µ eveil non respi, *n/h*	8 ± 10	5.2 ± 7.2	-3 ± 10.0	6 ± 5	14 ± 9	8 ± 9	0.01
IAH, *n/h*	55.1 ± 47.7	59.9 ± 38.2	4.9 ± 28.8	41.8 ± 42.0	6.1 ± 8.3	-35.6 ± 39.7	0.01
SpO_2 min, *%*	69.0 ± 17.7	70.4 ± 13.5	1.4 ± 9.5	70.5 ± 18.3	86.3 ± 5.5	15.9 ± 15.3	0.01
SpO_2 moy, *%*	91.7 ± 4.6	91.2 ± 6.0	-0.5 ± 2.6	89.2 ± 4.5	93.8 ± 1.7	5.0 ± 3.9	0.001
(SpO_2 < 90%), *%*	21.8 ± 28.3	23.7 ± 28.3	2.0 ± 14.6	40.8 ± 39.4	2.6 ± 4.1	-38.2 ± 38.5	0.003
Epworth	13.3 ± 4.4	10.6 ± 5.8	-2.7 ± 3.5	11.4 ± 6.4	8.3 ± 4.9	-3.1 ± 5.1	ns
Latence Osler, *min*	30.8 ± 14.2	32.1 ± 11.4	1.2 ± 9.1	34.3 ± 8.6	37.5 ± 7.9	3.2 ± 6.9	ns

* signifie $p<0.05$ et § signifie $p<0.01$ entre groupe différé vs. groupe traité pour les valeurs initiales.
p-value : p-valeur de la comparaison des variations (J30-initial) entre groupe différé et groupe traité.

Tableau 3 : Paramètres métaboliques et inflammatoires et évolution sous VNI pendant 1 mois par rapport au groupe contrôle.

	Traitement différé (n=14)			Traitement immédiat (n=13)			
	Initial	J30	Variation	Initial	J30	Variation	***p-value(Δ)***
Glycémie, *mmol.L^{-1}*	6.1 ± 1.2	6.1 ± 1.5	0.02 ± 0.83	7.8 ± 4.1	7.8 ± 3.9	-0.03 ± 1.43	ns
Insulinémie, *µu.mL^{-1}*	12.0 ± 10.3	15.5 ± 15.1	3.6 ± 7.1	21.0 ± 19.8	23.2 ± 34.6	2.2 ± 24.1	ns
HOMA-IR *(G*I/22.5)*	3.6 ± 4.5	5.0 ± 6.7	1.4 ± 2.7	9.50 ± 13.0	12.0 ± 27.3	2.5 ± 17.5	ns
HbA1C, %	6.3 ± 1.1	6.2 ± 0.9	-0.12 ± 0.34	7.1 ± 2.2	7.2 ± 2.1	0.06 ± 0.21	ns
Triglycérides, *gL^{-1}*	1.32 ± 0.58	1.37 ± 0.63	0.1 ± 0.3	1.99 ± 0.61*	2.27 ± 1.01	0.3 ± 0.8	ns
Cholesterol total, *gL^{-1}*	1.88 ± 0.63	1.69 ± 0.43	-0.2 ± 0.3	1.97 ± 0.41	1.75 ± 0.32	-0.2 ± 0.3	ns
LDL, *gL^{-1}*	1.15 ± 0.52	0.98 ± 0.35	-0.2 ± 0.3	1.15 ± 0.35	0.87 ± 0.29	-0.3 ± 0.3	ns
HDL, *gL^{-1}*	0.46 ± 0.17	0.44 ± 0.16	-0.02 ± 0.06	0.42 ± 0.13	0.42 ± 0.15	0.01 ± 0.06	ns
CHOL/HDL	4.33 ± 1.46	4.17 ± 1.47	-0.2 ± 0.9	4.93 ± 1.16	4.38 ± 0.99	-0.6 ± 0.6	ns
CRP-us, mg.L^{-1}	8.9 ± 11.3	8.5 ± 8.5	-0.4 ± 4.2	8.1 ± 8.3	7.6 ± 5.3	-0.6 ± 4.0	ns
Leptine, ng.mL^{-1} *(n=7 immédiat ; n=8 différé)*	52.5 ± 44.2	43.9 ± 27.4	-8.6 ± 20.7	41.0 ± 21.4	37.9 ± 18.1	-3.1 ± 6.6	ns

* signifie p<0.05 entre groupe différé vs. groupe traité pour les valeurs initiales.
p-value : p-valeur de la comparaison des variations (J30-initial) entre groupe différé et groupe traité.

Tableau 4 : Paramètres cardiovasculaires et évolution sous VNI pendant 1 mois par rapport au groupe contrôle

	Traitement différé (n=14)			Traitement immédiat (n=13)			
	Initial	J30	Variation	Initial	J30	Variation	***p-value***
PA_S, *mmHg*	135 ± 20	129 ± 16	-6.0 ± 11	137 ± 20	132 ± 17	-4.9 ± 21	ns
PA_D, *mmHg*	76 ± 10	71 ± 13	-5 ± 11	76 ± 10	71 ± 11	-5 ± 16	ns
VOP, *m.s^{-1}*	9.6 ± 2.3	9.1 ± 1.6	-0.50 ± 1.0	10.2 ± 2.5	9.2 ± 1.3	-1.0 ± 2.6	ns
RH-PAT	2.02 ± 0.51	1.94 ± 0.68	-0.1 ± 0.6	2.01 ± 0.59	1.88 ± 0.55	-0.1 ± 0.6	ns

* signifie p<0.05 entre groupe différé vs. groupe traité pour les valeurs initiales.
p-value : p-valeur de la comparaison des variations (J30-initial) entre groupe différé et groupe traité.

Analyse en intention de traiter :

Les paramètres respiratoires et leur évolution sont rapportés dans le tableau 1. Après 1 mois de VNI nocturne, les patients du groupe « traitement immédiat » diminuaient significativement leur $PaCO_2$ diurne (-0.4 ± 0.6 vs. 0.1 ± 0.4 kPa, p=0.04), leur [HCO_3^-] (-2.0 ± 1.5 vs. 0.5 ± 2.0 $mmol.L^{-1}$, p=0.001), augmentaient leur capacité pulmonaire totale (5 ± 5 vs. -0.3± 7% de la valeur prédite) et leur capacité résiduelle fonctionnelle (+2 ± 14 vs. -9 ± 9 % de la valeur prédite) par rapport au groupe « traitement par VNI différé ».

La structure du sommeil, les troubles respiratoires nocturnes, la vigilance diurne et leur évolution sous VNI sont rapportés dans le tableau 2. Sous VNI, les patients du groupe « traitement immédiat par VNI » diminuaient leur temps de sommeil total. La structure du sommeil était modifiée avec une diminution du sommeil lent léger (-11 ± 12 vs. 0.6 ± 10%, p=0.01) et une augmentation du sommeil paradoxal (+10 ± 9 vs. -0.1 ± 10%, p=0.02) par rapport au groupe contrôle. Les obstructions pharyngées étaient traitées (IAH : -35.6 ± 39.7 vs. 4.9 ± 28.8 /h, p=0.01) et les micro-éveils respiratoires diminuaient (-32 ± 29 vs. + 3.3 ± 24 /h, p=0.003). Le nombre de micro-éveils non respiratoires augmentait significativement sous VNI (+8±9 vs.-3± 10 /h). Les saturations en O_2 moyenne, minimale, et le pourcentage de temps passé avec une SpO2 <90% étaient améliorés. Après un mois de VNI nocturne, la diminution de [HCO_3-], reflétant l'amélioration de l'hypoventilation alvéolaire chronique, était corrélée à l'augmentation de la saturation moyenne nocturne (r=-0.71 p=0.02) et corrélée à la diminution du temps passé avec une SpO2<90% (r=0.6 p=0.048) (figure 1).

La vigilance diurne subjective (échelle d'Epworth) et objective (latence d'endormissement au test de OSLER) n'était pas significativement améliorée dans le groupe traité par rapport au groupe contrôle. Cependant, dans le groupe « traitement immédiat par VNI », tous les patients qui avaient une latence d'endormissement inférieure à 40 minutes sauf un, retrouvent un test d'OSLER normal après 1 mois de VNI. Le patient qui diminuait sa

Figure 2 : Corrélations entre variation de [HCO_3^-] et paramètres de l'oxymétrie nocturne

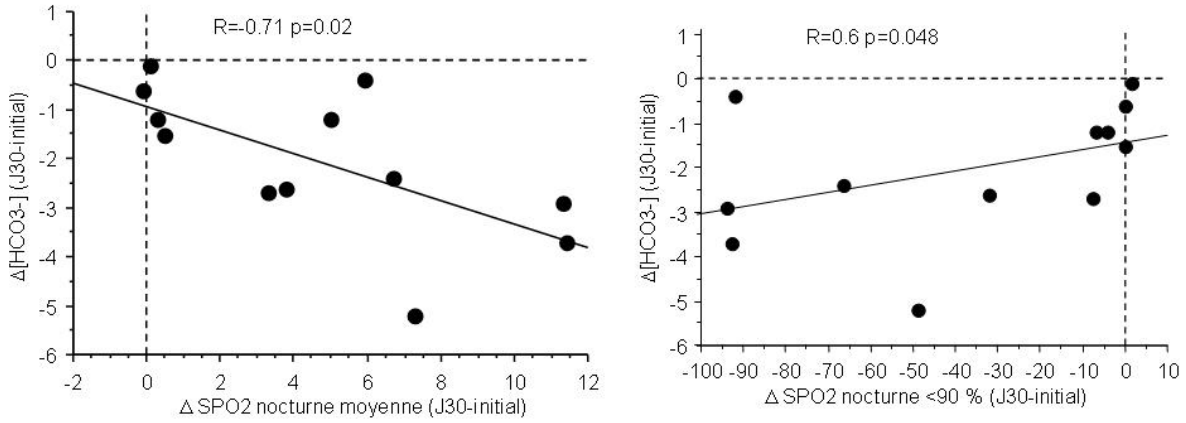
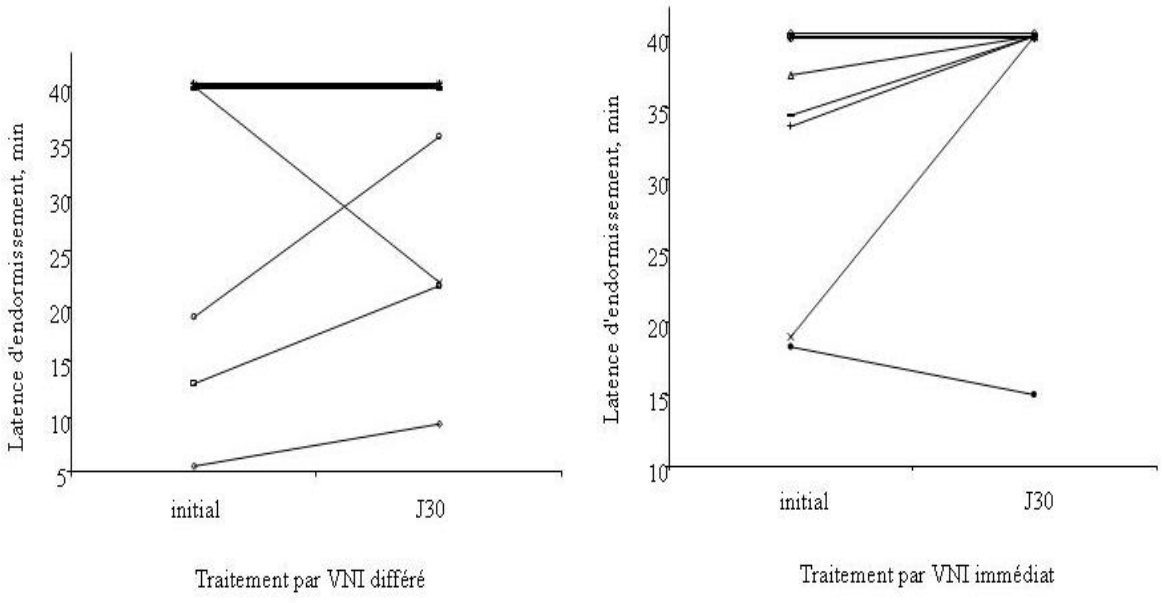


Figure 3 : Evolution de la latence d'endormissement au test de OSLER



latence d'endormissement au test d'OSLER (-3,3 min) augmentait son index de micro-éveils totaux sous VNI *(50/h sous VNI vs. 41/h sans VNI)* avec une augmentation importante de l'index des micro-éveils non-respiratoires *(35/h sous VNI vs. 10/h sans VNI)*. Dans le groupe « traitement par VNI différé » aucun des patients qui avaient une latence inférieure à 40 minutes au test d'OSLER ne retrouve une latence normale après 1 mois (figure 2).

Aucun des paramètres cardiovasculaires (Tableau 4) et métaboliques (Tableau 3) n'était modifié par un mois de VNI nocturne par comparaison au groupe contrôle.

Analyse per-protocole :

Trois patients du groupe « traitement immédiat par VNI » avaient une observance de la VNI inférieure à 4h/j. Ces patients ont été exclus de l'analyse. Les résultats de l'analyse per-protocole sont superposables à l'analyse en intention de traiter. Après un mois de VNI nocturne (observance moyenne = 6.3 ± 1.3 h/nuit), la $PaCO_2$ diurne était améliorée, la capacité pulmonaire totale et la capacité résiduelle fonctionnelle étaient augmentées par rapport au groupe « traitement différé ». La structure du sommeil était modifiée sous VNI, avec une diminution de la proportion de sommeil lent léger et une augmentation de la proportion de sommeil paradoxal. Les troubles respiratoires nocturnes, les micro-éveils respiratoires étaient corrigés par contre la vigilance diurne (objective ou subjective) ne s'améliorait pas plus dans le groupe « traitement immédiat » que dans le groupe « traitement différé ». Aucun des paramètres cardiovasculaires et métaboliques n'était modifié par un mois de VNI.

Discussion :

Cette étude est la première étude randomisée contrôlée qui évaluait dans le SOH, l'effet de la VNI nocturne sur des paramètres respiratoires, la structure du sommeil, la vigilance (objective et subjective), les paramètres cardio-vasculaires et métaboliques. Après un mois de VNI nocturne, l'hypoventilation alvéolaire diurne était corrigée, la capacité pulmonaire totale augmentait et la capacité résiduelle fonctionnelle restait stable par rapport au groupe contrôle. La structure du sommeil était améliorée avec une diminution de la proportion du stade lent léger et une augmentation de la proportion de sommeil paradoxal. La fragmentation de sommeil non respiratoire était significativement augmentée. Aucun paramètre métabolique et cardiovasculaire n'était modifié.

Amélioration de la $PaCO_2$ diurne et facteurs associés à cette amélioration.

Notre étude mettait en évidence une amélioration significative de la $PaCO_2$ diurne chez des patients SOH en état stables traités par VNI nocturne pendant un mois par rapport à un groupe contrôle. Cette amélioration était un résultat attendu par analogie aux patients insuffisants respiratoires restrictifs traités par VNI. Cependant, même si plusieurs études, à court et long terme, montrent que la $PaCO_2$ diurne était améliorée par la VNI nocturne dans le SOH (Masa, Celli et al. 2001; de Lucas-Ramos, de Miguel-Diez et al. 2004; Perez de Llano, Golpe et al. 2005), aucune de celles-ci n'avait de groupe contrôle. De plus, Perez de Llano incluaient des patients en décompensation respiratoire ce qui pouvait induire une surestimation de l'effet de la VNI sur la $PaCO_2$ diurne.

Les mécanismes par lesquels la $PaCO_2$ diurne s'améliore sous assistance ventilatoire dans le SOH sont discutés. Une des hypothèses principales est que la correction des événements respiratoires nocturnes pourrait améliorer la sensibilité des centres respiratoires au CO_2 (Lin 1994; Han, Chen et al. 2001; de Lucas-Ramos, de Miguel-Diez et al. 2004). Dans la présente étude, il n'y avait pas d'amélioration de la réponse ventilatoire au CO_2. Pourtant,

la diminution de [HCO_3-], reflétant l'amélioration de l'hypoventilation alvéolaire chronique, était corrélée à l'augmentation de la saturation nocturne en O_2 et à la diminution du temps de sommeil passé avec une SpO_2 inférieure à 90¨% (figure 2). Ceci suggère que la correction des troubles respiratoires au cours du sommeil est un des facteurs déterminant important de la correction de l'hypoventilation diurne. La durée de traitement par VNI d'un mois pourrait être insuffisante pour modifier la sensibilité des centres respiratoires.

Les patients traités par VNI avaient une augmentation de la capacité pulmonaire totale (+0.3 ± 0.3 L; +5 ± 5% des valeurs prédites) alors qu'elle restait stable chez les patients du groupe contrôle (-0.09 ± 0.5 ; -0.3 ± 7% des valeurs prédites) (Tableau 1). Cette variation était significativement différente entre les deux groupes, ce qui suggère que l'amélioration de la fonction respiratoire peut être un déterminant de l'amélioration de la $PaCO_2$. L'amélioration de la fonction respiratoire des patients SOH traités par VNI n'est pas systématiquement retrouvée dans la littérature (Masa, Celli et al. 2001; Perez de Llano, Golpe et al. 2005), bien qu'aucune des études antérieures n'avait de groupe contrôle. Cependant ces résultats sont en accord avec l'étude de Heinemann et coll (Heinemann, Budweiser et al. 2007) qui retrouvaient une amélioration de la CPT de 16% après 12 mois de VNI chez des patients OHS. Ces auteurs faisaient l'hypothèse que la VNI améliorait la compliance thoraco-pulmonaire ce qui permettait d'augmenter le volume de réserve expiratoire et la CPT.

Structure du sommeil et vigilance diurne

L'amélioration de la structure du sommeil sous PPC est un effet démontré chez les patients affectés d'un SAOS. Dans le SOH, Banergee et coll ont montré que la PPC améliorait la structure du sommeil, diminuait les micro-éveils respiratoires associés aux obstructions pharyngées (Banerjee, Yee et al. 2007). Ces résultats sont en accord avec ceux de la présente étude. Cependant, l'index des micro-éveils non-respiratoires était significativement augmenté sous VNI. Nous avions déjà rapporté cet effet de la VNI (Chouri-Pontarollo, Borel et al.

2007) qui pourrait être du à des fuites (Bach, Robert et al. 1995), des phénomènes d'inconfort liés au masque, du bruit lié au fonctionnement de l'appareil ou des asynchronismes patient-machine sans désaturation en O2 associée (Guo, Sforza et al. 2007). Pour la première fois, l'augmentation des micro-éveils « non respiratoires » sous VNI est calibrée par rapport à un groupe contrôle. Il est de l'ordre de 10/heure. Pour l'ensemble du groupe, cette augmentation des micro-éveils non-respiratoires reste cependant très inférieure à la diminution des micro-éveils respiratoires. Cependant chez le patient qui diminuait sa latence d'endormissement au test de OSLER après 1 mois de VNI, la polysomnographie sous VNI montrait une augmentation de l'index de micro-éveils totaux avec une augmentation de l'index des micro-éveils non respiratoires par rapport à la polysomnographie initiale sans VNI. Ceci met en évidence l'importance d'évaluer l'amélioration de la structure du sommeil au-delà de l'amélioration de la gazométrie artérielle diurne et de l'oxymétrie nocturne chez les patients SOH qui présentent une somnolence diurne persistante malgré un traitement par VNI.

Malgré l'amélioration de la structure du sommeil et la diminution des micro-éveils, la vigilance diurne objective n'était pas significativement améliorée dans le groupe traité par VNI par rapport au groupe contrôle. Perez de Lano et coll montraient une amélioration de la vigilance subjective des patients OHS traités par VNI mais incluaient des patients instables ce qui pouvait majorer l'évaluation de la sévérité de la somnolence initiale (Perez de Llano, Golpe et al. 2005). Hida et coll retrouvaient une amélioration de la somnolence subjective chez des patients OHS mais cette étude n'était pas contrôlée par un groupe de patients OHS non traités par VNI (Hida, Okabe et al. 2003). Dans la présente étude, tous les patients du groupe « traitement immédiat par VNI » qui avaient une latence d'endormissement inférieure à 40 minutes, sauf un, retrouvent un test d'OSLER normal après 1 mois de VNI alors qu'aucun des patients qui avaient une latence inférieure à 40 minutes au test d'OSLER dans le groupe contrôle ne retrouve une latence normale après 1 mois (figure 3). Ceci suggère que

l'analyse intermédiaire de cette étude peut manquer de puissance et avoir une erreur statistique de deuxième espèce.

Paramètres métaboliques et cardiovasculaires :

Aucun des paramètres métaboliques ne s'améliore après un mois de traitement par VNI. Deux études contrôlées randomisées, conduites chez des patients SAOS (Coughlin, Mawdsley et al. 2007; West, Nicoll et al. 2007), ne retrouvaient pas non plus d'amélioration du métabolisme du glucose après 6 semaines ou 3 mois de traitement par PPC. Plusieurs hypothèses peuvent être évoquées pour expliquer ces résultats. Si les troubles respiratoires du sommeil peuvent majorer l'insulino-résistance (Ip, Lam et al. 2002), leur contribution pourrait être relativement moins importante dans l'obésité sévère (Sharma, Kumpawat et al. 2007); Deuxièmement, le délai d'un mois pourrait être trop court pour induire des modifications significatives, cependant dans l'étude de West et coll, les patients recevaient trois mois de PPC sans modification de l'insulino-résistance (West, Nicoll et al. 2007). Troisièmement, notre étude incluait des patients diabétiques traités par insulino-sensibilisateurs ou/et insulinothérapie. Les effets respectifs de ces traitements sur l'homéostasie glucidique pourraient masquer des modifications plus fines, liées à l'amélioration des troubles respiratoires.

De façon similaire, aucun des paramètres cardio-vasculaires ne s'améliorait après 1 mois de VNI nocturne. Coughlin et coll retrouvaient une diminution des pressions artérielles cliniques diastolique et systolique après 6 semaines de PPC chez des patients obèses apnéiques (Coughlin, Mawdsley et al. 2007). Dans cette étude, les patients ne recevaient aucun traitement anti-hypertenseur et avaient une pression diastolique supérieure aux patients inclus dans notre étude. Dans ces conditions la mise en évidence de variation de la pression artérielle était plus aisée et il est possible que nous ayons eu un effet « plancher » dans la présente étude.

Forces et limites de l'étude, perspectives associées :

Cette étude était la première étude randomisée contrôlée évaluant l'effet de la VNI nocturne dans le syndrome obésité hypoventilation. L'analyse intermédiaire montrait des différences sur les caractéristiques initiales des patients inclus dans les deux groupes. Les patients inclus dans le groupe « traitement immédiat » avait une concentration en [HCO3-] significativement plus élevée, une capacité pulmonaire totale et une capacité résiduelle fonctionnelle plus basses que les patients contrôles. Ces différences devraient se corriger avec l'inclusion du dernier 1/3 de patients.

Il est possible que l'amélioration des paramètres métaboliques et cardio-vasculaires soit masquée par l'inclusion de patients diabétiques et hypertendus traités. Ceux-ci pourraient induire un « effet plancher » des bénéfices de la VNI, de part l'interférence des traitements médicamenteux. Nous pouvons faire l'hypothèse que les modifications métaboliques et cardiovasculaires liées à la correction des troubles respiratoires du sommeil soient dépendantes du degré d'obésité des sujets. En effet, chez les sujets non obèses apnéiques la correction d'un SAOS pourrait améliorer les paramètres cardio-vasculaires (épaisseur intima média, rigidité artérielle, fonction endothéliale) (Ip, Tse et al. 2004; Drager, Bortolotto et al. 2007) et l'insulino-résistance (Harsch, Schahin et al. 2004); chez les sujets obèses apnéiques, la correction du SAOS pourrait améliorer la pression artérielle (Coughlin, Mawdsley et al. 2007) mais pas les paramètres métaboliques (Coughlin, Mawdsley et al. 2007; West, Nicoll et al. 2007). Enfin, chez les sujets OHS, la correction des troubles respiratoires du sommeil et de l'hypoventilation alvéolaire diurne pourrait n'avoir qu'un impact limité compte tenu des co-morbidités fréquemment associées. Dans ce contexte il serait intéressant d'évaluer prospectivement l'évolution au long cours des paramètres cardiovasculaires et métaboliques en fonction de l'observance à la VNI. La VNI pourrait permettre de ralentir l'évolution péjorative de ces paramètres.

CHAPITRE 2 :

IMPACT DE LA VENTILATION NON-INVASIVE AU COURS DES EFFORTS CHEZ LE PATIENT INSUFFISANT RESPIRATOIRE CHRONIQUE PARIETO-RESTRICTIF

CHAPITRE 2 : IMPACT DE LA VENTILATION NON-INVASIVE AU COURS DES EFFORTS CHEZ LE PATIENT INSUFFISANT RESPIRATOIRE CHRONIQUE PARIETO-RESTRICTIF.

PREREQUIS

La ventilation non-invasive nocturne est le traitement de première intention des patients insuffisants respiratoires chroniques pariéto-restrictifs ; elle corrige l'hypoventilation diurne, améliore les symptômes, diminue l'utilisation du système de soin (Leger, Bedicam et al. 1994; Schonhofer, Wallstein et al. 2001; Gonzalez, Ferris et al. 2003). Malgré ce traitement, les patients restent limités à l'effort (Shneerson 1978), ce qui au final pourrait altérer leur qualité de vie (Ando, Mori et al. 2003). L'incapacité mécanique à augmenter la ventilation minute (Shneerson, 1978), l'augmentation à l'exercice du travail respiratoire et de la dyspnée (O'Donnell, Hong et al. 2000), la fatigue des muscles inspiratoires (Hussain and Pardy 1985), l'inaptitude à augmenter suffisamment leur débit cardiaque (Hijazi, Ramanathan et al. 1998; Miller, Beck et al. 2002) sont des facteurs explicatifs de l'intolérance à l'effort chez ces patients insuffisants respiratoires chroniques restrictifs. Le déconditionnement musculaire périphérique pourrait également contribuer (Kesten, Garfinkel et al. 1991).

L'intolérance à l'effort, la dyspnée, la fatigue, l'altération de la qualité de vie sont décrits par ces patients insuffisants respiratoires restrictifs avec des plaintes comparables à celle des patients BPCO. Pour ces derniers, ***la réhabilitation respiratoire*** améliore la tolérance à l'effort, la dyspnée, la qualité de vie, réduit la consommation de soins (Lacasse, Brosseau et al. 2002). Par analogie, il est recommandé de réhabiliter les patients non-BPCO, même sans évidence scientifique parfaitement documentée (Nici, Donner et al. 2006). Chez des patients thoraco-restrictifs, quelques études rétrospectives, non contrôlées (Ando, Mori et al. 2003; Ferreira, Feuerman et al. 2006) montrent que les patients améliorent leur tolérance à l'effort et leur qualité de vie de façon comparable aux patients BPCO. Il n'existe pas de

recommandation sur les stratégies optimales de réhabilitation chez ces patients restrictifs (Nici, Donner et al. 2006; Ries, Bauldoff et al. 2007).

Notre expérience de réhabilitation à domicile de plus de 400 patients sur 6 ans (Borel, Wuyam et al. 2004) nous a permis d'une part d'identifier que l'amélioration de la tolérance à l'effort était un déterminant important de l'amélioration de la qualité de vie et d'autre part, que les patients les plus sévères, quelque-soit l'étiologie du handicap respiratoire, répondaient mal à un simple programme de réentraînement à domicile sur ergocycle. Wedzicha et coll (Wedzicha, Bestall et al. 1998) montraient que les patients BPCO (VEMS <40% des valeurs prédites) souffrant d'une dyspnée sévère (échelle MRC=5) n'amélioraient pas leur capacité d'exercice ni leur qualité de vie après un programme de ré-entraînement contrairement à des patients dont la dyspnée initiale était moins sévère (échelle MRC=3-4). Toutefois, dans cette étude, les patients les plus sévères (MRC=5) réalisaient de la marche et de l'activité gymnique deux fois par semaine à domicile sans ergocycle alors que les patients moins sévères avaient deux séances d'ergocycle en plus. Plus récemment, la même équipe (Garrod, Marshall et al. 2006) confirmait ces résultats et montrait que 46% des BPCO sévères (VEMS < 40%, échelle MRC=5) arrêtaient le programme de réhabilitation avant les 7 semaines requises alors que les patients moins sévères (VEMS >40%; 1<échelle MRC<4) avaient un taux d'abandon significativement inférieur (24%). Dans cette étude, la qualité de vie, la dépression, la faiblesse musculaire étaient des facteurs associés à l'arrêt du programme ce qui suggère que la sévérité initiale du patient est un des déterminants des résultats et du risque d'abandon. Garrod et coll (Garrod, Mikelsons et al. 2000), dans une étude randomisée contrôlée, chez des patients BPCO sévères, évaluaient l'effet de la VNI nocturne associée à un programme de réentrainement et montrait que les patients sous VNI amélioraient significativement leur tolérance à l'effort et leur score global de qualité de vie. Cette amélioration du score global était principalement liée à l'amélioration plus spécifique du score de fatigue intégré dans ce

« Chronic Respiratory Questionnaire » (Tableau 2). Ces résultats suggèrent que les conditions de fatigue et de confort perçues au cours du réentraînement peuvent aussi être un déterminant important des bénéfices. En effet, dans cette étude, l'amélioration de la tolérance à l'effort a pu se faire en épargnant une fatigue supplémentaire.

Les difficultés rencontrées pour réhabiliter les patients les plus sévères ont permis le développement de nouvelles stratégies spécifiques de réentraînement à l'effort. L'électro-stimulation (Bourjeily-Habr, Rochester et al. 2002; Neder, Sword et al. 2002) est une de ces stratégies. Notre groupe a récemment mis en évidence qu'un programme de réentraînement associé à de l'électro-stimulation des quadriceps améliorait significativement le périmètre de marche, la force des quadriceps et la dyspnée comparativement à des patients BPCO sévères ré-entraînés sans électro-stimulation (Vivodtzev, Pepin et al. 2006). Plusieurs études ont aussi évalué l'efficacité de la VNI comme stratégie pour améliorer les résultats d'un programme de réhabilitation (Ambrosino and Strambi 2004). Costes et coll montraient chez des patients BPCO sévères (VEMS = 31.5 ± 9.2 %) une amélioration de la consommation maximale d'oxygène chez les patients ré-entraînés sous VNI par rapport au groupe contrôle (Costes, Agresti et al. 2003). Hawkins et coll retrouvaient chez des patients sévères (VEMS = 26±7 % de la valeur prédite), ré-entraînés sous VNI, une amélioration de la puissance maximale significative par rapport au groupe contrôle (Hawkins, Johnson et al. 2002). Dans cette étude, l'intensité des séances d'entraînement en fin de programme était plus importante dans le groupe sous VNI que dans le groupe contrôle. Enfin, Van'hull et coll montraient, chez des patients dont les limites ventilatoires au cours d'un test d'effort maximal étaient atteintes, une amélioration plus importante des capacités d'endurance (Shuttle test et test sur

Tableau 2 : Evolution de la qualité de vie après réentrainement diurne et VNI nocturne chez des sujets BPCO sévères. D'après Garrod et coll. Am J Resp Crit Care Med 2000.

CHANGE IN HEALTH STATUS FROM RANDOMIZATION TO END OF STUDY (12 wk) IN NPPV + ET AND ET GROUPS*

	NPPV + ET (*n* = 17)				ET (*n* = 20)			
	Pre	Post	Difference	95% CI	Pre	Post	Difference	95% CI
CRDQ§ (total)	68.1	92.2	24.1	15.1 to 33.0‡	73.3	85.1	11.8	4.34 to 19.2†
Dyspnea	13.1	18.0	4.90	0.63 to 9.24†	15.1	16.8	1.70	−0.74 to 4.04
Mastery	16.2	21.1	4.90	2.34 to 7.42‡	15.6	18.7	3.10	1.12 to 5.08†
Emotion	26.8	35.2	8.40	5.18 to 11.6‡	28.6	33.2	4.60	1.75 to 7.45†
Fatigue	11.9	17.8	5.90	3.94 to 7.71‡	13.9	16.4	2.50	0.44 to 4.36†
HAD (total)	16.3	15.0	−1.30	−4.17 to 7.17	17.6	13.8	−3.80	−1.20 to 8.80
Anxiety	8.18	7.64	−0.54	−2.82 to 4.20	8.85	7.65	−1.20	−1.11 to 3.51
Depression	8.13	7.35	−0.78	−2.16 to 3.78	8.75	6.15	−2.60	−0.38 to 5.58
LCADL‖ (total)	45.4	38.7	−6.70	−11.5 to −1.94‡	40.2	33.8	−6.40	−10.5 to −2.22‡
Self-care	9.94	8.24	−1.70	−0.27 to 3.67	9.60	8.30	−1.30	−0.05 to 2.65
Domestic	22.1	20.2	−1.90	−1.63 to 5.39	18.6	14.8	−3.80	−6.70 to −0.89†
Physical	6.00	4.65	−1.35	−2.33 to −0.37‡	5.75	5.05	−0.70	−1.25 to −0.15†
Leisure	7.47	5.82	−1.65	−2.46 to −0.83‡	6.25	5.70	−0.55	−0.14 to 1.24

Definition of abbreviations: CI = confidence interval; CRDQ = Chronic Respiratory Disease Questionnaire; ET = exercise training; HAD = Hospital Anxiety and Depression Scale; LCADL = London Chest Activity of Daily Living Scale; NPPV = noninvasive positive pressure ventilation.

* Values represent change over time.

† $p < 0.05$.

‡ $p < 0.001$.

§ Higher score reflects better symptoms.

‖ Higher score reflects greater disability.

ergocyle) chez ceux qui étaient entraînés sous VNI efficace (10 cm H2O d'aide inspiratoire) par rapport à ceux ré-entraînés sous VNI inefficace (5cmH2O d'aide inspiratoire) (van 't Hul, Gosselink et al. 2006). À l'inverse de ces trois études positives, Bianchi et coll chez des patients moins sévères (VEMS 44±16%) ne retrouvaient pas d'effet additionnel d'un support ventilatoire au cours des efforts par rapport à un groupe contrôle (Bianchi, Foglio et al. 2002). Par ailleurs, un quart des patients ré-entraînés sous VNI abandonnaient. *Ces études suggèrent que dans la BPCO, la VNI utilisée au cours des efforts n'est pas efficace chez des patients non sélectionnés, mais peut être une aide pour les patients les plus sévères*. Aucune n'étude n'avait évalué l'efficacité de la VNI au cours d'un programme de réentraînement à l'effort chez des patients insuffisants respiratoires chroniques restrictifs.

OBJECTIFS ASSOCIÉS À LA PROBLEMATIQUE DU RÉENTRAINEMENT À L'EFFORT

La contribution de ce travail de thèse à la problématique du réentraînement à l'effort est, premièrement, d'évaluer l'impact en aigu de l'assistance respiratoire non invasive utilisée au cours d'un effort dans un groupe de patient insuffisant respiratoire chronique pariéto-restrictif sévère (Etude N°4). Deuxièmement, d'étudier l'efficacité d'un programme de ré-entraînement à l'effort conduit sous VNI à domicile dans cette population (Etude N°5).

ETUDE N° 4 : IMPACT DE LA VNI AU COURS D'UN EXERCICE AIGU CHEZ L'INSUFFISANT RESPIRATOIRE CHRONIQUE PARIETO-RESTRICTIF.

DURING EXERCISE NON INVASIVE VENTILATION IN CHRONIC RESTRICTIVE RESPIRATORY FAILURE

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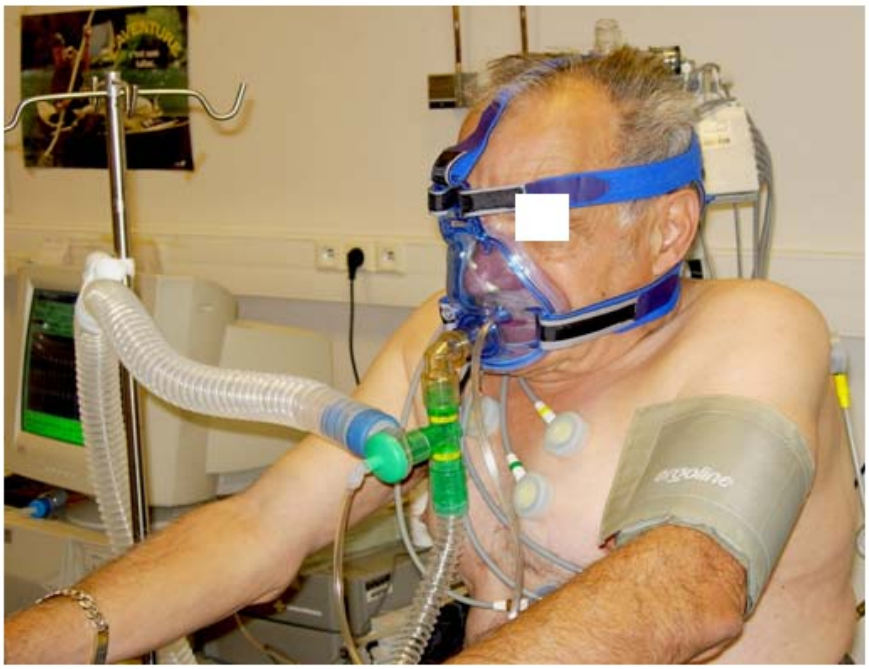
Prérequis : Les patients souffrant d'une insuffisance respiratoire pariéto-restrictive présentent une diminution de leur tolérance à l'effort (Shneerson 1978) qui pourrait être impliqué dans l'altération de leur qualité de vie (Ando, Mori et al. 2003). La réhabilitation respiratoire est une stratégie thérapeutique recommandée chez les patients pariéto-restrictifs par analogie aux patients BPCO, sans que la preuve de son efficacité ni des modalités particulières n'aient été étudiées (Nici, Donner et al. 2006; Ries, Bauldoff et al. 2007).

Objectifs : Le premier objectif de cette étude était d'évaluer l'impact de la VNI au cours d'un effort aigu chez des patients insuffisants respiratoires pariéto-restrictifs. Le deuxième objectif était de déterminer si l'efficacité de la VNI à l'effort était associée à la sévérité de la pathologie sous-jacente.

Méthodes : Les patients étaient évalués au cours de deux demi-journées séparées d'une semaine. Au cours de la première journée, ils réalisaient des épreuves fonctionnelles respiratoires, des gaz du sang en ventilation spontanée, un SNIP test, une épreuve d'effort incrémentale maximale sur ergocycle. Trente minutes après l'épreuve maximale, les patients réalisaient une épreuve de marche de six minutes. Au cours de la deuxième demi-journée, après s'être habitués à l'utilisation de la VNI pendant l'exercice sur ergo-cycle, les patients

Figure 5 : Test d'endurance sous VNI à 75% de la puissance maximale.



réalisaient dans un ordre randomisé deux épreuves d'endurance sur ergo-cycle à 75% de la puissance maximale avec et sans VNI (figure 5).

Résultats : 18 patients étaient inclus. Pour l'ensemble du groupe, le temps d'endurance sous VNI était significativement amélioré de 71 %. L'augmentation du temps d'endurance sous VNI était corrélée à la diminution de la dyspnée, la diminution de la fréquence cardiaque et à une moindre désaturation en oxygène. Les patients «répondeurs » à la VNI au cours de l'effort (ceux qui amélioraient le temps d'endurance de plus de 50% sous VNI par rapport au test en air libre) avaient une $PaCO_2$ diurne au repos plus élevée, une capacité vitale et une capacité pulmonaire totale inférieures aux « non-répondeurs ». À la fin de l'épreuve d'effort incrémentale maximale en ventilation spontanée, les patients « répondeurs » avaient un volume courant plus faible, un espace mort plus grand, un pouls d'oxygène plus bas que les patients « répondeurs ».

Discussion-Conclusion : En augmentant la ventilation minute, la VNI permet d'améliorer la dyspnée, et de diminuer la désaturation des patients les plus sévères. La limitation du pouls d'oxygène au cours de l'épreuve d'effort maximale en ventilation spontanée chez les patients « répondeurs » (les plus sévères) suggère que la diminution de la fraction d'éjection systolique pourrait être impliquée dans la limitation à l'effort chez ces patients. La corrélation entre l'amélioration du temps d'endurance sous VNI et la diminution de la fréquence cardiaque suggère que la VNI en plus de son effet ventilatoire, pourrait significativement améliorer cette dysfonction systolique.

La VNI améliore la tolérance à l'effort des patients insuffisants respiratoires pariéto-restrictifs sévères. Une capacité vitale basse (<1L) et une inefficacité ventilatoire (rapport Vd/vt élevé) à l'effort pourrait discriminer les répondeurs des non-répondeurs à la VNI au cours des efforts.

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During exercise non-invasive ventilation in chronic restrictive respiratory failure

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KEYWORDS
Chronic restrictive respiratory failure;
Exercise;
Non-invasive ventilation;
Kyphoscoliosis;
Respiratory function

Summary
Background: Exercise intolerance limits chronic restrictive respiratory failure (CRF) patients from participating in daily activities. The specific modalities that could improve exercise tolerance in these patients remain to be established.
Objective: To investigate exercise endurance and associated physiological responses with non-invasive ventilation (NIV) during exercise in restrictive CRF patients.
Methods: Eighteen patients (63 ± 11 years, total lung capacity (TLC) $= 59 \pm 16\%$ of predicted value) performed maximal exercise in spontaneous breathing conditions (MWLE) and during two constant workload exercise (CWLE) tests at 75% Pmax, with or without NIV in random order. "NIV Responders" were defined by an increase in CWLE duration of more than 50% when using NIV.
Results: For the whole group, CWLE duration when using NIV increased from 5.6 ± 4.6 to 9.6 ± 8.1 min. Increase in CWLE duration correlated with reduction in heart rate and oxygen desaturation, and dyspnea relief during exercise. NIV responders ($n = 9$) showed more severe lung restriction (TLC: 2.6 ± 0.7 versus 3.5 ± 1.1 L; forced vital capacity: 1.0 ± 0.16 versus 1.46 ± 0.38 L). At the end of MWLE, responders had a lower Vt (0.60 ± 0.09 versus 0.89 ± 0.34 L), a higher dead-space ratio (0.51 ± 0.06 versus 0.38 ± 0.12) and lower oxygen pulse (4.5 ± 1.2 versus 7.4 ± 3.9 ml/beat).
Conclusion: In severely restrictive patients, NIV during exercise significantly improved exercise duration and tolerance and increased alveolar ventilation.
Trial registration: The enrollment of the patients started before July 1, 2005.

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Introduction

Severe chest wall deformities, such as kyphoscoliosis and tuberculosis sequellae may lead to secondary chronic restrictive respiratory failure (CRF). In these patients, long-term nocturnal non-invasive mechanical ventilation (NIV) is now recognized as first line therapy. NIV has been reported to improve daytime arterial blood gases, survival and to reduce rates of hospitalizations.[1–3] Chest wall diseases represent 30% of home-treated NIV patients in Europe i.e. approximately 8000 patients.[4]

As these patients' exhibit increased survival, it becomes necessary to focus on their persistent disability and alterations in quality of life. Exercise intolerance and dyspnea are among the major complaints preventing patients with severe restrictive chest wall disease from participating in activities of daily life. Pulmonary rehabilitation may be of value for these patients in whom respiratory symptoms and diminished health-related quality of life may be observed. To date, there is no formal evidence-based guidelines for exercise activities in restrictive lung disease, and '*expert opinion based on pathophysiology and clinical experience is recommended*'.[5] Ambulatory oxygen therapy improves dyspnea but not a 6 min walking distance, thus suggesting a limited interest for such a treatment during rehabilitation in restrictive patients.[6] Using NIV during daily exercise could be a part of the rehabilitation program but few data are available on this strategy.

The use of NIV during exercise has been studied in chronic obstructive pulmonary disease patients (COPD) since the early 1990s.[7–15] For such patients, NIV during exercise may improve exercise endurance and reduce dyspnea.[15] To our knowledge, only two studies have assessed the role of NIV during exercise in CRF patients.[16,17] One study reported improvement in endurance time and reduction in breathlessness[17] in a small population ($n = 7$ patients) whereas the other study[16] did not find any improvement. Although the latter study evaluated the response, during exercise, NIV compared with spontaneous breathing also included a small number of patients ($n = 8$). Moreover, the mean preset inspiratory positive airway pressure (IPAP) (13.7 cm H_2O) led to a moderate increase in minute ventilation during exercise (18%) which may have modified the benefits of NIV. Since exercise limitation in chest wall restrictive patients may be related to the severity of the restrictive disorder, it is important to study the efficacy of NIV in relation to (i) the severity of the underlying disease and (ii) the ability of NIV to maximize the increase in minute ventilation during exercise. This prospective randomized trial set out to study the acute effects of the application of support ventilation as an aid to increase exercise endurance in a group of CRF patients with a broad range of functional impairment.

Materials and methods

Patients

Patients were eligible for the study if they presented the following criteria:

(i) restrictive thoracic disease (idiopathic kyphoscoliosis, tuberculosis sequellae, poliomyelitis sequellae with respiratory involvement) without bronchial obstruction [forced expiratory volume 1 s (FEV_1)/ forced vital capacity (FVC) >75%];
(ii) stable state for more than 3 months;
(iii) previously diagnosed chronic respiratory failure treated by nocturnal NIV for more than 6 months ($PaCO_2$ > 45 mmHg before the initiation of NIV) without other causes of restrictive disorders such as progressive neuro-muscular disease. This study was approved by the university hospital ethics committee and all patients signed a written informed consent in order to participate. This research complies with the Helsinki Declaration.

Study design

Patients were seen on two different occasions 1 week apart. On the first visit, patients underwent pulmonary function tests, a maximal incremental exercise test (MWLE) and a 6 min walking test (6MWT). On a second visit, patients were initially adapted to the use of NIV during exercise, and then were allowed to rest for 30 min. Patients subsequently performed two constant workload exercise tests (CWLE) at 75% of peak workload, with and without NIV in a random order. Subjects were allowed to rest during 30–45 min between the two tests.

Respiratory function and maximal workload exercise testing

Spirometry and thoracic gas volumes were measured using Pitot pneumotachograph and pressure plethysmograph (MEDICAL GRAPHICS Corporation, St. Paul, MN, USA). sniff nasal inspiratory pressure (SNIP) was determined at functional residual capacity using a pressure sensor (Validyne ± 200 cm H_2O) connected to a digital recorder (Direc NEP System 200, Raytech Instruments Inc.; Vancouver; Canada) according to ATS/ERS statement. A 6 MWT was performed in ambient air along a straight 30 m long corridor. All these tests were performed according to the ATS guidelines statement.[18–20] Arterial blood gases (Radiometer, Cophenhagen) were performed at rest, at least 4 h after the end of nocturnal NIV treatment.

Maximal workload exercise test was performed on an electromechanically braked cycle Ergometer (900PC, ERGOLINE, Germany). Work rate was increased every minute by 10% of the expected maximal workload until exhaustion. Minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide exhalation (VCO_2), respiratory rate (RR), tidal volume (Vt) were measured using breath-by-breath automated exercise metabolic system (Sensormedics, Vmax 229; Yorba Linda, CA, USA). Peak power (W_{peak}) was determined as the highest work rate that the patient completed during 1 full minute.

Constant workload exercise testing (CWLE)

The two endurance tests were performed at 75% W_{peak} on the same cycle-ergometer, with NIV or in spontaneous breathing (SB) in random order. Expired gases were collected in a mixing chamber for analysis of ventilatory

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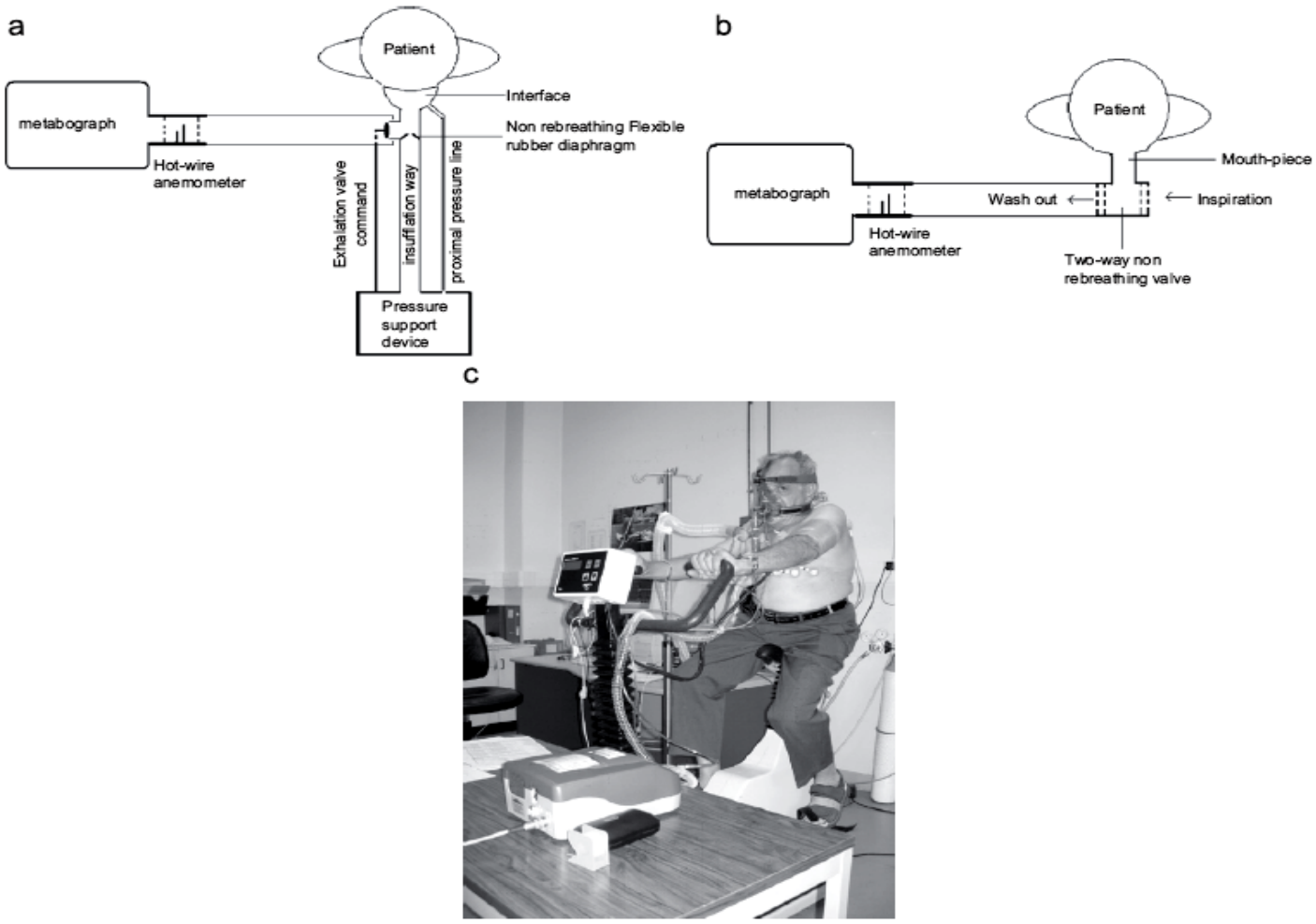

Figure 1 Experimental setting for the two constant workload exercises (a) with non-invasive ventilation, (b) spontaneous breathing and (c) photo.

and metabolic variables. VO_2, VCO_2, RR, Vt were averaged over 20 s time intervals. For the test in spontaneous breathing, the patient was connected via a mouth-piece to a two-way non-re-breathing valve (Model 2700, Hans Rudolph Inc., Kansas City, MO USA); the exhalation port was connected to the mixing chamber (see Figure 1b). For the test with NIV, the exhalation valve of the ventilator was connected to the mixing chamber with a 30 mm diameter tubing (see Figure 1a).

The patient warmed up at the lowest available work rate (20 W). The workload was then abruptly increased until the predetermined workload and continued until exhaustion. At the end of each minute, the patient indicated his level of dyspnea. The test was over when the patient could not maintain exercise because of dyspnea, fatigue or could not maintain 55 cycles/min.

All the tests were performed at the beginning of the afternoon.

Both during MWLE and CWLE, 12-lead electrocardiogram was monitored. SpO_2 was also continuously monitored. There was no oxygen supplementation even in case of desaturation. End-exercise arterial blood gases were sampled by direct arterial sampling.

Non-invasive positive pressure ventilation (NIV) (Figure 1a–c)

The ventilatory mode used for exercise was pressure support ventilation (PSV) in all patients. To avoid bias related to the choice of device, a single ventilator was used for all the patients (SMARTAIR +, AIROX, Pau, France). Settings during exercise were specifically tailored for appropriate ventilation during exercise and were systematically different from the nigh time settings. The patient chose the best-tolerated interface (nasal mask, naso-buccal mask, mouth-piece). IPAP was increased until the patient had a comfortable respiratory sensation ('enough air' at each insufflation). Flow trigger was set at the most sensitive value that prevented involuntary triggering during expiration. Expiratory trigger was set at −50% of maximal inspiratory flow. In order to avoid underestimation of VO_2 due to continuous

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flow in the breathing circuit favored by positive end expiratory pressure (PEEP), we deliberately avoided PEEP in the ventilator settings.

Responders versus non-responders to acute NIV during exercise

We considered as '*responders to NIV*', patients who increased CWLE time under NIV by more than 50% compared with spontaneous breathing. The threshold of 50% was chosen because it corresponds to approximately two times the coefficient of variance of test–retest CWLE time in COPD patients at the same exercise load.[21]

Statistical analysis

Results are expressed as mean±SD. NCSS 97 (Kaysville, Utah, USA) software was used for the statistical analysis. Correlations were analyzed using non-parametric correlation Spearman test. Comparison between CWLE, under either NIV or spontaneous breathing was done with non-parametric paired test (Wilcoxon test).

Comparison between responders and non-responders to NIV were made using a non-parametric unpaired test (Mann–Withney test). For the two endurance tests (with NIV and in SB), ventilatory, metabolic and cardiac variables were compared at iso-time as defined by the longest duration achieved under either condition.

For all tests, a significance level of $p<0.05$ was used.

Results

Patients (Table 1)

Eighteen CRF patients [Total lung capacity (TLC) = 59±16% of predicted value] with a mean age of 63±11 years were included in the study. All had significant reduction in lung volumes (mean FVC of 44±7% of predicted value) and none had significant bronchial obstruction (FEV_1/FVC ratio of 79±10%). Nocturnal NIV had been initiated for 7±6 years on the basis of chronic hypoventilation (mean $PaCO_2$ at initiation of NIV: 52±12 mmHg). All patients used their NIV at nighttime, but none was dependant upon respiratory assistance during the daytime. At the time of inclusion, mean $PaCO_2$ had improved with the regular use of nocturnal NIV (43±5 mmHg). However, all patients complained of dyspnea during activities of daily life. 6MWT distance was reduced (392±131 m i.e. 80±24% of predicted value) with a mean value of dyspnea on a Borg scale of 4±2 at the end of the test. The severity of impairment during exercise was also demonstrated by the mean VO_{2peak} = 12±4 ml/min/kg obtained during MWLE.

Table 1 Patient Characteristics ($n = 18$).

Cause of respiratory failure	16 KS/2 TS
Age, Years	63±11
Men/women	11/7
BMI, kg/m^2	25±6
TLC, l (% of pred value)	3.0±1.0 (59±16)
FEV_1, l (% of pred value)	0.99±0.33 (44±9)
FVC, l (% of pred value)	1.3±0.4 (44±7)
FEV_1/FVC, %	79±10
SNIP, mmHg	45.0±13.2
PaO_2, mmHg	73±7
$PaCO_2$, mmHg	43±5
PH	7.42±0.03
HCO_3-, mmol/l	27.1±1.7
P_{peak}, W	51±22
VO_2 peak, l	0.78±0.36
6 MWT, m	392±131

KS: kyphoscoliosis; TS: tuberculosis sequellae; BMI: body mass index; TLC: total lung capacity; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SNIP: sniff nasal inspiratory pressure; P_{peak}: maximal work rate obtained during incremental exercise test; VO_2 peak: maximal O_2 consumption during incremental exercise test. 6 MWT: Six minute walk test distance.

Effects of NIV during constant workload exercise in the whole group ($n = 18$) (Table 2)

The mean NIV pressure support adjusted for exercise was 19±2 cm H_2O. One patient chose to perform the test with a mouthpiece, nine with a nasal mask and eight with a naso-buccal mask. We did not find that the type of interface had a significant impact on the results (χ^2 = NS). CWLE time increased by 71% with NIV ($p = 0.01$). Iso-time exercises VO_2 and VCO_2 were not significantly different using NIV or during SB. With NIV compared to SB, minute ventilation (VE) increased by 16±7 l/min ($p<0.001$) both by increasing tidal volume (Vt) by 0.6±0.2 litter ($p<0.001$) and reducing respiratory rate (RR) by 4±5/min ($p<0.01$). Mean SpO_2 increased by 4±6% ($p<0.01$) with NIV. Mean heart rate (HR) was also significantly reduced with NIV at iso-time ($p = 0.04$).

Several factors were associated with the increase in endurance time obtained with NIV. The increase in CWLE time during NIV significantly correlated with the reduction in exercise oxygen desaturation ($r = 0.67$, $p = 0.006$) (Figure 2a). Moreover, the increase in CWLE time was related to the reduction in heart rate with NIV ($r = -0.53$, $p = 0.03$) (Figure 2c). Finally, CWLE time correlated with the reduction in dyspnea at iso-time ($r = -0.60$, $p = 0.02$) (Figure 2b).

Comparison between responders and non-responders to NIV

(i) *Spontaneous breathing endurance test*: Despite NIV-responders exhibiting a shorter duration of CWLE than non-responders during spontaneous breathing ($p = 0.05$), the former had more severe desaturation ($p<0.01$), lower Vt ($p = 0.02$) and tended to have lower VE ($p = 0.06$) at the end of this test (Table 2).

(ii) *Ventilatory and cardiovascular changes induced by NIV in responders and non-responders*: Exercise tidal volume increased by 109±41% of spontaneously breathing tidal volume in responders whereas it increased by

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Table 2 Constant-workload exercise (CWLE at 75% Ppeak) during spontaneous breathing and NIV for the whole group ($n = 18$) and comparison between NIV responders ($n = 9$) and non-responders ($n = 9$).

	Total, $n = 18$		Responders, $n = 9$		Non-responders, $n = 9$	
	SB	NIV	SB	NIV	SB	NIV
Work rate, watt	39±17		31±8		43±22	
Endurance-time, min	5.6±4.6	9.6±8.1*	4.0±2.5	12.3±9.3†	7.1±5.8§	6.9±6.1
VE iso-time l/min	26±8	41±13*	23±8	37±11†	30±7	45±14‡
RR iso-time /min	35±8	31±7*	36±7	29±5†	35±10	33±9
Vt iso-time, l	0.77±0.3	1.37±0.4*	0.63±0.1	1.28±0.3†	0.92±0.4§	1.45±0.4‡
HR iso-time, b/min	127±21	123±17*	125±21	118±13	129±21	128±20
SpO_2 iso-time, %	87±7	91±3*	83±7	91±3†	91±4§	91±3
VO_2 iso-time l/min	0.87±0.3	0.89±0.3	0.75±0.3	0.75±0.3	0.98±0.3	1.0±0.4
VCO_2 iso-time l/min	0.75±0.3	0.75±0.3	0.63±0.3	0.65±0.3	0.86±0.3	0.85±0.3
Dys iso-time, Borg	5±2	4±3*	4±1	2±1†	6±2	6±2

SB: spontaneous breathing; NIV: non invasive ventilation; VE: minute ventilation; RR: respiratory rate; Vt: tidal volume; HR: heart rate; VO_2: O_2 consumption; VCO_2: CO_2 exhalation; Dys: dyspnea (modified Borg scale). For the two endurance tests (with NIV and spontaneous breathing), ventilatory, metabolic and cardiac variables were compared at iso-time defined by the longest duration achieved in either condition.

*Comparison between CWLE with NIV versus CWLE in spontaneous breathing for the whole group ($p<0.05$).

†Comparison between CWLE with NIV versus CWLE in spontaneous breathing for "Responders" ($p<0.05$).

‡Comparison between CWLE with NIV versus CWLE in spontaneous breathing for "Non-responders" ($p<0.05$).

§Comparison between "responders" and "non-responders" during CWLE in spontaneous breathing ($p<0.05$).

only 64±30% in non-responders ($p = 0.03$) (Table 2). Respiratory rate significantly decreased with NIV in the responders group only ($p = 0.01$) (Table 2). Overall, responders tended to increase VE to a greater extent (70±24% versus 52±20% in responders and non-responders, respectively ($p = 0.17$)) (Table 2). Again, the mean HR during exercise tended to be reduced by NIV ($p = 0.1$) whilst SpO_2 was significantly increased ($p = 0.008$) (Table 2). As a consequence, dyspnea score at iso-time exercise was relieved with NIV ($p = 0.03$) in the responder group only (Table 2).

(iii) *Lung function and exercise parameters associated with a positive response with NIV.*

Differences in lung function as well in exercise response were associated with a positive response to NIV support during exercise. Thus, responders had a lower TLC (2.6±0.7 versus 3.5±1.1 litter, $p = 0.05$) and lower FVC (1.0±0.16 versus 1.46±0.38 litter, $p = 0.04$) than non-responders (Figure 3). Moreover, responders had higher resting $PaCO_2$ level (respectively 45±5 mmHg versus 40±4, $p = 0.04$).

At the end of MWLE, both VE ($p = 0.04$) and peak Vt (expressed in absolute value $p = 0.003$), were significantly lower in responders (Table 3). In addition, functional dead space ratio (V_D/V_T ratio) was higher in responders ($p = 0.04$). Finally, oxygen pulse at peak exercise was lower in responders ($p = 0.03$).

Discussion

In patients with restrictive chronic respiratory failure, acute NIV during exercise allowed to extend constant workload exercise time by 71% as a mean value. The degree of improvement in CWLE time was significantly related to the reduction of oxygen desaturation, and the decrease in dyspnea and heart rate. Responders to NIV during exercise had lower TLC and FVC. At the end of MWLE in spontaneous breathing, tidal volume was lower in responders with a higher dead space on tidal volume ratio and a lower oxygen pulse. Responders to NIV were thus more severe in terms of ventilatory failure but also demonstrated more cardiac limitation as suggested by lower oxygen pulse.

NIV efficacy during constant workload exercise: comparison with previous studies

Only two studies have assessed the impact of acute NIV during effort in patients with CRF.[16,17] Tsuboi et al.[17] studied seven restrictive patients (tuberculosis sequellae) and demonstrated that NIV significantly prolonged exercise endurance time. During exercise, NIV effectively decreased their breathlessness and significantly improved arterial blood gases measurements. This is in accordance with our results, even though in Tsuboi's study, the experimental setup was different including the use of volumetric ventilators and performing exercise in the supine position. In contrast with Tsuboi et al. and the current study, Highcock et al.[16] in a randomized controlled trial including eight restrictive patients showed a decrease in treadmill walk distance in patients when using PSV compared to an unencumbered test. Minute ventilation at breakpoint of exercise was only slightly increased (+17%) with NIV and oxygen saturation was not improved in this latter study. Given that expiratory pressure was set at 4 cm H_2O means that mean pressure support was about 10 cm H_2O whereas this pressure was about 19 cm H_2O in the present study thus

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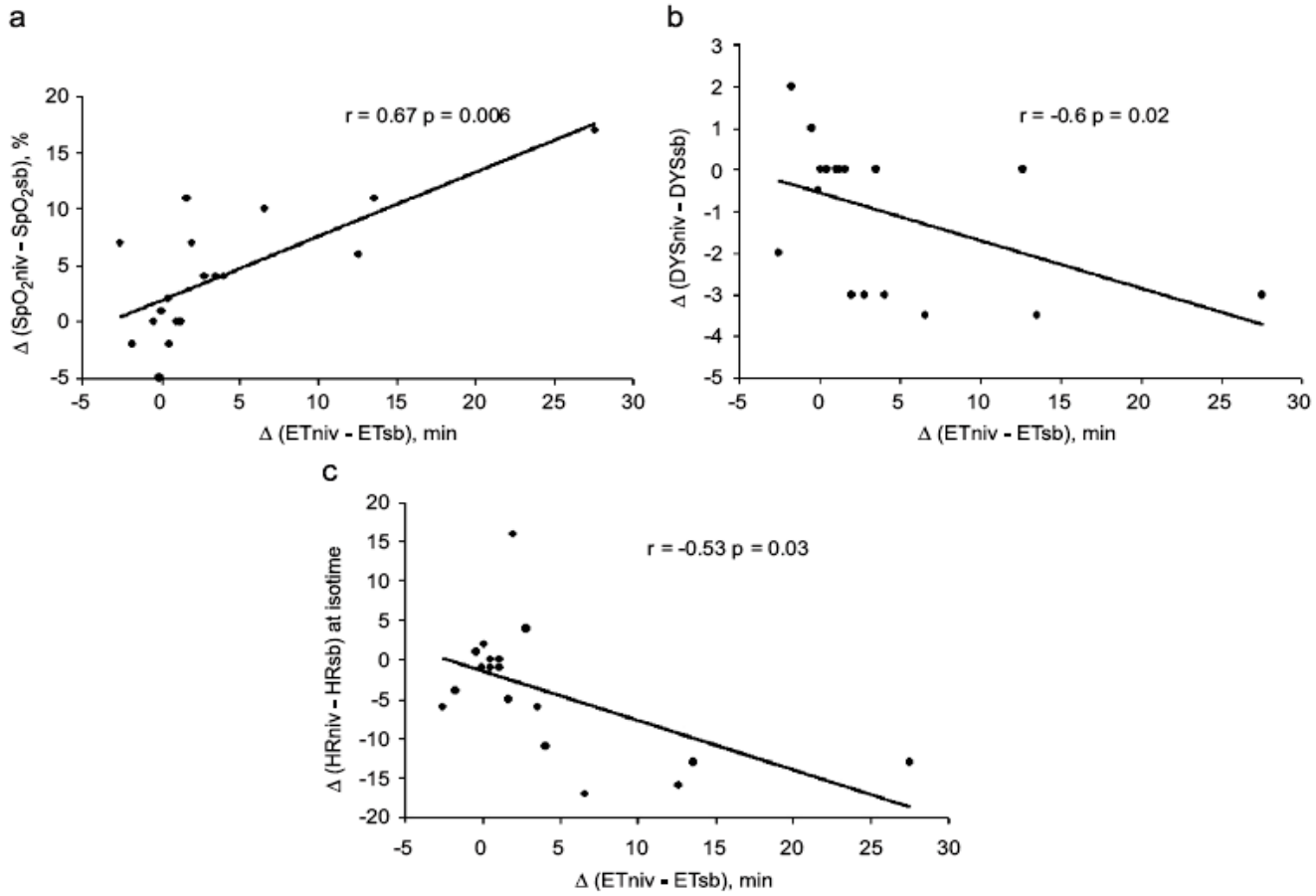

Figure 2 Correlations between constant workload exercise (CWLE) time variation and (a) SpO_2 improvement, (b) reduction of the dyspnea, (c) reduction of heart rate with NIV compared to spontaneous breathing test. (a) Correlation between CWLE time variation and SpO_2 improvement at iso-time with NIV compared to spontaneous ventilation test ($n = 18$) (b) correlation between CWLE variation and the reduction of the dyspnea at iso-time with NIV compared to spontaneous ventilation test ($n = 16$). (c) Correlation between CWLE time variation and the reduction of heart at iso-time ($n = 18$). Δ(Etniv-Etsb): Variation between endurance time with spontaneous breathing and endurance time with NIV; Δ(SpO_2niv-SpO_2sb): Variation between oxygen saturation with spontaneous breathing and oxygen saturation with NIV at iso-time (iso-time: the highest equivalent timed achieved in the two tests); Δ(DYSniv-DYSsb): Variation between dyspnea with spontaneous breathing and dyspnea with NIV at iso-time; Δ(HRniv-HRSsb): Variation between heart rate with spontaneous breathing and heart rate with NIV at iso-time.

leading to a 60% increase in minute ventilation. As a consequence, in our patients, VE was increased by a mean of 16 l/min and mean oxygen saturation was improved by 4% on average. In summary, when compared to previous studies, the strengths of our study are as follows: (i) A randomized controlled trial design, (ii) a twofold increase in enrolled patients compared to previous studies, (iii) ventilator settings permitted a clinically significant increase in exercise ventilation when using NIV. The current study also exhibited some limitations. Even if our study is the largest one in the field, the number of included patients was relatively small and results need to be replicated in further large-scale studies. As patients had experienced NIV for a mean of 7 ± 6 years, it was impossible to use Sham ventilation. A placebo effect could be part of the explanation for increase in exercise duration but could not account for reduction of oxygen desaturation and other physiological changes associated with NIV.

Ventilatory and cardiovascular changes associated with increased endurance with NIV

The mean range for improvement in exercise duration using PSV was 71% in this study. This is more than 40–50% of the improvement previously demonstrated in COPD patients.[7,14,15] In restrictive patients, Naji et al.[22] showed an increase in exercise endurance (treadmill) of a mean of 8.7 min, which was associated with a significant improvement in quality of life. One may speculate that the 71% improvement that we achieved with NIV is at least as significant. The wide range of change in exercise duration when using NIV in the present study (i.e. from −2.6 to +27.5 min) as in others[14,17,23] illustrates that some patients benefit greatly from ventilatory support, although others do not or are even slightly impaired. NIV responders had both lower TLC and lower FVC which suggests that the most severe patients are those most likely to benefit. Secondly,

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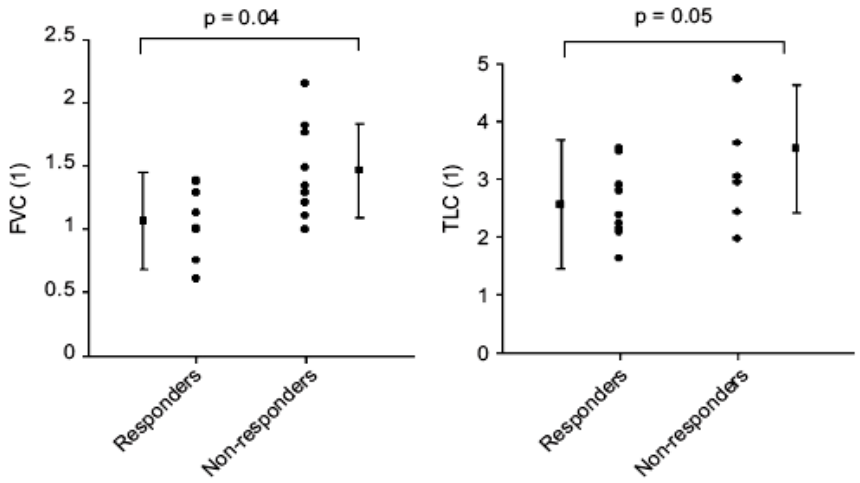

Figure 3 Forced vital capacity (FVC) and total lung capacity (TLC) for responders and non-responders to NIV during exercise ($n = 17$ for TLC, $n = 18$ for FVC).

Table 3 Comparative analysis of maximal exercise workload test between responders and non-responders to NIV during exercise, $n = 18$.

	Responders (9)	Non-responders (9)	p
P_{peak}, W	45±14	57±27	ns
HR_{peak}, b/min	133±18	134±21	ns
$VO_{2\ peak}$ l/min	0.64±0.24	0.91±0.41	ns
$VCO_{2\ peak}$ l/min	0.63±0.25	0.89±0.39	ns
VE_{peak}, l/min	25.0±6.3	34.2±9.61	0.04
Vt_{peak}, l	0.60±0.09*	0.89±0.34	0.003
Vt_{peak}, (% FVC)	58±8	61±11	ns
RR_{peak}, /min	41±7	40±12	ns
O_2 $Pulse_{peak}$, ml/beat	4.5±1.2*	7.4±3.9	0.03
(pred value)	(58±8)	(70±21)	
Vd/Vt (blood gaz $n = 12$) (6/6)	0.51±0.06	0.38±0.12	0.04
D(A-a), mmHg	4.74±1.18	3.82±1.7	ns
$PaO_{2\ peak}$, mmHg (6/6)	59±11	72±18	0.1
$PaCO_{2\ peak}$, mmHg (6/6)	51±5	44±5	0.05
pH_{peak}	7.33±0.03	7.35±0.05	ns
$SaO_{2\ peak}$, (%)	85±7	91±4	0.08

P_{peak}: Maximal work rate obtained during incremental exercise test; VO_{2peak}: Maximal O_2 consumption during incremental exercise test; HR_{peak}: heart rate; VE_{peak}: minute ventilation; Vt_{peak}: tidal volume (expressed in absolute value and as percentage of forced vital capacity); RR_{peak}: respiratory rate; O_2 $Pulse_{peak}$: oxygen pulse (VO_2/HR ratio—expressed in ml/beat and percentage of predicted value) Vd/Vt ratios were determined with blood gases analyze. D(A-a): Alvelo-arterial difference.
*$p < 0.05$.

during the MWLE in spontaneous breathing, responders had lower minute ventilation with lower tidal volume. As a consequence, reduced alveolar ventilation, higher V_D/V_T ratio and greater oxygen desaturation were observed at the end of exercise. Thus, one can understand that in responders the two-fold increase in Vt and 70% increase in VE provided by NIV have improved gas exchange and subsequent exercise ability. Surprisingly, VE was also significantly improved with NIV in non-responders (+52%) without benefit in terms of exercise tolerance. Ventilatory mechanical limitation was presumably not the main mechanism limiting exercise in these patients, and peripheral muscle fatigue may have a potential role. Even without NIV, these patients were able to perform CWLE for a longer duration (7.1±5.8 min versus 4.0±2.5, $p = 0.05$) with limited oxygen desaturation. In such less severe patients, NIV does not seem to provide any additional effect.

Another important difference between responders and non-responders could have been the ability to adjust cardiac output during exercise. Responders had lower oxygen pulse at the end of the MWLE suggesting limited ability to increase cardiac ejection during heavy exercise. Previous studies

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have demonstrated that cardiac output might be involved in exercise limitation in patients with thoracic or pulmonary restriction (see below).[24,25]

Mechanisms explaining improvement in exercise ability using NIV

A large increase in VE (61±23%) and also Vt were obtained for the whole group when using NIV during exercise. The significant correlations between improvement in CWLE duration and SpO_2 improvement and dyspnea relief using NIV during exercise suggest that improving alveolar ventilation and gas exchange and/or minimizing symptoms by using NIV are the main factors explaining the increase in exercise duration. The present study is the first to demonstrate that an increase in minute ventilation sufficient to improve alveolar ventilation during exercise and presumably to avoid oxygen desaturation improves exercise tolerance in patients with thoracic restriction. Tuggey and Elliot[26] have demonstrated that a high-pressure support (+19 cm H_2O in our study) is needed to achieve blood gases normalization whereas more limited support allows rapid unloading of respiratory muscles.

The reduction in oxygen pulse at the end of exercise observed in the most severe patients in the present study suggests that reduced ejection fraction may contribute to exercise limitation. In a model of thoracic restriction in healthy volunteers, Miller et al.[25] showed a fall in cardiac output during moderate intensity exercise. Also, in primary pulmonary hypertension, patients had low oxygen pulse value during exercise corresponding to a limited increase in stroke volume.[27,28] In our study, NIV could reduce heart rate directly by preventing oxygen desaturation and indirectly by limiting hypoxic vasoconstriction and reducing pulmonary hypertension. This could lead to a higher stroke volume and allow reduction in heart rate at the same cardiac output for a given level of exercise.[29] Moreover, a higher Vt during NIV being associated with a lung volume-dependant decrease in sympathetic tone may have had additional effects in decreasing sympathetic activation.[30,31]

Considering that oxygen desaturation is one of the main factors limiting exercise in restrictive patients, one can argue that oxygen supplementation during exercise could have led to similar results than NIV application. However, whereas oxygen therapy could relieve dyspnea, its use did not improve the 6 min walking distance in patients with kyphoscoliosis.[6] In patients with tuberculosis sequellae, Tsuboï et al.[17] compared oxygen therapy versus VNI+O_2 and showed a significant increase in endurance time (from 227±64 to 465±201 s). These data suggest that VNI per se has a specific and synergistic role with oxygen in improving exercise capacity in CRF.

Clinical implications and conclusion

In severely restrictive patients, NIV during exercise increases exercise duration, improves exercise tolerance and alveolar ventilation. Both the presence of low vital capacity at rest (one liter or less) and inefficient ventilation during exercise (high V_D/V_T ratio) could discriminate responders and non-responders to NIV during exercise.

The magnitude of changes in exercise endurance is much more pronounced than previously reported in COPD. Thus, with NIV, restrictive patients could be able to exercise longer and therefore get a greater training effect during a pulmonary rehabilitation program. This however remains to be demonstrated.

Conflict of interest statement

All the authors have no conflicts to disclose.

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ETUDE N° 5 : IMPACT DE LA VNI AU COURS D'UN RÉENTRAINEMENT A L'EFFORT CHEZ L'INSUFFISANT RESPIRATOIRE CHRONIQUE PARIETO-RESTRICTIF.

EXERCISE TRAINING WITH NON INVASIVE VENTILATION IN CHRONIC RESTRICITVE RESPIRATORY FAILURE

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Prérequis : Quelques études, montrent que la réhabilitation respiratoire améliore la tolérance à l'effort et la qualité de vie des patients souffrant de pathologies respiratoires pariéto-restrictives. Cependant il n'existe pas de recommandations sur les stratégies optimales de réentraînement à l'effort chez ces patients (Nici, Donner et al. 2006; Ries, Bauldoff et al. 2007). La VNI utilisée au cours d'un exercice aigu, améliore la tolérance à l'effort en réduisant la dyspnée des patients insuffisants respiratoires restrictifs (Borel, Wuyam et al. 2008). Un support ventilatoire utilisé au cours des séances d'un programme de réentrainement pourrait en augmenter les bénéfices cliniques au long cours pour les patients.

Objectifs : Le premier objectif de cette étude était d'évaluer l'efficacité d'un programme de réentrainement de huit semaines à domicile sur la qualité de vie, la dyspnée et la tolérance à l'effort des patients insuffisants respiratoires chroniques restrictifs sévères. Le second objectif était d'évaluer si la VNI utilisée au cours des efforts permettait un bénéfice plus important du programme de réentrainement dans cette population.

Méthodes : Les patients inclus effectuaient 8 semaines de réentrainement à l'effort sur ergo-cycle à domicile. Ils étaient randomisés en deux groupes et réalisaient le programme de réentraînement avec ou sans VNI au cours des séances. Comme décrit en détail ci-dessus (Borel, Wuyam et al. 2008), l'évaluation initiale, faite sur deux demi-journées, comprenait des

épreuves fonctionnelles respiratoires, un test d'effort incrémental maximal, un test de marche de six minutes, deux tests d'endurance à 75% de la puissance maximale avec et sans VNI et un questionnaire de qualité de vie (CRQ, i.e. chronic respiratory questionnaire). L'évaluation finale était identique excepté le test d'endurance sous VNI qui n'était pas refait.

Résultats : Pour l'ensemble des patients, le programme de réentraînement permettait d'améliorer significativement la distance de marche (+22±35m, p=0.035), la puissance maximale (+5±9W, p=0.036), le temps d'endurance sur ergo-cyle (+75±94%, p=0.018) et la qualité de vie (score CRQ = +10±13 points, p=0.009). Il n'y avait pas de différence entre les patients réentraînés avec ou sans VNI au cours des efforts. Cependant, parmi les patients qui amélioraient leur test d'endurance initial sous VNI de plus de 50% (i.e. répondeurs à la VNI, n=10), ceux qui étaient réentrainés sous VNI (6 patients) avaient une amélioration plus importante du test de marche de six minutes (+48±31 vs. +12±24m p=0.09) et du score du CRQ (+15±15 vs. -2±2 points p=0.09) par rapport à ceux réentrainés sans VNI (4 patients), et ce sans augmentation significative de l'intensité de réentrainement. Les domaines « fatigue » et « émotion » étaient les domaines du CRQ qui s'amélioraient significativement. Les patients « répondeurs » avaient une capacité pulmonaire totale (2.54 ± 0.38 vs. 3.69 ± 1.08 L, p = 0.020), une capacité vitale forcée (1.05 ± 0.06 vs. 1.57 ± 0.18 L, p = 0.020) plus basses et une PaCO2 diurne au repos plus élevée (6.0 ± 0.4 vs. 5.4 ± 0.1 kPa, p = 0.045) que les patients « non-répondeurs ».

Discussion-Conclusion : Cette étude montre qu'un programme de réentrainement à domicile de 8 semaines améliore la tolérance à l'effort, la qualité de vie des patients insuffisants respiratoires pariéto-restrictifs. La VNI utilisée au cours des efforts n'améliore pas les bénéfices d'un réentrainement chez des patients non sélectionnés. Par contre, chez les patients «répondeurs » (i.e. les plus sévères), la VNI au cours des efforts pourrait permettre un

bénéfice plus important, particulièrement en termes de qualité de vie et de périmètre de marche, en les préservant d'une fatigue excessive.

Exercise training with non-invasive ventilation in chronic restrictive respiratory failure

Exercise training and restrictive disorders

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ABSTRACT

Objective. We assessed the effect of exercise training and non-invasive ventilation (NIV) applied during exercise on exercise tolerance and quality of life in patients with restrictive disorders.

Design. Sixteen patients (TLC 55% predicted) underwent an 8-week home-based cycle exercise program. Nine patients were randomized to exercise with NIV and 7 without. Before and after training, evaluations included an incremental and a constant-load cycling test, a 6-min walking test and completion of the Chronic Respiratory Questionnaire (CRQ).

Results. For the whole group, training increased walking distance (+22±35m), maximal cycling power output (+5±9W), cycling endurance (+75±94%) and CRQ score (+10±13pts). These changes did not differ between patients training with or without NIV. However, in patients increasing cycling endurance with NIV by >50% before training (n=10), training with NIV induced greater improvement in walking distance (+48±31 vs. +12±24m) and CRQ score (+15±15 vs. -2±2 pts).

Conclusions. We concluded that in patients with restrictive disorders i) exercise training including NIV is feasible at home, ii) whatever the modalities, exercise training induces significant benefits in exercise tolerance and quality of life, and iii) in acute NIV responders, chronic use of NIV during exercise may lead to a synergetic effect compared to traditional training.

Key words: Home rehabilitation, Chronic Respiratory Failure, Non-invasive ventilation, Exercise training.

INTRODUCTION

Patients with thoracic restrictive respiratory disorders like severe scoliosis or tuberculosis sequelae face an increased work of breathing leading to impaired alveolar ventilation, increased perception of dyspnea, ventilatory limitations during exercise [1] and, finally impaired quality of life. Nocturnal non-invasive positive-pressure ventilation (NIV) is the widespread treatment improving both overnight and daytime blood gases, patient's symptoms and survival [2-4].

Studies showed that NIV can be applied during exercise in patients with restrictive disorders leading to substantial improvement in exercise tolerance [5-7-8-10]. Our group has demonstrated that NIV applied during exercise in restricted patients improves exercise endurance by 71% on average together with a reduction in dyspnea and oxygen desaturation[8]. Recent reports in COPD patients have shown similarly that the use of NIV during exercise training enhances the post-training improvement in exercise capacity [11-13]. In patients with restrictive respiratory disorders, only few studies evaluated the effect of pulmonary rehabilitation [5,14-16]. Moreover, whether the use of NIV during exercise training may enhance the efficiency of pulmonary rehabilitation in restrictive patients remains to be evaluated.

We therefore hypothesized that a home-based exercise rehabilitation program i) would increase exercise tolerance, reduce dyspnea and improve quality of life in patients with restrictive disorders and ii) would lead to greater improvements in the former variables when NIV is applied during exercise training.

MATERIALS AND METHODS

Patients

Patients treated by long term nocturnal NIV for thoracic restrictive disorders (FEV1/FVC >75%), in stable state for more than three months who attended our centre for NIV treatment follow-up were included. Exclusion criteria were obesity (BMI>30 $kg \cdot m^2$), history of chronic heart failure or progressive neuromuscular disorders. On 40 patients, 19 were included, 16 of them completed the study (Fig. 1). Fourteen of them had kyphoscoliosis (all idiopathic except two poliomyelitis sequellae) and 2 had tuberculosis sequellae (Table 1). The 21 patients who refused participating were not different in terms of severity, age and gender. Initial assessment data (before exercise training) from several of the patients included in the present study have been published previously [8].

All subjects gave their written informed consent. The study was approved by the University Hospital ethics committee and complies with the Declaration of Helsinki.

Study design (Figure 1)

Initial assessment. It consisted in two visits. In the first visit, patients underwent pulmonary function tests, a maximal incremental exercise test (MWLE) and, after 30 min of rest, a six-minute walk test (6MWT). In the second visit, patients were familiarized to the use of NIV during exercise. Then, after 30 min of rest, patients performed two constant-load exercise tests (CWLE) at 75% of peak workload ($\dot{W}_{max}$) measured during MWLE, with and

without NIV in a random order. Between the two CWLE, subjects rested for 30 min and completed the chronic respiratory disease questionnaire (CRQ) [17].

Non-invasive ventilation setting. The ventilatory mode used for exercise was pressure support ventilation (SMARTAIR +; AIROX; Pau, France). Settings during exercise were specifically tailored for appropriate ventilation during exercise [8]. Patients individually chose the best-tolerated interface (nasal masks, naso-buccal masks or mouth-piece). Inspiratory pressure was increased until the patient had a comfortable respiratory sensation ('enough air' at each insufflations).

Exercise training. Patients were allocated in random order to an 8-week home-based exercise training program with or without NIV during exercise. The program consisted in 3 to 5 exercise sessions per week on a calibrated cycle ergometer (Ergobike 2002 PC, Daum Electronic, Obermichelbach, Germany), each session lasting 20 to 40 min, as previously described [18]. Initial cycling intensity was fixed at 50% $\dot{W}_{max}$. When the patient achieved at least 30 min at this intensity, without excessive dyspnea (<6 on a modified Borg Scale), he was instructed to progressively increase the intensity by 10% $\dot{W}_{max}$ increment in order to maintain 30 min of exercise. For the NIV group, all sessions were performed with NIV. For the control group, oxygen was added during exercise if arterial oxygen saturation (SpO_2) was less than 90% during effort. A physiotherapist coached one session every 2 weeks, and phone-called the patients once a week. Finally, the patients recorded the intensity (watt) and duration (minutes) of every session on a diary.

Final assessment. It was performed 2-4 days after the end of the training program and included the same evaluations than the initial assessment except that patients performed only one CWLE, without NIV.

Measurements

Pulmonary function tests. Spirometry and thoracic gas volumes (MEDICAL GRAPHICS Corporation, St Paul, MN, USA) as well as Sniff Nasal Inspiratory Pressure (Direc NEP System 200, Raytech Instruments Inc.; Vancouver; Canada) were measured according to ATS/ERS guidelines [19,20].

6-minutes walking test (6MWT). The test was performed in ambient air along a straight 30-m long corridor according to ATS guidelines [21].

Maximal incremental exercise test (MWLE). The test was performed on a cycle-ergometer (900PC, ERGOLINE, Germany). Work rate was increased every minute by 10% of the expected maximal workload until exhaustion. Minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), respiratory rate (RR) and tidal volume (Vt) were measured continuously by using a breath by breath automated exercise metabolic system (Sensormedics, Vmax 229; Yorba Linda, CA, USA). $\dot{W}_{max}$ was defined as the highest work rate the patient could maintain for one minute.

Constant workload exercise testing (CWLE). The methods for the CWLEs were described in detail previously [8]. In brief, after a standardized warm-up, the tests were performed at 75% $\dot{W}_{max}$ until exhaustion, with or without NIV. The patient indicated every

minute his level of dyspnea and leg fatigue by using a modified Borg scale. The test was over when the patient could not exercise anymore because of dyspnea, fatigue or when he could not maintain a pedaling frequency of at least 55 cycles/min. Based on previous results [8], we defined patients increasing endurance time during CWLE by >50% before training as "acute NIV responders".

The experimenter who supervised the exercise tests was blind to treatment allocation (i.e. exercise training with or without NIV).

Statistical analysis

First, the effect of exercise training (with and without NIV) was assessed by comparing variables measured before and after exercise training for all patients as a whole. Second, the effect of NIV applied during exercise training was assessed by comparing the post-exercise training changes in patients training with NIV (NIV group) and without NIV (control group). Third, based on previous results from our group [8], the effect of NIV applied during exercise training was assessed in acute NIV responders only by comparing the post-exercise training changes in acute NIV responders training with NIV and without NIV.

Cardio-respiratory variables and sensations measured during the cycling tests were compared before and after exercise training at isotime, i.e. at the longest duration achieved before and after exercise training.

Comparisons before and after exercise training were performed with Wilcoxon test. Comparisons between groups were performed with Mann-Witthney test. Analyses were

performed using standard software (Statview 5.0, SAS Institute, Cary, NC, USA). All results are presented as means ± SD and $p < 0.05$ was considered to be statistically significant.

RESULTS

Patients' characteristics are reported in Table 1. Nine patients were allocated to exercise training with NIV (NIV group, mean positive inspiratory pressure = 19 ± 3 cmH_2O) and 7 without (control group). No significant difference was observed between the two groups. As determined by the MWLE and the 6MWT, exercise capacity ($\dot{W}_{max}$, 6-min walking distance) was severely impaired in both groups.

Effects of exercise training in patients with restrictive disorders (n = 16)

During MWLE, $\dot{W}_{max}$ increased by 5 ± 9 W after exercise training ($p = 0.045$). Analysis of physiological variables at isotime before and after training (Table 2) showed that $\dot{V}_E$, SpO_2, HR and dyspnea were significantly reduced after training.

CWLE duration was increased after training (+75 ± 94 %; Fig. 2) although the physiological response was unchanged at isotime compared to before training (Table 3).

During 6MWT, walking distance significantly increased after training (+22 ± 35 m, i.e. + 8 ± 14%; Fig.2). Minimal SpO_2 (83 ± 8 vs. 82 ± 8%; $p = 0.418$) and mean HR (119 ± 15 vs. 119 ± 13 bpm; $p = 0.693$) did not differ before and after training while perceived level of exertion (4.1 ± 2.1 vs. 3.3 ± 2.0 points; $p = 0.075$) tended to be reduced after training.

Exercise training induced no change in pulmonary function tests (results not shown, all $p > 0.05$).

Total CRQ score increased significantly after training (83 ± 14 vs. 93 ± 15 points; $p = 0.009$), with a significant increase observed for dyspnea (15 ± 4 vs. 19 ± 5 points; $p = 0.004$) and emotion (32 ± 7 vs. 35 ± 6 points; $p = 0.041$) domains and no significant change in fatigue (17 ± 4 vs. 18 ± 4 points; $p = 0.301$) and mastery (19 ± 6 vs. 20 ± 5 points; $p = 0.173$) domains.

Effect of NIV on training-induced changes in exercise response and CRQ scores

When comparing the NIV and the control groups, no significant difference in post-training changes in $\dot{W}_{max}$ during MWLE (with NIV +8 ± 10 W vs. without NIV +1 ± 6 W; $p = 0.204$), in cycling time during CWLE (+59 ± 61 vs. +95 ± 127%; $p = 0.958$) and in walking distance during 6MWT (+35 ± 36 vs. +9 ± 30 m; $p = 0.180$) was observed. Changes in cardio-respiratory variables and sensations during all exercise tests (results not shown, all $p > 0.05$) as well as changes in CRQ scores (Fig. 3) did not differ between both groups.

The increase in exercise intensity throughout the training period (Fig. 4) as well as the amount of exercise training (2.4 ± 1.1 vs. 2.6 ± 0.9 $h \cdot week^{-1}$, $p = 0.908$) did not differ between the NIV group and the control group.

Effect of NIV on training-induced changes in acute NIV responders

Ten "acute NIV responders" increased exercise duration during CWLE by >50% before training, 6 of them trained with NIV and 4 of them trained without NIV. Acute NIV responders had lower total lung capacity (2.54 ± 0.38 vs. 3.69 ± 1.08 l, p = 0.020), forced vital capacity (1.05 ± 0.06 vs. 1.57 ± 0.18 l, p = 0.020), forced expiratory volume in one second (0.83 ± 0.05 vs. 1.24 ± 0.15 l, p = 0.039) and higher resting arterial carbon dioxide tension (6.0 ± 0.4 vs. 5.4 ± 0.1 kPa, p = 0.045) compared to non-responders.

In acute NIV responders, post-training changes in performance, cardio-respiratory variables and sensations during MWLE and CWLE did not differ between patients training with or without NIV (results not shown, all p > 0.05). The increase in 6-minute walking distance tended however to be greater in acute NIV responders training with NIV vs. acute NIV responders training without NIV (+ 48 ± 31 vs. + 12 ± 24 m; p = 0.086). The change in total CRQ score also tended to be greater in acute NIV responders training with NIV vs. acute NIV responders training without NIV (+ 15 ± 15 vs. - 2 ± 2 points; p = 0.088), with a significant difference between groups for the fatigue and emotion domains (Fig. 3). Conversely, in acute NIV non-responders training with (n = 3) or without (n = 3), NIV induced similar changes in 6MWT and total CRQ score.

In acute NIV responders, the increase in exercise intensity throughout the training period as well as the amount of exercise training did not differ between patients training with and without NIV (results not shown, p > 0.05). Similarly, in patients being trained with NIV,

exercise training compliance was similar between acute NIV responders and non-responders (results not shown, $p > 0.05$).

DISCUSSION

The present study showed a significant increase in exercise tolerance and quality of life following an 8-week home-based exercise training program in patients with thoracic restrictive disorders. Changes in $\dot{V}_{O_2}$ max, cycling endurance, 6-min walking distance and CRQ scores did not differ between patients training with or without NIV. However, in acute NIV responders (increasing endurance by >50% during acute exercise with NIV), the use of NIV during exercise training induced greater improvement in 6-min walking distance as well as in quality of life, especially in emotion and fatigue CRQ domains.

Critique of methods

The present study did not include a control group performing no exercise training in order to evaluate the actual benefits of rehabilitation. As patients had experienced long term nocturnal NIV (mean of 7 ± 6 years), it was mostly impossible to use a sham NIV. In addition, the sample size was relatively small, increasing the risk of type 2 error. However, the prevalence of restrictive thoracic diseases is clearly lower than obstructive diseases, therefore limiting the possibility of recruiting large sample cohorts.

Exercise training in patients with restrictive disorders

To date, conversely to COPD patients [22], there are no formal evidence-based guidelines for exercise activities in restrictive disorders [16]. Only few studies indeed investigated the efficiency of pulmonary rehabilitation in patients with restrictive respiratory diseases [5,14,15]. Ando et al. [5] compared the effect of an 8-week outpatient exercise training program in patients with post-tuberculosis lung disorders and in patients with COPD. The two groups of patients showed similar improvements in 6-min walking distance, dyspnea and quality of life following the training program. The present study showed that an exercise training program was feasible in a home-based setting in patients with restrictive disorders and that such a program induced significant improvements in exercise tolerance and quality of life. Therefore, these results together with previous studies from the literature indicate that exercise training should be considered as an attractive tool for the management of these patients.

Effect of NIV during exercise training

The present study investigated for the first time the effect of using ventilatory support during exercise training in patients with restrictive disorders. The use of NIV during acute exercise has been shown to improve exercise tolerance in patients with restrictive disorders [8-10]. Therefore, by analogy to the study of Hawkins et al. [23] performed in COPD patients, we hypothesized that the use of NIV during exercise training would allow them to increase the training stimulus during exercise and lead to greater training effects. When comparing the NIV and the control groups, we did not observe a significant difference in intensity and duration of exercise training throughout the rehabilitation program (Fig. 4). Moreover, the

improvement in exercise performances and CRQ scores did not differ between both groups. Therefore, these results suggest that using NIV during exercise training in an unselected group of patients with restrictive disorders does not increase the efficiency of an exercise training program.

However, when evaluating the effect of NIV during acute exercise in patients with restrictive disorders, we observed that not all patients improved exercise endurance with NIV compared to control conditions [8]. Half of them were considered as acute NIV responders with an improvement in cycling endurance >50%. Hence, in the present study, we specifically evaluated the effect of using NIV during exercise training in patients improving cycling endurance >50% before training, i.e. in acute NIV responders (n = 10). The use of NIV during training in these patients tended to induce greater improvements in 6-min walking distance as well as in CRQ scores ($p < 0.09$), with a significant effect for the fatigue and emotion domains (Fig. 3) but without effect on training intensity. These results suggest that NIV during exercise training should be considered only in patients acute NIV responders. Although this subgroup post-hoc analysis is associated with some limitations, it provides useful information for the care of these patients and for designing future research [24].

Interestingly, acute NIV responders had more severe respiratory function impairment than non-responders. The results from van't Hul et al. [13] showing a substantial effect of using NIV during exercise training in COPD patients selected on the basis of ventilatory impaired exercise capacity, including marked inspiratory muscle weakness, may confirm that patients selection is critical for the effect of NIV during exercise training. The fact that using NIV during exercise training leads to additional benefits in severe COPD [12,13,23] but not in less severe patients [25] also supports the importance of patient selection. Furthermore, when

analyzing the group of patients acute NIV responders, i.e. the most severe patients, we observed that those patients training without NIV had worse CRQ scores (in particular in fatigue, emotion and mastery domains; Fig.3) after training, suggesting poor efficiency and tolerance to the training program as previously reported in severe respiratory patients [26]. Therefore, in these patients, strategies to improve standard exercise training efficiency, like NIV during exercise, may be useful although additional investigations are needed to define criteria for selecting patients.

In conclusion, the present study showed that an 8-week home-based exercise training program induced significant improvements in exercise tolerance and quality of life in patients with restrictive disorders. In addition, the use of NIV during exercise training at home appeared to be a feasible training modality but did not lead to significant additional improvement in the general population of patients with restrictive disorders. However, in most severe patients the use of NIV during exercise during home-based training tended to induce greater improvements in 6-min walking distance and quality of life.

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Table 1. Characteristics of the patients training with (NIV group) or without (control group) non-invasive intermittent positive-pressure ventilation.

		NIV group	Control group
Patient (n)		9	7
Cause of respiratory failure		8 KS / 1 TS	6 KS / 1 TS
Sex (female/male)		2 / 9	3 / 4
Age (yrs)		60 (8)	67 (10)
BMI ($kg \cdot m^2$)		26.5 (8.2)	22.4 (1.8)
TLC	(l)	3.17 (1.11)	2.64 (0.63)
	(% pred)	56.0 (14.2)	54.8 (11.1)
FVC	(l)	1.32 (0.42)	1.13 (0.40)
	(% pred)	42.1 (12.3)	42.5 (5.9)
FEV1	(l)	1.05 (0.36)	0.90 (0.34)
	(% pred)	42.3 (15.6)	43.0 (5.2)
FEV1/FVC	(%)	77.1 (16.0)	79.4 (6.1)
SNIP	(cmH_2O)	44.9 (13.2)	42.1 (14.1)
	(% pred)	42.5 (14.8)	51.3 (11.3)
PaO_2 (kPa)		9.6 (1.4)	9.9 (0.7)
$PaCO_2$ (kPa)		5.7 (0.7)	5.9 (0.5)
pH		7.43 (0.03)	7.41 (0.02)
HCO_3^- ($mmol \cdot l^{-1}$)		27.5 (2.2)	27.7 (1.3)
$\dot{W}_{max}$ (W)		48 (20)	55 (28)
$\dot{V}_{O_2 max}$ ($l \cdot min^{-1}$)		0.84 (0.42)	0.68 (0.33)
6 MWT (m)		362 (108)	433 (131)

Values are mean (SD); KS: kyphoscoliosis (all idiopathic except two poliomyelitis sequellae in the NIV group and one in the Control group) ; TS: tuberculosis sequellae; BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; TLC, total lung capacity; SNIP, sniff nasal inspiratory pressure; PaO_2, arterial oxygen tension at rest; $PaCO_2$, arterial carbon dioxide tension at rest; $\dot{W}_{max}$, maximal power output during the incremental cycling test; $\dot{V}_{O_2 max}$, maximal oxygen consumption during the incremental cycling test; 6 MWT, walking distance during the 6-min walking test.

Table 2. Physiological response at isotime during the incremental cycling test before and after training in all patients.

	Before training	After training
$\dot{V}_{O_2}$ (l·min^{-1})	0.74 (0.34)	0.72 (0.37)
$\dot{V}_{CO_2}$ (l·min^{-1})	0.73 (0.35)	0.69 (0.35)
$\dot{V}_E$ (l·min^{-1})	28.9 (9.5)	26.8 (7.8)*
Vt (l)	0.73 (0.29)	0.72 (0.25)
RR (cycles·min^{-1})	41.1 (10.0)	38.6 (7.1)
SpO_2 (%)	87 (7)	85 (7)*
HR (bpm)	131 (7)	124 (17)*
Dyspnoea (points)	5.2 (1.6)	3.8 (1.8)*
Leg fatigue (points)	3.5 (2.9)	3.4 (2.4)

Values are mean (SD) at isotime; $\dot{V}_{O_2}$, oxygen consumption; $\dot{V}_{CO_2}$, carbon dioxide production; $\dot{V}_E$, minute ventilation; Vt, tidal volume; RR, breathing frequency; SpO_2, arterial blood oxygen saturation; HR, heart rate; * significantly different from Before training ($p<0.05$).

Table 3. Physiological response at isotime during the constant load endurance cycling test before and after training in all patients.

	Before training	After training
$\dot{V}_{O_2}$ ($l \cdot min^{-1}$)	0.89 (0.32)	0.85 (0.37)
$\dot{V}_{CO2}$ ($l \cdot min^{-1}$)	0.76 (0.34)	0.77 (0.35)
$\dot{V}_E$ ($l \cdot min^{-1}$)	26.3 (8.4)	26.4 (8.3)
Vt (l)	0.77 (0.31)	0.76 (0.26)
RR ($cycles \cdot min^{-1}$)	35.5 (8.8)	34.8 (6.8)
SpO_2 (%)	86 (6)	84 (8)
HR (bpm)	126 (21)	126 (17)
Dyspnoea (points)	4.6 (1.8)	3.5 (2.5)
Leg fatigue (points)	3.5 (2.6)	2.8 (2.1)

Values are mean (SD) at isotime; see Table 2 for abbreviations.

Figure 1. Flow chart of the study. 40 patients with long term nocturnal NIV secondary to thoracic restrictive disorders were referred to our centre. Nineteen of them accepted to participate in the study. Following the initial assessment, 2 patients declined exercise training and 1 had exacerbation. Sixteen patients performed the 8-week home-based exercise training program and were randomized in a NIV group and a control group. After the exercise training program, all patients performed the final assessment.

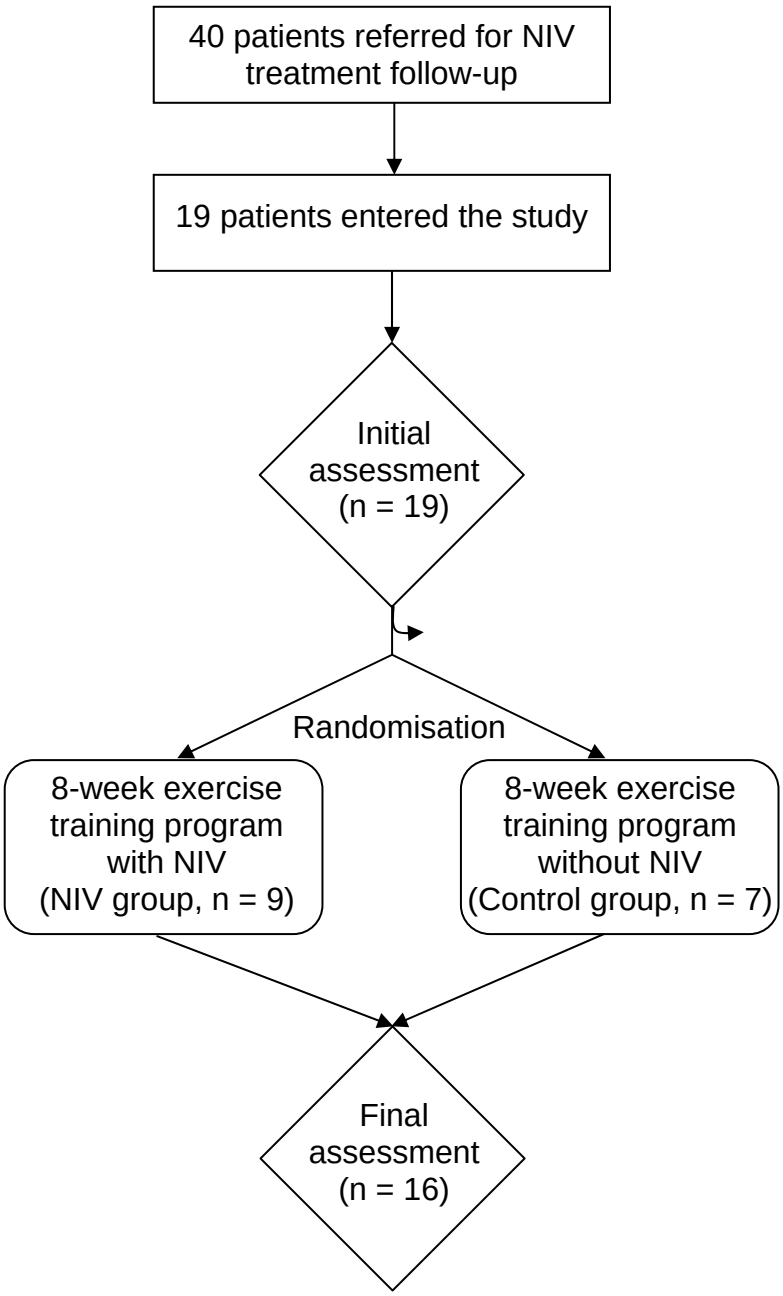


Figure 2. Exercise time during the constant load cycling endurance test and walking distance during the 6-min walking test before and after training. * difference between before and after training ($p < 0.05$)

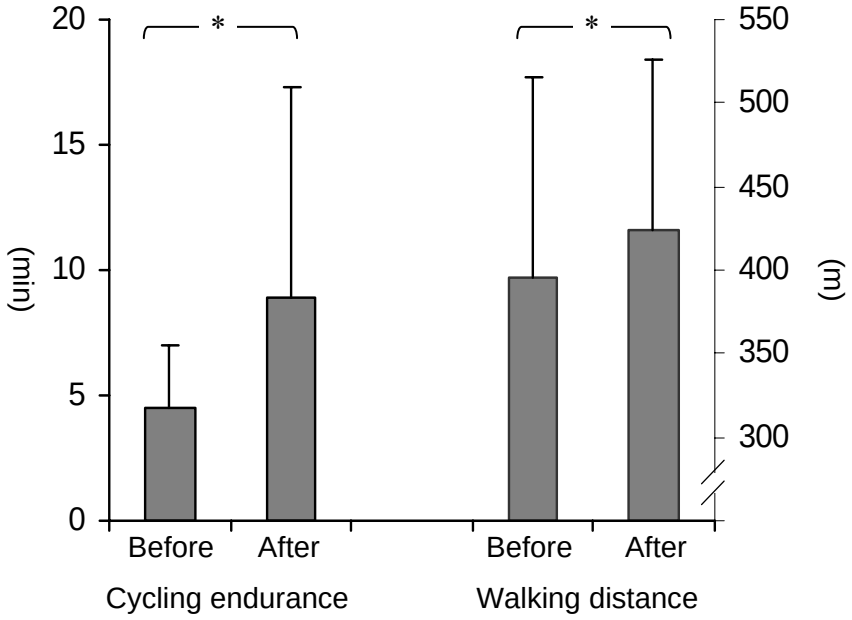


Figure 3. Changes in Chronic Respiratory Questionnaire scores (A, dyspnea domain; B, fatigue domain; C, emotion domain; D, mastery domain) after exercise training in the whole group of patients (All patients) and in acute NIV responders (Acute NIV responders) training with (with NIV) or without (without NIV) NIV. * difference between with and without NIV ($p < 0.05$)

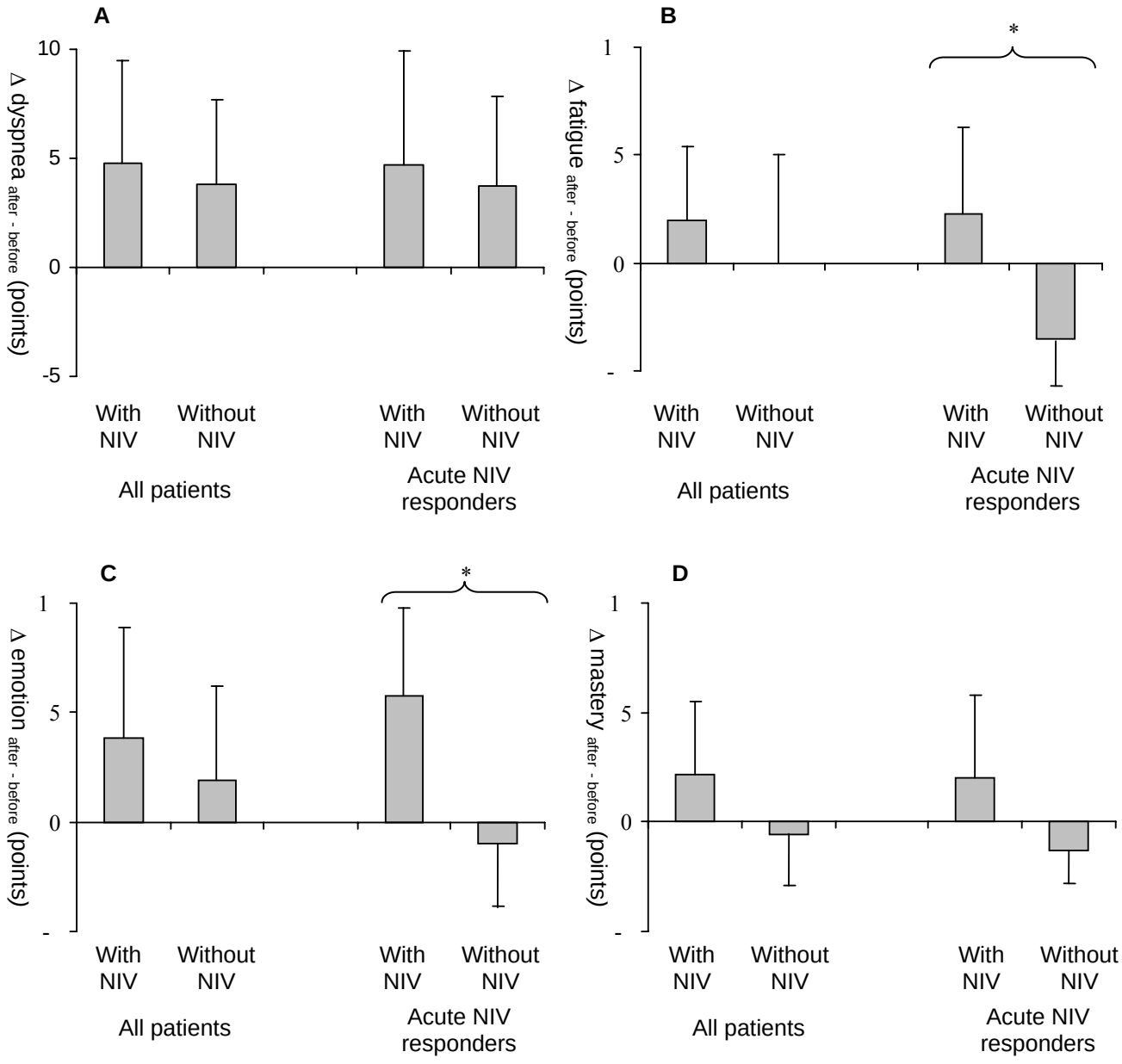
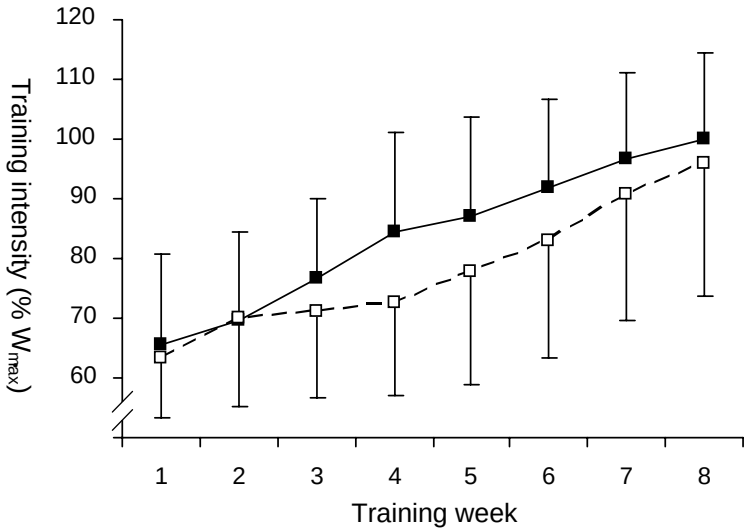


Figure 4. Training intensities [expressed as percentage of maximal power output ($\dot{W}_{max}$) achieved during the incremental cycling test before training] in patients training with (black symbols) or without (white symbols) non-invasive ventilation.



CHAPITRE 3 :

ASPECTS TECHNIQUES DE L'ASSISTANCE VENTILATOIRE NON-INVASIVE

CHAPITRE 3 : ASPECTS TECHNIQUES DE L'ASSISTANCE VENTILATOIRE NON-INVASIVE

PREREQUIS :

L'assistance ventilatoire non-invasive peut-être envisagée en pression négative (ventilation en pression négative) ou en pression positive (ventilation en pression positive). Dans le premier cas, un système péri-thoracique étanche génère des dépressions intermittentes autour du thorax et donc dans l'espace pleural, qui reproduisent le principe physique de la respiration spontanée (Mehta and Hill 2001). La ventilation non invasive en pression positive, au contraire, insuffle de l'air dans le patient en génèrant des surpressions intra-thoraciques intermittentes par l'intermédiaire d'une interface placée sur le nez/et ou la bouche du patient. Si la ventilation en pression négative a joué un rôle historique majeur au cours des épidémies de poliomyélite, actuellement la VNI s'envisage essentiellement en pression positive (Corrado and Gorini 2002). La VNI en pression positive peut se décliner en mode volumétrique ou en mode barométrique. Dans le premier cas, l'appareil d'assistance ventilatoire a pour consigne de fournir un volume d'air déterminé à chaque cycle délivré ; dans le second cas l'appareil a pour consigne en générant un débit d'air d'atteindre une pression déterminée dans les voies aériennes du patient. Depuis une quinzaine d'années, la ventilation barométrique est la plus utilisée (Janssens, Derivaz et al. 2003; Lloyd-Owen, Donaldson et al. 2005), et plus particulièrement la ventilation barométrique à deux niveaux de pressions. Les appareils à deux niveaux de pressions utilisent une technologie à turbine. Un simple tuyau est connecté entre l'appareil de ventilation et le masque du patient. Après avoir été insufflé, le patient expire par l'intermédiaire de fuites intentionnelles calibrées situées sur le masque ou à l'extrémité distale du tuyau. Une pression expiratoire positive systématique (4-5 cmH_2O) est essentielle à l'évacuation des gaz expirés aux travers de ces fuites intentionnelles évitant ainsi le phénomène de « rebreathing » (Ferguson and Gilmartin 1995). Les appareils de VNI sont

moins coûteux, plus légers, et cliniquement efficaces dans la plupart des cas (Janssens, Derivaz et al. 2003). La technologie à turbine permet, jusqu'à un certain point, de maintenir les pressions de consignes malgré des fuites non intentionnelles qui se produisent entre le masque et le patient ou des fuites par ouverture buccale. Cependant les seuils de sensibilité de l'appareil pour détecter l'effort inspiratoire du patient et la fin de l'inspiration du patient sont asservis aux variations de débits générés par l'appareil pour maintenir les pressions de consignes. C'est pourquoi les fuites non-intentionnelles, en modifiant les débits nécessaires au maintien des pressions de consignes, peuvent perturber le fonctionnement des respirateurs (Hotchkiss, Adams et al. 2001; Battisti, Tassaux et al. 2005; Miyoshi, Fujino et al. 2005). Les industriels optimisent les algorithmes des machines dans le but d'atténuer l'effet de ces fuites.

Parallèlement, ils développent ou optimisent sans cesse des interfaces pour améliorer la tolérance, éviter les fuites non intentionnelles, et permettre un traitement efficace (Elliott 2004), ceci permet d'avoir aujourd'hui une large gamme d'interfaces nasales, faciales, ou buccales. Cependant tous les systèmes de fuites intentionnelles des masques ne sont pas identiques et des variations importantes du calibre de ces fuites pourraient modifier le fonctionnement des ventilateurs.

OBJECTIF ASSOCIÉ À LA PROBLEMATIQUE DE LA TECHNOLOGIE DE LA VNI

La contribution de ce travail de thèse à la problématique de la technologie de la VNI à deux niveaux de pressions est d'évaluer le niveau des fuites intentionnelles d'une série de masques industriels actuellement sur le marché et d'évaluer l'impact de ces fuites sur les performances des machines à deux niveaux de pressions sur un banc-test (Etude N°6).

ETUDE N° 6 : IMPACT DES FUITES INTENTIONNELLES DES MASQUES INDUSTRIELS SUR L'EFFICACITE DE LA VNI A DEUX NIVEAUX DE PRESSIONS : ETUDE SUR BANC-TEST.

INTENTIONAL LEAKS IN INDUSTRIAL MASKS HAVE A SIGNIFICANT IMPACT ON EFFICACY OF BI-LEVEL NON-INVASIVE VENTILATION: A BENCH TEST STUDY

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CHEST 2008; sous presse

Prérequis : Les appareils de ventilation non invasive à deux niveaux de pressions fonctionnent avec des masques munis de fuites intentionnelles pour évacuer les gaz exhalés. Ces appareils dotés d'une technologie à turbine, peuvent, jusqu'à un certain point, compenser les fuites non-intentionnelles qui se produisent entre le masque et le visage du patient ou par ouverture buccale (Scala 2004). Néanmoins, ces fuites peuvent perturber le fonctionnement de ces appareils (Hotchkiss, Adams et al. 2001; Battisti, Tassaux et al. 2005; Miyoshi, Fujino et al. 2005). Actuellement il existe, sur le marché, une large gamme de masques nasaux ou buco-nasaux munis de différentes fuites intentionnelles. L'impact de la variation de ces fuites intentionnelles sur les performances des ventilateurs à deux niveaux de pression n'avait jamais été évalué.

Objectifs : Les objectifs de cette étude étaient de mesurer le niveau des fuites intentionnelles de 7 masques industriels et d'évaluer si des fuites intentionnelles importantes modifiaient les performances des ventilateurs et la ventilation délivrée.

Méthodes : Sept masques (4 nasaux, 3 naso-buccaux) étaient consécutivement adaptés sur le visage d'un mannequin relié à un modèle de poumon test (ASL5000, IngMar Medical™). Le couple "mannequin/poumon test" était ventilé, via les 7 différents masques, par 4 ventilateurs différents (VPAP3-RESMED™; HARMONY2- RESPIRONICS™; SMARTAIR-ST-

AIROX^{TM}; GK425ST-TYCO^{TM}). La pression d'insufflation était réglée à 14 cmH_2O, la pression expiratoire à 4 cmH_2O. Le poumon test était programmé à une fréquence respiratoire de 15 cycles/minutes et un temps d'inspiration d'une seconde dans trois conditions de compliances (C) et de résistances (R) différentes (condition normale : [C=30ml/cm$H_2$0, R= 5.6cmH_2O/L/s] ; obstructive : [C=20ml/cm$H_2$0, R=20cmH_2O/L/s]; restrictive: [C=20ml/cmH_2O; R=5.6cmH_2O/L/s] . La performance du déclenchement inspiratoire (délai de déclenchement *(Td)* et rapidité de re-pressurisation *(PTP)*), la capacité du ventilateur à atteindre et à maintenir la pression d'insufflation *(PTP500)*, le cyclage expiratoire *(*passage de la pression d'insufflation à la pression d'expiration ; *Ti-assis*t) (figure 6) et le volume courant étaient analysés pour tous les masques avec chaque ventilateur dans les trois conditions simulées du poumon test.

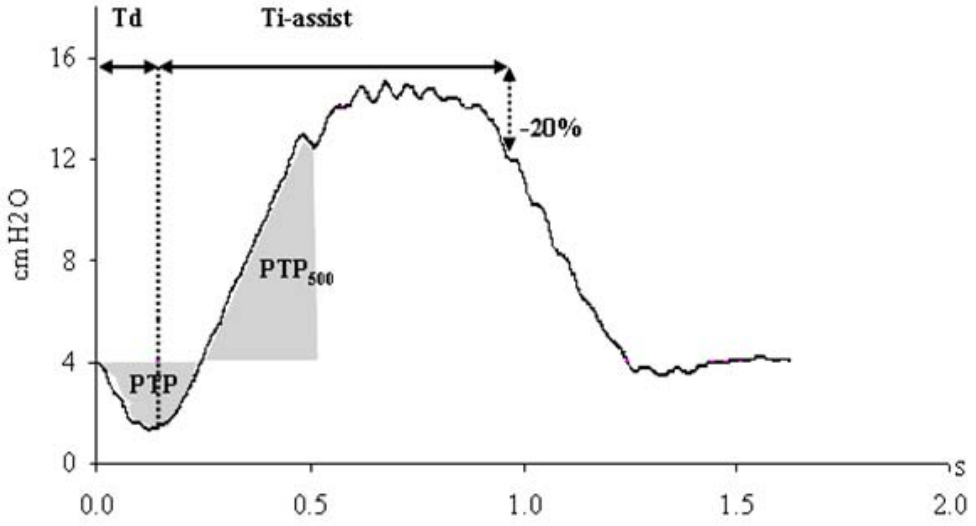
Résultats : Pour les 7 masques testés, le niveau des fuites intentionnelles s'échelonnait de 30 à 45 L.min^{-1} à une pression de 14 cmH_2O. Les fuites intentionnelles n'influençaient pas les performances du déclenchement inspiratoire. Quand les fuites intentionnelles augmentaient, la capacité du ventilateur à atteindre et maintenir la pression d'insufflation était diminuée avec les quatre ventilateurs dans les 3 conditions (obstructive ($p=0.12$), restrictive ($p<0.01$) normale ($p<0.02$)). Le volume courant délivré était significativement diminué jusqu'à un maximum de 48mL par cycle (conditions obstructive ($p<0.004$), restrictive ($p=0.12$) normale ($p<0.006$)). Le cyclage expiratoire n'était pas modifié sauf dans la condition du poumon obstructif. Dans cette condition, l'augmentation des fuites intentionnelles était associée à réduction du temps de pressurisation ($p= 0.04$).

Discussion-Conclusion : L'augmentation du niveau des fuites intentionnelles des masques n'affecte pas les performances de déclenchement des ventilateurs ni le cyclage. Par contre, elle diminue les capacités des appareils à atteindre et maintenir la pression d'insufflation. En conséquence, la diminution du volume courant peut atteindre 48 ml par cycle et peut induire

une hypoventilation nocturne. De plus la diminution des capacités à atteindre la pression d'insufflation peut majorer le travail respiratoire. Ces effets semblent survenir pour des fuites intentionnelles de plus de 40 $L.min^{-1}$ (à une pression de 14 cm H_20).

La principale implication clinique de cette étude est que si le masque habituel d'un patient est changé pour un masque à haut niveau de fuites intentionnelles, ce changement doit faire l'objet d'une évaluation de l'efficacité et de la tolérance de la VNI et d'une adaptation des paramètres du ventilateur en conséquence. Enfin, le niveau des fuites intentionnelles ne devrait pas dépasser le seuil de 40 $L.min^{-1}$ (à une pression de 14 cm H_20) lors du développement de nouveaux masques.

Figure 6 : Paramètres évaluant l'efficacité de la VNI.



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Intentional Leaks in Industrial Masks Have a Significant Impact on Efficacy of BiLevel Noninvasive Ventilation: A Bench Test Study

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Intentional leaks in industrial masks have a significant impact on efficacy of bi-level non-invasive ventilation: a bench test study

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Running title: industrial masks and efficacy of bi-level pressure non-invasive ventilation

Key-words: Masks for non-invasive ventilation, Bi-Level pressure cycled ventilators, Performance of ventilators, Bench test study.

Word count for the text: words

Abbreviations:

BPPV: Bi-level positive pressure cycled ventilators

C: Compliance

CPAP: Continuous positive airway pressure

EPAP: Expiratory positive airway pressure

IPAP: Inspiratory positive airway pressure

NIV: Non-Invasive Ventilation

PTP_{500}: Pressure time product at 500 ms

R: Resistance

Ti-assist: the time interval between onset of detectable pressurization and end of inspiratory pressurization

Td: trigger delay

Trigger PTP: Trigger pressure time product

Vt: Tidal volume

ABSTRACT: 250 words

Background: During non-invasive ventilation, non intentional leaks have a detrimental effect on the efficacy of ventilation. A wide range of industrial masks are available, with intentional leaks of different importance. The potential impact of this variability in intentional leaks on performances of bi-level ventilators has not been assessed.

Objective: To measure intentional leaks in 7 different industrial masks and determine whether higher leaks modify ventilator performances and quality of ventilation.

Methods: 7 interfaces connected to four ventilators (VPAP3-RESMED™; HARMONY2-RESPIRONICS™; SMARTAIR-ST-AIROX™; GK425ST-TYCO™) were adapted on a mannequin connected to a lung model (ASL5000, IngMar Medical™). Inspiratory (IPAP) and expiratory pressures were respectively 14 and 4cmH_2O. Lung model was set with a respiratory rate at 15/minute and duration of inspiration at 1 second in three simulated conditions (normal, restrictive, obstructive). Inspiratory trigger delay and effort, capacity to achieve and maintain IPAP, expiratory cycling and tidal volume (Vt) were analyzed for all masks and ventilators in the three simulated lung conditions.

Results: The level of intentional leaks in the 7 masks ranged from 30 to 45L*min^{-1} (for a IPAP of 14cmH_2O). Importance of leaks did not influence trigger performances. However, capacity to achieve and maintain IPAP was significantly decreased with all ventilators and in all simulated lung conditions when intentional leaks increased. This led to a maximum reduction in delivered Vt of 48ml. Expiratory cycling was not affected by the level of intentional leaks except in obstructive lung conditions.

Conclusion: Mask intentional leaks can impair efficacy of ventilation, especially when above 40L*min^{-1}.

INTRODUCTION:

Over the past 20 years, the prevalence of patients treated by home nocturnal non-invasive ventilation (NIV) for chronic hypercapnic respiratory failure has markedly increased presently exceeding 6000 in France and 20000 in the European community [1]. Bi-Level pressure cycled ventilators (BPPV) are the most widely used devices since the middle of the 90's [2]. BPPV ventilators are lighter and less expensive than volumetric ventilators and compensate a certain level of non intentional leaks [3]. They are usually used with a single tubing and exhaled gazes are evacuated through an expiratory port placed on the tube close to or directly on the mask (intentional leak). As no expiratory valve is included in the circuit, a minimal positive end expiratory pressure is required to flush exhaled CO_2 from the circuit and prevent CO_2 re-breathing [4]. The major increase in prescription of both continuous positive airway pressure (CPAP) and BPPV therapies and the need to improve tolerance and avoid non intentional leaks for providing successful NIV [5] have stimulated industrial companies to produce a wide variety of interfaces, such as nasal, facial or oral masks. These different interfaces are associated with important variations in intentional leak flow.

Whereas non intentional leaks around the mask are known to influence time/pressure product and to potentially explain inspiratory and/or expiratory trigger failures during pressure support ventilation [6-8], to our knowledge, no study has assessed the impact of different mask intentional leak levels on the performances of ventilators designed for NIV.

We thus aimed to assess the level of intentional leaks in 7 different industrial masks, and to analyse the relationship between the level of mask intentional leaks and effectiveness of inspiratory trigger, capacity of ventilators to achieve and maintain the pre-set pressure level and success of expiratory cycling. As BPPV ventilators differ in terms of performances [6,9-12], this study was performed with four ventilators on a bench test simulating normal, restrictive and obstructive lung mechanics.

MATERIALS AND METHODS:

Assessment of intentional leaks of the masks

Seven industrial masks were tested: Nasal-HC405® and Facial-HC431® (Fischer & Paykel, Auckland, New Zealand), Ultra-Mirage® nasal and facial (RESMED, NorthRyde, Australia), nasal-Confort Classic® and facial Confort-full® (RESPIRONICS, Murrysville, PA) and nasal IQ-Sleepnet® (L3-Médical, Vienne, France). The intentional leak valve of each mask was isolated from the mask and adapted on a tight support. This support was connected to a CPAP via a 22 mm diameter tubing. CPAP pressure was progressively increased from 4 to 14 cm H_20 and the flow, corresponding to the intentional leak, was measured with a flow meter (Ventest™, SODEREL Medical, Heillecourt, France)(Figure 1).

Bench test study design:

The masks were consecutively adapted to a mannequin head, connected via a tube (22 mm of diameter and 60 cm long) to a test-lung model ASL 5000 (IngMar Medical, Pittsburgh, PA USA). The mannequin-test lung couple was ventilated using a bi-level positive pressure ventilator (BPPV); a software connected to the test-lung model allowed adjustment of compliance (C), resistance (R), respiratory rate, and inspiratory time and recording of flow, pressure and tidal volume (Vt). These variables were acquired at a frequency of 512 Hz and stored for subsequent analysis.

For each mask tested, three different test-lung model settings were used: normal lung ($C=30ml/cmH_20$; $R= 5.6cmH_2O/L/s$); restrictive lung ($C=20ml/cmH_2O$; $R=5.6cmH_2O/L/s$); and obstructive lung ($C=20ml/cmH_20$; $R=20cmH_2O/L/s$). Respiratory rate was set at 15 cycles/minute and inspiratory duration at one second in all three lung conditions. During the

experiment, in order to verify the absence of non-intentional leaks, we applied a gas leak detector (Airbul, Molydal; Saint Maximin, France) around the mask.

Ventilators tested and settings:

Four different BPPV ventilators (VPAP-IIIST, Resmed,; HARMONY II, Respironics; SMARTAIR ST, Airox, subsidiary of Covidien group, Pau, France and GK425, Tyco-Nellcor Puritan Bennett; Pleasanton, CA) were tested with each mask in all three test-lung model settings. All ventilators were programmed in a bi-level pressure support mode; inspiratory (IPAP) and expiratory (EPAP) pressures were respectively set at 14 and 4 cmH_20. The pressurization slope was set to steepest value. For the VPAP IIIST and HARMONY II, inspiratory and expiratory flow triggers were automated. Inspiratory and expiratory triggers were adjustable for SMARTAIR-ST-AIROX^{TM}; GK425ST-TYCO^{TM}. Inspiratory flow triggers were set at 2 on a 5 arbitrary units (AU) scale for the Smartair and 2 on a 10 AU scale for the GK425; expiratory flow triggers were set at -50% of peak inspiratory flow for the Smartair and at 10 on a 10 AU scale for the GK425. For these two ventilators, prior to testing the different masks, we connected the lung model directly to the ventilator via the 60 cm long tube in association with a benchmark intentional leak of 4mm of diameter. We then set inspiratory trigger sensitivity at the most sensitive value without autotriggering and the expiratory trigger was set to obtain pressurisation time close to 1 second. These settings were fixed for subsequent tests with the different masks. As a consequence, for these ventilators, autotriggering detection was not assessed throughout the different trigger sensitivities.

Parameters evaluating ventilation efficacy:

The following parameters were used to assess changes in efficacy of ventilation and model-ventilator synchronisation induced by changes in intentional leaks (Figure 2):

For assessing inspiratory trigger, we measured *Trigger delay* (**Td**), defined as the time interval between onset of inspiratory effort and onset of detectable pressurization, and *Trigger Pressure time product* (**PTP**), defined as the area under the pressure-time curve between onset of inspiratory effort and the return to end expiratory pressure level (EPAP). Trigger PTP reflects both sensitivity of the ventilator in detecting inspiratory effort (i.e sensitivity of flow sensor and quality of ventilator algorithm) as well as ventilator ability in acutely delivering high flow rates (i.e power of ventilator turbine). Physiologically, PTP reflects work of breathing generated by inspiratory muscles to trigger the ventilator, or part of it in the presence of auto positive-end-expiratory-pressure (auto-PEEP).

Pressure time product at 500 ms (**PTP_{500}**), defined as the area under the pressure-time curve between return to EPAP and 500ms after onset of inspiratory effort, was used to quantify the speed of pressurization (i.e. achieve set pressure) and the ventilator capacity to maintain the set pressure during the first 500 ms of inspiratory effort [6,13]. Physiologically, a high PTP500 is mandatory to minimize the work of breathing. A lower PTP500 corresponds to underassistance of the ventilator, impaired pressurization rate and then increase in inpiratory effort for the patient.

Ti-assist, the time interval between onset of detectable pressurization and end of inspiratory pressurization (20% drop from peak inspiratory pressure), quantified changes in expiratory cycling performances of the BPPV ventilators. As ventilators showed small oscillations in pressure around IPAP (figure 2), such a drop was considered as significant for recognizing the end of pressurization with a maximal feasibility.

Finally, the resulting tidal volume (**Vt**) was automatically calculated at each insufflation by integration of the flow signal.

Data analysis:

The seven different masks were tested in 12 conditions (4 BPPV devices * 3 different lungs). For each condition, we analyzed 5 reproducible recorded cycles.

Statistical analysis:

NCSS 97 (Kaysville, Utah, USA) software was used for statistical analysis. For each BPPV ventilator, relationship between importance of intentional leaks and above-mentioned parameters of interest were analyzed using Spearman's rank sum test; a p-value less than 0.05 was considered significant. Results are expressed as mean ± standard deviation and minimal – maximal of each variable (Td, trigger PTP, PTP_{500}, Ti-assist, Vt).

Single-factor repeated-measures analysis was performed for assessing respectively the impact of intentional leaks levels (mask effect) and the type of ventilator (ventilator effect) on each variable.

RESULTS:

Mean ± SD values of trigger delay (Td), trigger PTP, PTP_{500}, TI-assist and Vt are given in tables 1-3 in respectively normal, restrictive and obstructive simulated lung mechanics. Rho values (Spearman's rank sum test), listed when significant, quantify for each ventilator the correlation between these parameters and the importance of intentional leaks among the 7 tested masks. Figures 3 & 5 illustrate this relationship for PTP_{500} and Vt, for all 4 ventilators tested. Figure 4 shows the relationship between importance of intentional leaks, Vt and pressure curve for each ventilator tested.

The type of ventilator had a significant impact on Td ($p<0.02$), Trigger PTP ($p\leq0.02$), PTP_{500} ($p\leq0.001$), Ti-assist ($p<0.0001$) and tidal volume ($p<0.0001$), in all simulated lung conditions.

Inspiratory trigger effectiveness (Td, PTP):

When averaging data for all four ventilators, the level of intentional leaks affected trigger delay only in normal lung condition ($p=0.02$); trigger PTP was unaffected by intentional leaks level in all simulated lung conditions.

We did not record any autotriggering with RESMED-VPAP3 and RESPIRONICS-HARMONY2.

Capability to achieve and maintain preset pressure (PTP_{500}):

Combining data for all ventilators, intentional leak levels significantly reduced PTP_{500} in both restrictive and normal conditions ($p\leq0.02$) (Figure 3). The mean decrease in PTP_{500} between masks with minimal and maximal leak levels [$PTP_{500\ (maximal\ leak)} - PTP_{500\ (minimal\ leak)} / PTP_{500\ (minimal\ leak)}$] reached 30 ± 3 % in normal lung mechanics and 20 ± 18 % in restrictive lung mechanics. This difference was only 7 ± 2 % in the obstructive lung conditions.

Inspiratory/expiratory cycling:

Ti-assist was significantly related to levels of intentional leaks in obstructive lung conditions ($p=0.04$) but not in normal and restrictive lung conditions. The mean variation of Ti-assist between the masks with minimal and maximal leaks level [$Ti_{(maximal\ leak)} - Ti_{(minimal\ leak)} / Ti_{(minimal\ leak)}$] reached 15 ± 8 % and 13 ± 7 % in normal and restrictive lung models respectively which means late cycling with higher intentional leak. Contrarily, this difference was - 4± 4 % in obstructive lung model (premature cycling)

Overall effect as determined by Vt measurements

Intentional mask leaks were significantly related to the tidal volume ($p=0.004$ and $p=0.006$ for obstructive and normal conditions respectively), but the trend did not reach significance in restrictive lung conditions ($p=0.12$).

To determine whether a Resmed or Respironics ventilator performed better with Resmed or Respironics masks than when using mask from other manufacturers, we compared the performances of RESMED VPAP3™ and RESPIRONICS HARMONY™ ventilators when using the masks recommended by the company versus the other masks. Results are rather related to amount of intentional leaks than to the trademark of the mask.

DISCUSSION:

Non intentional leaks, occurring during non invasive ventilation, have a detrimental effect on efficacy of NIV in both acute and chronic conditions [14-16]. To our knowledge, the present study is the first to assess a wide range of masks with different intentional leaks and analyze the consequences of increasing intentional leaks on trigger efficacy, capacity to achieve and maintain preset pressure and inpiratory/expiratory cycling. Our results can be summarized as follow: (i) Within a 30 to 45L/min range (at 14 cm H_2O of inspiratory pressure), intentional leaks did not significantly influence inspiratory trigger delay or work of breathing; (ii) increasing intentional leaks significantly impaired the capacity of all ventilators to attain and maintain preset inspiratory pressure in normal and pathologic simulated lung mechanics. This led to a maximum reduction in delivered Vt of 48ml; (iii) These significant effects occurred mainly for intentional leaks above 40l/min; (iv) Inpiratory/expiratory cycling was not affected by the level of mask intentional leaks except in obstructive lung conditions.

Differences in performance of BPPV ventilators available for long term ventilation have been previously documented [6,9-11,17]. This study takes into account these observations and shows that there was a significant effect of intentional leaks on relevant endpoints of ventilation independently of the BPPV ventilator chosen. Impact of ventilator performance and intentional leaks can be cumulative. In normal lung conditions, there was a maximal difference of 48 ml in Vt for a maximal increase of intentional leak of about 15l/min (figure 4). Devices with lower Vt were less affected by the increase in intentional leaks. It is important to document these relationships so that, when changing masks, physicians can adjust ventilator parameters appropriately. Manufacturers should provide recommendations for ventilator settings adjustments with the different masks available.

Trigger effectiveness

The only impact of intentional leaks level on trigger effectiveness was observed in trigger delay under normal lung condition (p=0.02). Owing to respiratory mechanical characteristics, trigger delay is generally measured as significantly higher in normal lung condition compared to obstructive or restrictive conditions [18]. Accordingly, by increasing leaks the major lengthening effect is also observed in normal lung condition. This limited effect of increasing mask leaks on trigger effort could be unexpected at first glance. In agreement with our results, Stell et al. did not find any impact of a similar range of leaks (15L/min) on inspiratory triggering [17]. Miyoshi et al. found that, in BPPV ventilators, inspiratory triggering was not affected as leaks increased [8]. This is at least partly explained by improvement of triggering mechanisms implemented in mechanical ventilators in general and among BPPV ventilators in particular [12,19,20]. It could also result from bench test conditions. With a higher EPAP, as used for instance in patients with obesity hypoventilation syndrome or in acute conditions, similar levels of leaks could have a more important impact on triggering. Also, it has been demonstrated that ineffective efforts and patient/ventilator asynchrony are highly prevalent during sleep [21,22]. Ineffective efforts seem to be more frequent in the presence of air leaks [21]. Thus, even if we did not observe any change in triggering effort with increasing intentional leaks in our bench test study, further studies should address the impact of variations in intentional leaks with different ventilators settings and in clinical studies of patient/ventilator asynchrony during sleep.

Pressurization

This is probably the item for which differences between ICU ventilators and BPPV ventilators are the most significant [12]. Thus, the impact of intentional leaks on PTP_{500} was somewhat expected. In our study, reduction in PTP_{500} was found mainly in normal and restrictive lung conditions. Accordingly, reduction in ventilator capacity to reach preset

pressure and associated increase in work of breathing would probably be more significant in clinical situations such as morbid obesity or diseases with low thoracic compliance such as kyphoscoliosis. In these situations the choice of masks should, whenever possible, favor those with low intentional leaks.

Inspiratory/expiratory cycling

Ti-assist was not affected by intentional leaks in normal and restrictive lung conditions but it was shorter for larger leaks in obstructive lung conditions. It is usually accepted that the presence of leaks during pressure support ventilation increases the probability of a prolonged pressurization time and a shortened expiratory phase [11]. Battisti and colleagues [6] have shown that leaks as low as 10 L/min can modify pressurization time according to the BPPV ventilators tested. The authors showed that leaks modified cycling, leading to either delayed or premature cycling according to BPPV ventilator studied or lung mechanics. In obstructive lung conditions, four out of ten ventilators cycled prematurely in the presence of leaks (from -6% to -22% comparing to without leaks) whereas the others six delayed cycling [6]. In summary, expiratory trigger can be inappropriate in the presence of abnormal respiratory mechanics, leading to inadequate cycling [6,23]. This general pattern was for the most part exacerbated by the presence of leaks.

Tidal volume available for the patient

Increasing the level of intentional leaks on masks led to a maximal decrease in Vt of 48 ml with a range depending upon ventilator and lung mechanics. This is mainly explained by the reduction in ventilator pressurization capabilities without significant changes in Ti assist. A recent study [24] showed that such a 50 ml mean variation of Vt during sleep could be associated with a significant nocturnal hypoventilation. In addition, Gonzalez et al [25] showed that a rate of non intentional leaks about 200 mL per cycle was associated with daytime hypercapnia. A cumulative increase in the level of intentional leaks by changing the

mask can be responsible for up to 25% of such leaks and can aggravate nocturnal and diurnal hypoventilation. At the end, Teschler et al [16] showed that a median non intentional mouth leak of 21 l.min^{-1} (close to the maximal variation we observed in the 7 tested masks (15 L.min^{-1})) induced an increase of nocturnal $PtCO_2$. Reaching this leak threshold can be facilitated by changing the mask. Thus, when using a mask with an intentional leak above 40L/min (for an IPAP of 14cm H2O), increasing pressure support to compensate reduction in Vt, could be recommended. For a given increase in pressure support, the induced increase in intentional leaks does not have sufficiently important detrimental effects to counterbalance the associated increase in ventilation

Limitations of the study

Although undoubtedly useful, bench test modeling of non-invasive ventilation (NIV) is an oversimplification of the complex phenomenon's occurring during NIV when associated with leaks. Accordingly, results provided should indeed be corroborated by clinical sleep studies. Pressure support above the 10 cm H_2O that we used are frequently applied in clinical practice. Measurements performed with higher IPAP values (18 cmH_2O) frequently led to non intentional leaks between the mannequin and the masks. Thus, for controlling the quality of the data we finally chose 14 cmH20.

Clinical significance of findings and conclusions

The amount of intentional leaks of industrial masks did not impact on inspiratory trigger or on inspiratory/expiratory cycling in bench test conditions. Conversely, high levels of intentional leaks (above 40L/min for an IPAP of 14cmH20) can reduce Vt up to 50ml. Such a drop in tidal volume has been shown to be sufficient to induce nocturnal hypoventilation in patients. Finally, as PTP_{500} was systematically reduced by such large intentional leaks, work of breathing is increased by using these masks. This may impair

patient-machine synchronization and patient tolerance. Additionally, consequences of leaks may be more important with pressures above 14 cm H20. Such pressures have not been assessed in the current study for methodological reasons but can be used in clinical practice. Obviously, the first step is to use a well fitting mask. Nevertheless, the main clinical implication is thus that changing the ventilator circuit for a mask with higher intentional leaks should be cautiously monitored in order to adjust ventilator parameters when a decrease in non invasive ventilation efficiency or tolerance occur. Furthermore, an intentional leak above 40l/min (for an IPAP of 14cm H2O) is probably not desirable when developing new masks.

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Table 1: Correlation between intentional leaks and variables of interest in test-lung model simulating normal lung mechanics (C=30ml/cmH_20; R= 5.6cmH_2O/L/s)

	Td (ms)		PTP (cmH_2O*s)		PTP 500 (cmH_2O*s)		Ti-assist (s)		Vt (ml)	
	rho	Mean ± SD min –max	rho	Mean ± SD min –max	rho	Mean ± SD min –max	rho	Mean ± SD min –max	rho	Mean ± SD min –max
RESMED VPAP 3 ST	0.89 *	155± 7 145 - 164	n.s.	0.6 ± 0.02 0.58 - 0.64	-0.87*	3.0 ± 0.4 2.2 – 3.4	n.s.	0.60 ± 0.03 0.6 - 0.69	-0.85*	900 ± 18 860 -920
RESPIRONICS Harmony II	n.s.	83 ± 5 75- 90	0.88*	0.5 ± 0.12 0.40 - 0.73	n.s.	3.0 ± 0.4 2.2 - 3.3	n.s.	0.80 ± 0.05 0.72- 0.89	n.s.	860 ± 5 850-870
AIROX Smartair ST	n.s.	161 ± 20 140 - 200	n.s.	0.8 ± 0.04 0.71 - 0.82	-0.86*	1.9 ± 0.3 1.5 - 2.2	n.s.	0.90 ± 0.06 0.81-1.0	-0.86*	940 ± 16 910-950
TYCO 425 ST	n.s.	190 ± 20 170- 210	n.s.	0.7 ± 0.03 0.66 - 0.74	n.s.	0.9 ± 0.1 0.70 – 1.0	n.s.	1 ± 0.1 0.88 – 1.11	n.s.	910 ± 8 890 – 914

*: $p<0.05$; n.s.: non significant

Table 2: Correlations between intentional leaks and variables of interest in Restrictive lung model (C=20ml/cmH_20; R= 5.6cmH_2O/L/s)

	Td (ms)		PTP (cmH_2O*s)		PTP 500 (cmH_2O*s)		Ti-assist (s)		Vt (ml)	
	rho	Mean ± SD min –max	rho	Mean ± SD min –max	rho	Mean ± SD min –max	rho	Mean ± SD min –max	rho	Mean ± SD min –max
RESMED VPAP 3 ST	ns	100 ± 15 80 – 120	ns	0.5 ± 0.01 0.49 - 0.52	ns	4.0 ± 0.1 3.8 – 4.2	ns	0.60 ± 0.05 0.51 - 0.63	ns	620 ± 15 594 -631
RESPIRONICS Harmony II	0.68#	74 ± 2 72 – 76	ns	0.4 ± 0.05 0.38-0.54	-0.61#	3.6 ± 0.3 3.0 - 3.8	ns	0.60 ±0.1 0.54-0.81	ns	560 ± 6 555-570
AIROX Smartair ST	0.75#	130 ± 13 120 - 150	ns	0.5 ± 0.05 0.43-0.56	-0.82*	2.6 ± 0.4 2.0 - 2.9	ns	0.80 ± 0.05 0.65-0.80	-0.64#	640 ± 17 610-650
TYCO 425 ST	ns	140 ± 3 135 - 143	ns	0.5 ± 0.02 0.49 – 0.54	-0.88*	1.5 ± 0.2 1.1 – 1. 63	ns	1 ± 0.06 0.88 – 1.1	ns	600 ± 8 590 - 620

*: $p<0.05$

#: $p\leq0.1$

Table 3: Correlations between intentional leaks and variables of interest in Obstructive lung model (C=20ml/cmH_20; R= 20 cmH_2O/L/s)

	Td (s)		PTP (cmH2O*s)		PTP 500(cmH2O*s)		Ti-assist (s)		Vt (ml)	
	R	Mean ± SD min –max	R	Mean ± SD min –max	R	Mean ± SD min –max	R	Mean ± SD min –max	R	Mean ± SD min –max
RESMED VPAP 3 ST	0.68 #	51 ± 24 40 - 110	ns	0.7 ± 0.01 0.67 - 0.69	-0.86*	3.9 ± 0.3 3.5 – 4.5	-0.69#	1.1 ± 0.06 1.07 – 1.2	-0.75#	530 ± 8 520 -539
RESPIRONICS Harmony II	ns	54 ± 3 50 - 57	ns	0.5 ± 0.05 0.44-0.59	ns	4.2 ± 0.2 3.9-4.6	ns	1.2 ± 0.1 1.04-1.33	-0.86*	540 ± 15 516-553
AIROX Smartair ST	0.68#	77 ± 9 60 - 90	0.67#	0.5 ± 0.03 0.43-0.50	ns	4.1 ± 0.2 3.7- 4.4	ns	1.5 ± 0.05 1.40-1.55	ns	570 ± 6 558-572
TYCO 425 ST	0.86*	110 ± 2 110 - 120	ns	0.8 ±0.04 0.69-0.82	ns	2.1 ± 0.2 1.7 - 2.4	ns	1.4 ±0.06 1.27 – 1.45	-0.71#	540 ± 4 533-547

*: $p<0.05$

#:$p\leq0.1$

Figure 1: A) Intentional leaks expressed as function of the pressure in seven different masks; B) pressure-time plot of VPAP3-RESMED with the 7 masks for the normal lung condition

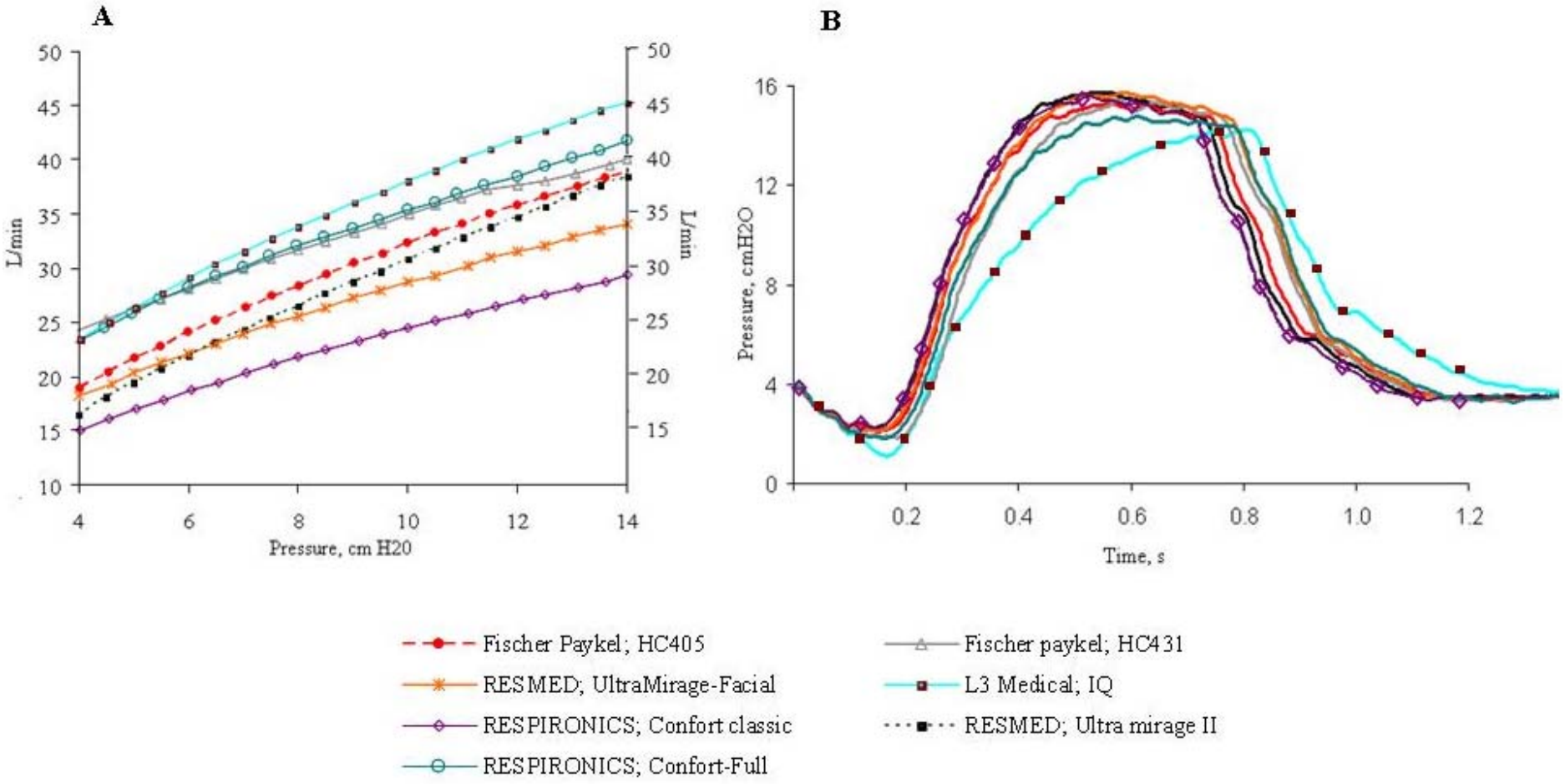


Figure 2: Parameters evaluating ventilation efficacy

Td: Time between the onset of inspiratory effort and the onset of detectable pressurization; **PTP:** Area under the pressure-time curve between the onset of inspiratory effort and the return to EPAP level; Td and PTP both reflect effectiveness of inspiratory trigger. **PTP500:** reflects the speed of pressurization (the capacity of the device to achieve and maintain the preset pressure during inspiratory effort); **Ti-assist:** Time between the onset of detectable pressurisation and drop of pressure curve. Ti-assist is a marker of expiratory cycling.

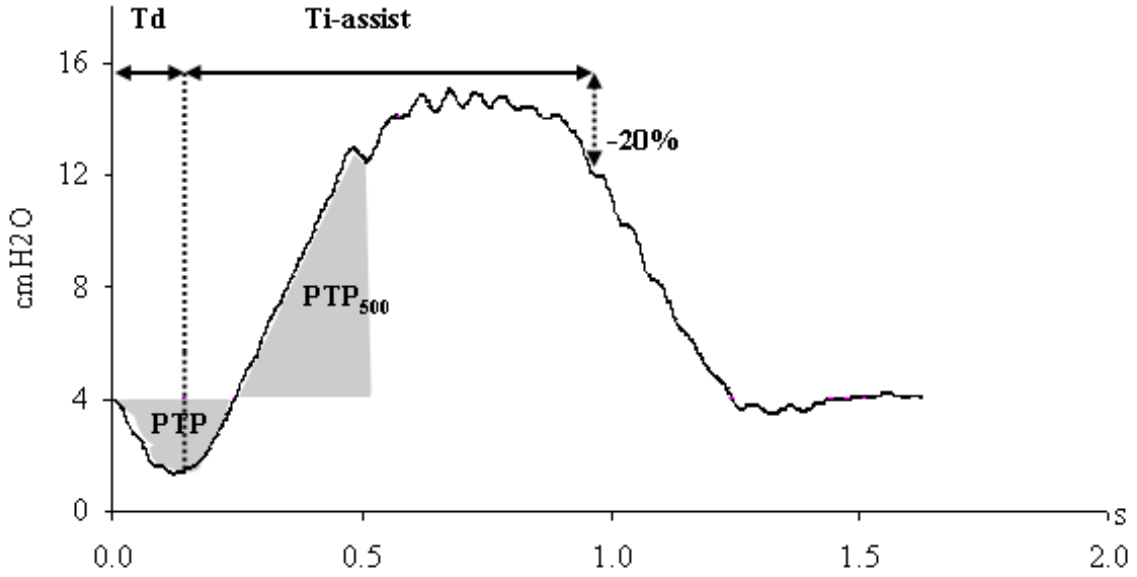


Figure 3: Capacity to achieve and maintain preset pressure (PTP500) according to intentional leaks of the 7 masks and the 4 BPPV ventilators (Single-factor repeated-measures analysis)

A: RESPIRONICS Confort-classic; B: RESMED Ultramirage Facial; C:RESMED ultramirage nasal; D: Fischer Paykel HC405u; E: Fischer Paykel HC431; F: RESPIRONICS Confortfull; G: L3 Medical IQ. Each point of Vt represents mean ± SD of the 4 apparatus tested for each mask .
A : 29.4 l/mn, B : 34.1 l/mn, C : 38.5 l/mn, D : 39.1 l/mn, E : 40 l/mn, F : 41.7 l/mn, G : 45.2 l/mn at 14 cm H2O of inspiratory pressure

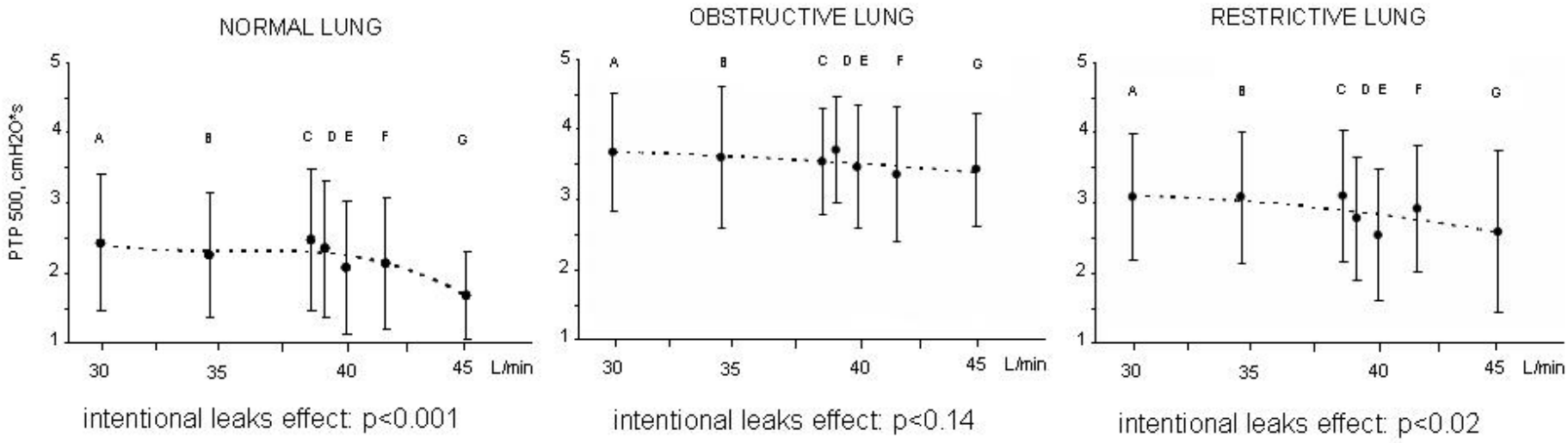


Figure 4: Graph showing the pressure curves for the masks with minimal leaks level (thick line) versus maximal leaks level (in thin line with empty scare) and the relationships between tidal volume and intentional leak levels (NORMAL LUNG MODEL)
Correlation were analyzed with Spearman correlation test (r and p values are reported in the table 1)

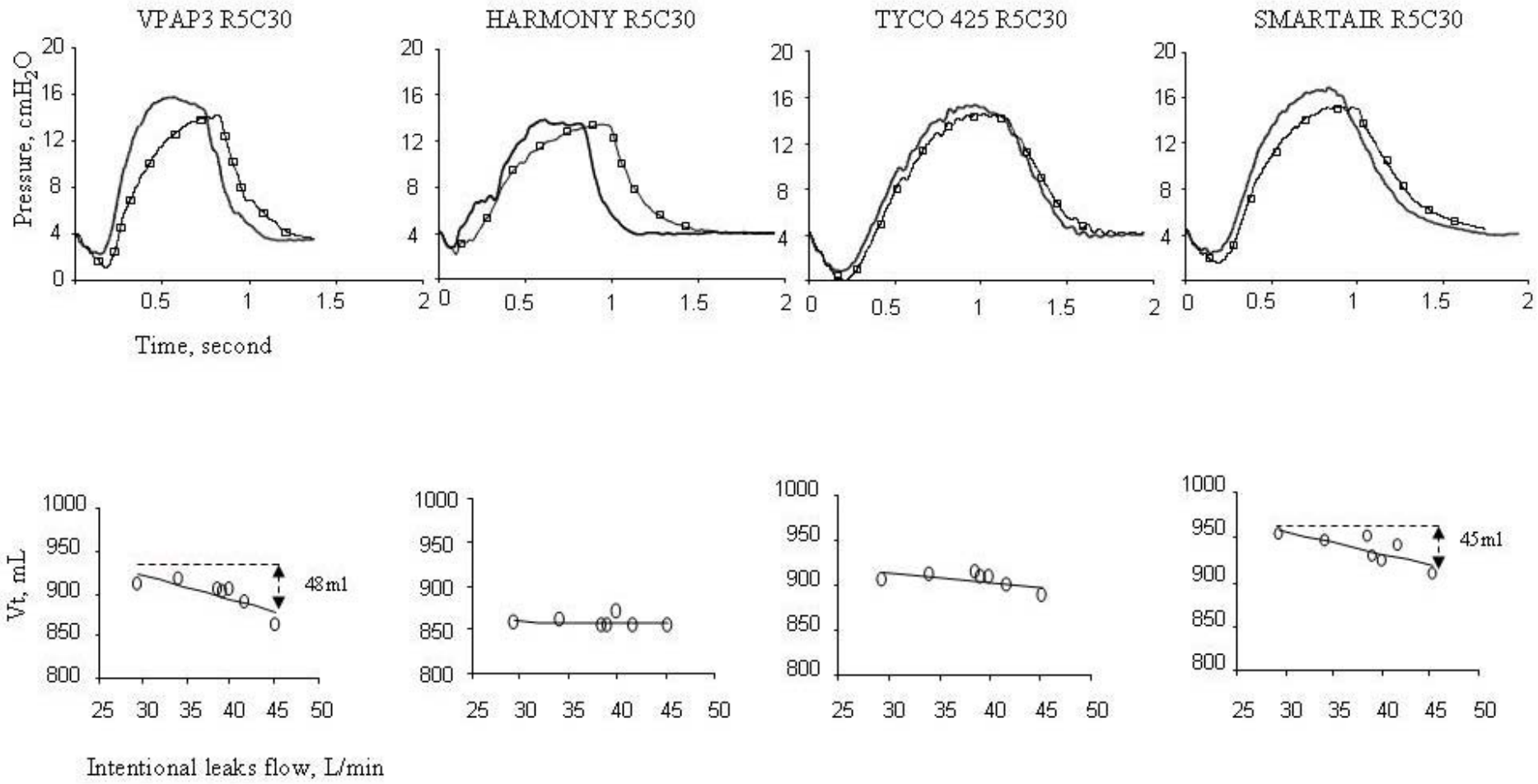
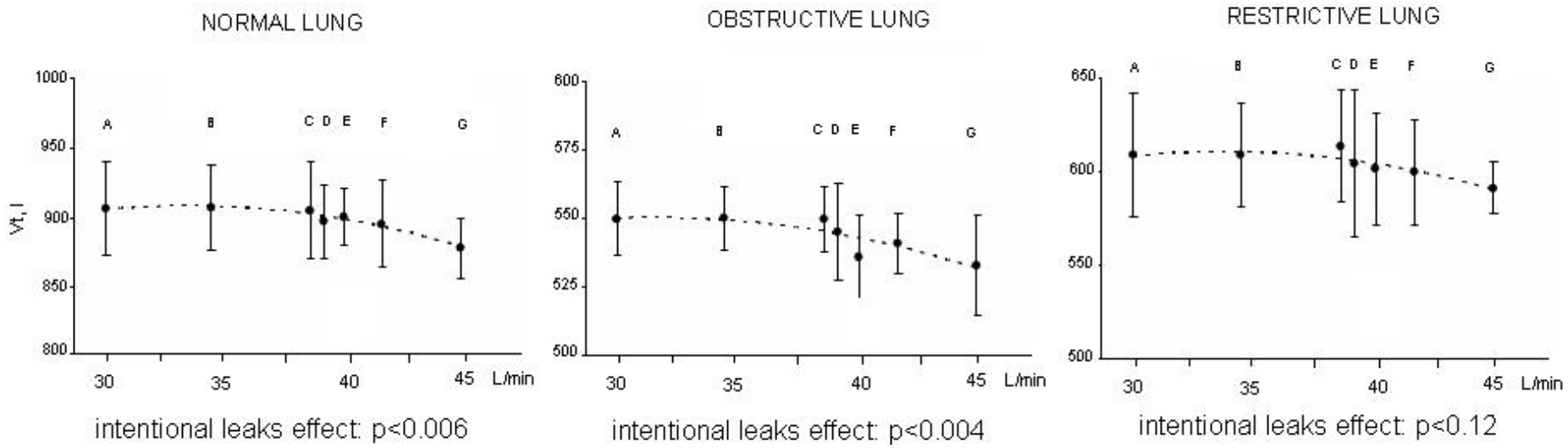


Figure 5: Resulting tidal volume according to the 7 masks and the 4 NIV devices (Single-factor repeated-measures analysis)
A: RESPIRONICS Confort-classic; B: RESMED Ultramirage Facial; C: RESMED ultramirage nasal; D: Fischer Paykel HC405u; E: Fischer Paykel HC431; F: RESPIRONICS Confortfull; G: L3 Medical IQ. Each point of Vt represents mean ± SD of the 4 apparatus tested for each mask .
A : 29.4 l/mn, B : 34.1 l/mn, C : 38.5 l/mn, D : 39.1 l/mn, E : 40 l/mn, F : 41.7 l/mn, G : 45.2 l/mn at 14 cm H2O of inspiratory pressure.



CONCLUSION GÉNÉRALE :

Nous avons montré que l'hypoventilation alvéolaire chronique habituellement considérée uniquement comme un marqueur d'évolution péjorative de différentes pathologies respiratoires est aussi un des déterminants physiopathologiques des dysfonctions systémiques cardiovasculaires, métabolique et d'intolérance à l'effort.

Au cours du Syndrome Obésité Hypoventilation (SOH), la vigilance diurne, la fonction endothéliale et l'inflammation systémique sont plus sévèrement altérées du fait de l'hypoventilation alvéolaire. De plus, les patients SOH présentent une insulino-résistance plus importante que des patients obèses non hypoventilateurs appariés. La première étude randomisée contrôlée, réalisée dans le domaine, montrait que la ventilation non invasive corrigeait l'hypoventilation alvéolaire diurne, permettait d'améliorer la vigilance mais ne modifiait pas la fonction endothéliale ni les facteurs métaboliques. L'obésité en elle-même pourrait être le facteur principal des dysfonctions métaboliques et cardio-vasculaires persistantes. Cependant nous faisons l'hypothèse que la correction de l'hypoventilation alvéolaire chronique et des troubles respiratoires du sommeil permettraient de ralentir l'évolution péjorative des paramètres cardio-vasculaires et métaboliques. Une des perspectives de ce travail sera donc de suivre prospectivement ces patients obèses et obèse hypoventilateurs, pour étudier l'évolution au long cours (1an -2ans) de ces paramètres, en fonction de l'observance des patients à leur traitement par VNI ou PPC.

Dans l'insuffisance respiratoire chronique pariéto-restrictive (IRC-R), la tolérance à l'effort est améliorée en utilisant la VNI au cours de l'activité physique, en particulier chez les patients les plus sévères. Elle permet à ceux-ci d'optimiser les bénéfices d'un réentraînement en évitant une fatigue excessive en cours de ce réentraînement. L'hypoventilation alvéolaire chronique est donc un des facteurs d'intolérance à l'effort. Les perspectives sont d'évaluer l'effet de la VNI au cours de programmes de réhabilitation au long cours chez les restrictifs

les plus sévères, les plus fatigués et les plus hypoventilateurs. La miniaturisation des appareils de VNI pourrait également permettre d'envisager d'intégrer la VNI pour favoriser les actes de la vie quotidienne.

Enfin, notre étude sur l'impact des fuites intentionnelles des masques de VNI bi-pressionnelle montre que les progrès technologiques réalisés par les constructeurs (appareillage et interfaces) ne dispensent pas de la nécessité d'évaluer de façon indépendante la pertinence de ces avancées et leurs limites potentielles. Ceci est vrai pour des aspects interfaces mais probablement encore plus pour les « nouveaux » modes ventilatoires qui sont proposés sans validation clinique convaincante.

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ANNEXE : AUTRES ACTIVITES DE PUBLICATION EN COURS DE THESE

INTERMITTENT HYPOXIA AND SLEEP-DISORDERED BREATHING: CURRENT CONCEPTS AND PERSPECTIVES.

P. Levy, JL. Pépin, C. Arnaud, R. Tamisier, JC. Borel, M. Dematteis, D. Godin-Ribuot, C. Ribuot. Eur Resp J 2008; 32:1082-1095

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SERIES "HYPOXIA: ERS LUNG SCIENCE CONFERENCE"
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Intermittent hypoxia and sleep-disordered breathing: current concepts and perspectives

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ABSTRACT: There are three major types of sleep-disordered breathing (SDB) with respect to prevalence and health consequences, *i.e.* obstructive sleep apnoea syndrome (OSAS), Cheyne–Stokes respiration and central sleep apnoea (CSR-CSA) in chronic heart failure, and obesity hypoventilation syndrome (OHS). In all three conditions, hypoxia appears to affect body functioning in different ways. Most of the molecular and cellular mechanisms that occur in response to SDB-related hypoxia remain unknown.

In OSAS, an inflammatory cascade mainly dependent upon intermittent hypoxia has been described. There is a strong interaction between haemodynamic and inflammatory changes in promoting vascular remodelling. Moreover, during OSAS, most organ, tissue or functional impairment is related to the severity of nocturnal hypoxia. CSR-CSA occurring during heart failure is primarily a consequence of cardiac impairment. CSR-CSA has deleterious consequences for cardiac prognosis and mortality since it favours sympathetic activation, ventricular ectopy and atrial fibrillation. Although correction of CSR-CSA seems to be critical, there is a need to establish therapy guidelines in large randomised controlled trials.

Finally, OHS is a growing health concern, owing to the worldwide obesity epidemic and OHS morbidities. The pathophysiology of OHS remains largely unknown. However, resistance to leptin, obesity and severe nocturnal hypoxia lead to insulin resistance and endothelial dysfunction. In addition, several adipokines may be triggered by hypoxia and explain, at least in part, OHS morbidity and mortality.

Overall, chronic intermittent hypoxia appears to have specific genomic effects that differ notably from continuous hypoxia. Further research is required to fully elucidate the molecular and cellular mechanisms.

KEYWORDS: Atherosclerosis, Cheyne–Stokes respiration, inflammation, intermittent hypoxia, obesity hypoventilation syndrome, sleep apnoea

Sleep-disordered breathing (SDB) represents a growing health concern. Sleep apnoea has been known for centuries and was rediscovered at the beginning of the 20th century. In the late 1990s, however, different types of SDB have been recognised, with specific consequences and morbidities. At the end of the 1990s, a revised classification was suggested by the American Academy of Sleep Medicine [1] and further confirmed through the International Classification of Sleep Disorders, second edition (ICDS-2) [2], published in 2005. There are three major SDB types with respect to prevalence and health consequences, *i.e.* obstructive sleep apnoea

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(OSA) syndrome (OSAS), Cheyne–Stokes respiration (CSR) and central sleep apnoea (CSA) in chronic heart failure (CHF), and obesity hypoventilation syndrome (OHS). Figure 1 shows the type of respiratory events occurring in all three conditions, as reflected by oxygen saturation and ventilatory changes during 5-min recordings.

In all three conditions, hypoxia appears to affect body functioning in different ways, with specific mechanisms. Moreover, experimental models have been developed that permit a better understanding of the molecular and cellular mechanisms in response to SBD-related hypoxia. The present paper covers all of these specific issues.

OBSTRUCTIVE SLEEP APNOEA SYNDROME

Definition, prevalence and main consequences

OSAS is defined by symptoms such as excessive daytime sleepiness (EDS) and daytime functioning impairment, with >5 obstructive events·h^{-1} occurring during sleep. The scoring of ventilatory events includes apnoeas, hypopnoeas and also episodes of increased upper airway resistance. Both the ICSD-2 [2] and American Academy of Sleep Medicine [1] guidelines recommend that this latter type of event should be included in OSAS, since the specificity of upper airway resistance syndrome [3] has not been considered, until now, to be supported by sufficient epidemiological, pathophysiological and clinical data.

The prevalence of the disease is very high, ranging 5–15%, increasing linearly up to the age of 60 yrs and becoming more variable above this threshold age, at least regarding obstructive events [4]. Regarding OSAS morbidity [5], there is now substantial evidence that there is a causal relationship between OSA and EDS, with cognitive impairment, including increased risk of traffic accidents [6, 7], and cardiovascular morbidity and mortality [7–9]. The cardiovascular consequences, *e.g.* occurrence of atherosclerosis without significant classical cardiovascular risks in OSA, seem to appear early in the disease [10, 11]. This supports the need for early diagnosis and treatment, especially since the mortality rate is maximal in males aged <50 yrs and thereafter declines with age [12].

Intermittent hypoxia, a major stimulus

The desaturation–reoxygenation sequence is a typical pattern coupled with the majority of respiratory events. This sequence, defining intermittent hypoxia (IH), leads to oxidative stress, with production of reactive oxygen species (ROS) [13]. Numerous studies have shown increased oxidative stress using various biological markers, although comorbid conditions such as diabetes, hypertension and obesity may account for some of these results [13–16]. The increased levels of ROS contribute to the generation of adhesion molecules [17], activation of leukocytes [18] and production of systemic inflammation [19]. Together, these mechanisms generate vascular endothelial damage and dysfunction [20, 21]. Moreover, high sympathetic output, as consistently found in OSA, may lead to insulin resistance, even in nonobese OSA patients [22], representing an additional source of oxidative stress. Oxidative stress is characterised by an imbalance between the production and degradation of ROS. Although numerous studies have addressed the issue of increased ROS production, there are only a limited number of studies

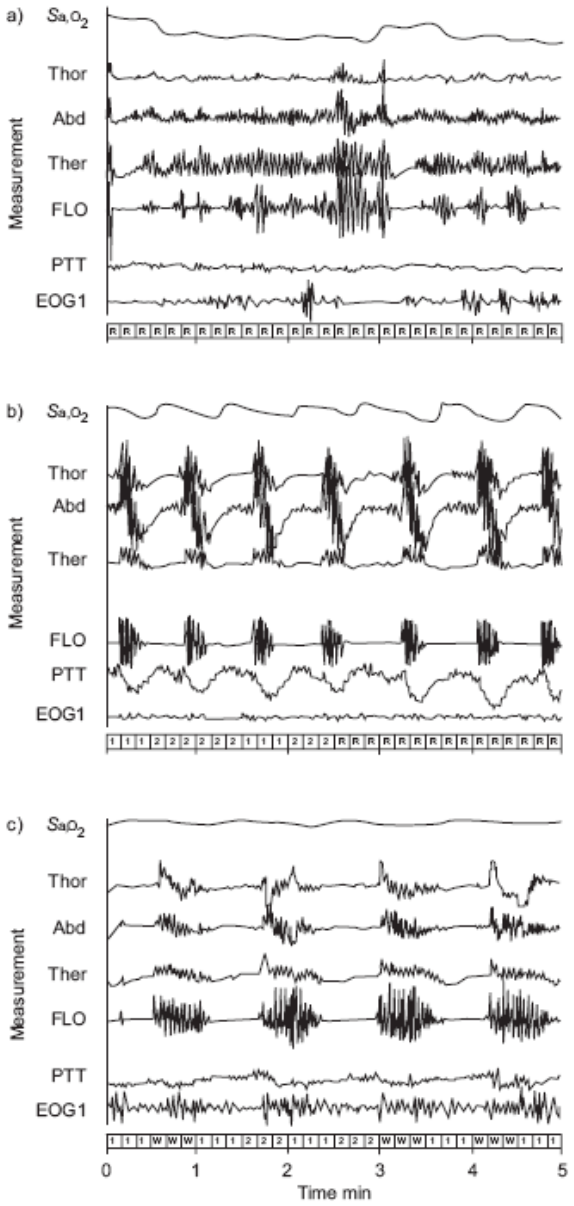

FIGURE 1. Polysomnographic comparison of three characteristic ventilatory patterns in the three major types of sleep-disordered breathing: a) rapid eye movement sleep hypoventilation in obesity hypoventilation syndrome, b) obstructive sleep apnoea syndrome, and c) periodic breathing during Cheyne–Stokes respiration in congestive heart failure (5-min epochs). Sleep stage is indicated on the *x*-axis: R: rapid eye movement; 1: stage 1; 2: stage 2; W: wakefulness. Sa,O_2: arterial oxygen saturation; Thor: thoracic movements; Abd: abdominal movements; Ther: oronasal thermistor (to assess persistent nose or mouth breathing by temperature measurement); FLO: nasal pressure; PTT: pulse transit time; EOG: electro-oculogram.

addressing the role of antioxidant capacities in OSA patients. BARCELO *et al.* [23] reported an alteration in antioxidant capacities, with a reduction in total antioxidant status, and a decrease in both vitamin A and E levels. In the same study, continuous positive airway pressure (CPAP) treatment normalised total antioxidant status [23]. In 2008, impairment of albumin antioxidant properties independent of body mass index (BMI) and related only to OSA severity has been demonstrated [24].

OSA has also been shown to be associated with a reduction in nitric oxide bioavailability. Nitric oxide derivatives include the nitrosonium ion (NO^+), which results from the auto-oxidation of nitric oxide under certain conditions, and peroxynitrite ($ONOO^-$), which is the product of the reaction between nitric oxide and the superoxide ion ($O_2^{\cdot-}$), since peroxynitrite is generated in situations associated with increased oxidative stress, *e.g.* hypoxia and ischaemia–reperfusion, particularly at the level of the vascular wall. Peroxynitrite has been shown to modulate the activity of several key enzymes of vascular homeostasis, such as endothelial nitric oxide synthase, Akt kinase and catalase. By inhibiting endothelial nitric oxide synthase activity through AMP kinase [25] and catalase [26], peroxynitrite favours the generation of superoxide ions, thus inducing a vicious cycle leading to increasing local oxidative stress with deleterious consequences. In OSA, a reduction in nitric oxide availability has been demonstrated, as well as an increase in levels of its derivatives [27, 28], although this has not always been confirmed [29]. It is viewed as being an important determinant of the endothelial dysfunction associated with OSA [13].

Oxidative stress generates an inflammatory cascade *via* nuclear factor-κB (NF-κB) activation [30]. However, there is still much discussion regarding the confounding influence of obesity and the associated cardiovascular morbidity on the relationship between sleep apnoea severity and inflammatory markers. This is presumably responsible for the conflicting results obtained regarding C-reactive protein in OSA. Although C-reactive protein levels were found to be elevated in several studies [31–33], other reports failed to demonstrate any linear relationship with the severity of OSA [34].

The inflammatory cascade increases adhesion molecule expression [35] and further activates monocytes and lymphocytes [36, 37]. In 2007, it was shown that impairment of endothelium-dependent vasodilation correlated with the degree of endothelial cell apoptosis. Also, CPAP therapy led to a significant decline in circulating apoptotic endothelial cell numbers [38]. All of these mechanisms lead to endothelial dysfunction and damage. Moreover, IH is associated with significant cyclical haemodynamic changes that may also contribute to endothelial dysfunction.

Cellular and molecular consequences of IH

There is now substantial evidence that IH and continuous hypoxia (CH) lead to differential gene activation. Studies on cell cultures have revealed that IH is a more potent stimulus for transcriptional activation than CH at a comparable level of hypoxia intensity and duration. Hypoxia-inducible factor 1 has been shown to be more activated during CH than during IH in some [39] but not all studies [30]. Indeed, several experimental factors may be critical to explaining these discrepancies, *i.e.* cellular type, and intensity and duration of the hypoxic stimulus. As a consequence, downstream end-products such as erythropoietin and vascular endothelial growth factor on the one hand, and tumour necrosis factor (TNF)-α and other pro-inflammatory cytokines on the other, have been shown to be differently affected [30, 40–42].

IH has been studied in various models. Cellular models of IH are still poorly developed. There is major difficulty in establishing such models since changing intracellular oxygen content implies rapid modification of the oxygen fraction in the media surrounding the cells. Thus it remains difficult to obtain rapid cyclical intracellular oxygen content changes, whatever the cellular type [43], owing to gas exchange inertia in the media. Some models are also essentially acute and far from chronic IH (CIH) as seen in OSA [30], whereas others seem to be more realistic [44]. This has permitted the demonstration of selective activation of NF-κB [30], ROS production and mitochondrial dysfunction [44]. Increased dopamine secretion also occurs *via* IH induction of tyrosine hydroxylase (TH) phosphorylation in rat pheochromocytoma 12 cells. TH is the rate-limiting enzyme that catalyses the conversion of tyrosine into dihydroxyphenylalanine in catecholamine biosynthesis. This TH activation has been shown to involve increased serine phosphorylation without augmenting TH protein expression, in contrast with chronic CH [45]. This represents one of the differential cellular changes expressed in response to IH.

There have been great advances in animal models since the early 1990s. One major advance, although the experiments were difficult to perform on a long-term basis, was the canine model, in which upper airway obstruction and sleep fragmentation were compared in terms of the acute and chronic cardiovascular consequences [46–48]. However, much more research in the field of hypoxia has been performed using wild-type or genetically modified rodents [49]. This is also true regarding IH [50]. Starting with the early evidence provided by FLETCHER *et al.* [51] that night-time CIH results in permanent daytime hypertension, there have been many reports on IH effects, mainly on the cardiovascular system. Vascular reactivity has been shown to be altered in various fashions in rodents [52–55]. A variety of biological and pathophysiological changes have also been demonstrated, *i.e.* altered baroreflex activity [56], increased pulmonary arterial pressure and haematocrit [57], changes in heart structure and function [58], altered endothelium-dependent vasodilation in cerebral and muscular arteries [59], and an increased response to endothelin (ET)-1 [54], presumably mediated almost exclusively by ETA receptors [60]. During IH, both blood pressure (BP) and myocardial changes might be critically dependent upon ET-1. Evidence has recently been found for an increase in ETA receptor expression and large ET-1 concentration at the level of the heart in spontaneously hypertensive rats submitted to IH (E Belaïdi, Hypoxia PathoPhysiology laboratory, Grenoble University, Grenoble, France; personal communication). This was associated with aggravation of both the IH-related increase in BP, in contrast with a previous report [58], and increased infarct size during ischaemia, both being suppressed by ET-1 receptor antagonists (E Belaïdi; personal communication). There is also altered sensitivity to ischaemia, which is reduced when IH is acute, acting as a pre-conditioning

stimulus [61], and increased when chronic [62]. Overall, these results support further therapeutic perspectives regarding cardiovascular modulation in OSA patients. In this context, ET-1 receptors might represent an adequate pharmacological target requiring further testing.

More recently, metabolic and atherosclerotic changes have been shown in mice exposed to CIH [63, 64]. At the arterial level, significant systemic inflammation occurs, as evidenced by T-cell activation characterised by spleen-derived T-cell proliferation and chemokine mRNA expression. In the present authors' experience, this occurs from day 5 of IH. In mesenteric resistance arteries, intercellular adhesion molecule-1 expression increased at day 14 of IH and was associated with increased leukocyte rolling. Aorta from hypoxic mice exhibited both activation of the pro-inflammatory transcription factor NF-κB and increased intima–media thickness at 14 days. Thus there was both systemic and localised inflammation of small and large arteries due to IH. Moreover, there was recovery of lymphocyte proliferation, chemokine expression and NF-κB activation after oxygen fraction normalisation for several days (data not shown). In another study, there was also a reduction in levels of platelet–endothelial cell adhesion molecule-1, a marker of the endothelial cell, at both the heart and aorta level, with a specific gradient and without loss of endothelial cells, suggesting a role of shear forces applied to both the heart and the aorta [65]. Thus, in both studies, there was vascular remodelling resulting from either haemodynamic or inflammatory changes. From these two studies and other previously published studies [30, 64, 66–68], it can be suggested that there are strong interactions in response to CIH between haemodynamic alterations, systemic inflammation and metabolic changes, modulated by the genetic background (fig. 2).

Other noncardiovascular changes related to IH have also been reported, including serotonin-dependent neuronal plasticity in the central control of breathing [69], long-term facilitation of diaphragmatic [70] and genioglossus muscle activity [71], and improved diaphragmatic anoxic tolerance [72]. Sensory long-term facilitation occurs at the level of the carotid body during CIH but not during CH of the same magnitude, suggesting that enzymatic changes at the carotid body level are related to ROS production. This effect is abolished on pre-treatment with a superoxide anion scavenger. Thus, this appears to be ROS-dependent reversible functional plasticity of carotid body sensory activity [73]. There are also brain adaptations and damage that have been described. These include behavioural and brain anatomical and functional changes, also partly specifically related to oxidative stress [74, 75]. IH increases levels of protein oxidation, lipid peroxidation and nucleic acid oxidation in mouse brain cortex, promoting cell apoptosis [76]. It also promotes the reduced nicotinamide adenine dinucleotide phosphate oxidase gene and protein responses in wake-active brain regions, a possible mechanism of sleepiness [77]. In rat hippocampal slice preparations, a reduction in the ability of neuronal tissue to express and sustain long-term potentiation has also been shown. Long-term potentiation correlated with biphasic changes in cyclic AMP-response element-binding protein phosphorylation and programmed cell death [78]. There were also specific proteic changes at this level, with various susceptibilities to IH. Hypoxia-regulated proteins in the cornu ammonis 1 region of the hippocampus included structural proteins, proteins related to apoptosis, primarily chaperone proteins, and proteins involved in cellular metabolic pathways [79]. These functional and structural changes may contribute to the IH-induced changes in cognitive function in rodents, and may also alter neurogenesis [80]. It may explain part of the cognitive dysfunction in apnoeic patients. Cognitive changes occurring in sleep apnoea patients [81–83] may be linked to anatomical and functional changes occurring at the level of the brain, specifically at the pre-frontal cortex [84] and hippocampal levels [85, 86].

IH-related tissular and functional impairment in OSA

Although there is no ideal animal model in OSA, IH has been established as a successful model since it reproduces many of the cognitive, cardiovascular and metabolic alterations seen in OSA. One very complementary approach is to look at sleep apnoea consequences and determine whether or not hypoxia is a major determinant thereof. One way to do so is to determine predictive or explanatory factors using logistic regression analysis. Reversing symptoms and various impairments with CPAP application, the first-line treatment in OSA, does not provide direct evidence of an IH contribution, since it also suppresses sleep fragmentation, changes in plasmatic carbon dioxide content and intrathoracic pressure fluctuations. However, most, if not all, sleep apnoea consequences are related to IH severity. This may be illustrated by the three following different examples in various organs and systems.

Peripheral nerve

Peripheral nerve is very sensitive to changes in nutrient and oxygen content. This has been strongly evidenced previously in diabetes and chronic respiratory failure. Assessment of the peripheral nerve in OSA has been made using the usual clinical and neurophysiological indices [86]. There were multiple peripheral nerve anomalies in OSA patients compared to controls. Median pre-ischaemic sensory and mixed nerve potential amplitudes and sensory conduction velocities were lower in OSA patients than in control subjects despite higher supramaximal stimulation. Interestingly, the most severe OSA patients exhibited a very specific pattern of conduction during ischaemia. During ischaemia, OSA patients with the most severe nocturnal oxygen desaturation manifested resistance to ischaemic conduction failure (RICF), whereas both OSA patients with limited oxygen desaturation and controls did not show RICF. Under CPAP, RICF disappeared in all OSA–RICF patients. Oxygen saturation was the critical factor since CPAP suppressed RICF without any change in BMI [87]. This is presumably an adaptive mechanism to the severity of hypoxia, whereas axonal defects that persisted after treatment may instead represent hypoxic lesions.

Blood pressure

It is now well established and recognised in international guidelines that hypertension can be caused by OSA [88, 89]. However, nonapnoeic respiratory events generating no or very little oxygen desaturation, such as upper airway resistance syndrome, although generating increased nocturnal sympathetic activity, may not be associated with daytime hypertension. Conversely, upper airway resistance syndrome seems to be associated with hypotension in ~20% [90]. This underlines the role of hypoxia in promoting hypertension, as also

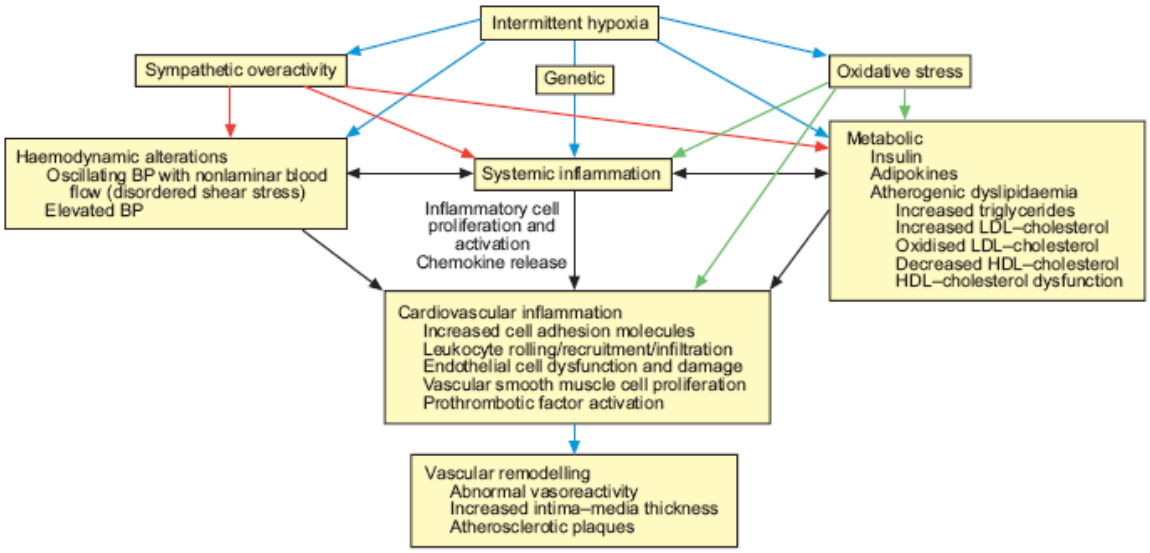

FIGURE 2. Intermittent hypoxia leads to sympathetic overactivity, oxidative stress, systemic inflammation and metabolic changes. There is a very complex interaction between all of these factors in promoting vascular impairment and remodelling during intermittent hypoxia. Red arrows denote the overall impact of sympathetic overactivity, blue arrows denote intermittent hypoxia and green arrows denote oxidative stress. BP: blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

evidenced in animal models [48]. The response to CPAP also indicates that a significant reduction in BP may mainly be seen in the most severe patients [9, 91]. In 2007, this was evidenced in a meta-regression analysis showing a significant increase in the effect size of CPAP on BP with apnoea/hypopnoea index (AHI) and duration of CPAP use but not with EDS [92], although this latter point remains the subject of discussion [93, 94]. Thus the contribution of IH may be critical, even though severe OSA patients also present with marked sleep fragmentation and respiratory efforts.

Atherosclerosis

There have been significant efforts in this field of clinical research in reducing the number of confounding factors and comorbid conditions. In 2005, three reports were published almost simultaneously evidencing that sleep apnoea may lead to early atherosclerosis, as reflected at the carotid level by an increase in intima–media thickness and occurrence of plaques, in the absence of any significant comorbidity [10, 11, 95]. In the present series of patients, severity of oxygen desaturation and BP status were the best predictors of carotid wall hypertrophy. Plaque occurrence in this group of OSA patients without known cardiovascular disease was also strictly related to the amount of oxygen desaturation [11]. Interestingly enough, in 2007, DRAGER *et al.* [96] published data showing that CPAP treatment reverses early signs of atherosclerosis.

Confounding factors

There are clearly confounding factors when investigating the relationship between sleep apnoea, IH and their cardiovascular or metabolic consequences. The most important factor is obesity since ~50% of apnoeic patients present with significant overweight. Moreover, obesity, and specifically visceral obesity, correlates closely with OSA prevalence. Finally, most biological parameters, such as inflammatory and oxidative stress markers and most clinical or subclinical metabolic and cardiovascular changes, can be, at least partly, explained by the presence of concomitant visceral obesity. It should also be mentioned that there is a synergistic effect of obesity and sleep apnoea on both metabolic and cardiovascular morbidity [34, 42, 97–99]. Regarding metabolic changes induced by OSA, CPAP has been suggested as improving insulin sensitivity [100]. However, the effects of CPAP on insulin sensitivity were smaller in obese patients than in nonobese patients, suggesting that, in obese individuals, insulin sensitivity is mainly determined by obesity [100]. There are also conflicting results from type 2 diabetic patients concurrently having OSA. A recent well-designed randomised controlled trial comparing therapeutic (n=20) or placebo CPAP (n=22) for 3 months found no difference in terms of glycaemic control or insulin resistance in these patients [101]. Again, in obese males with metabolic syndrome, COUGHLIN *et al.* [102], in a randomised placebo-controlled blinded crossover trial comparing cardiovascular and metabolic outcomes after 6 weeks of therapeutic or sham CPAP, did not observe any change in glucose, lipids, insulin resistance or the proportion of patients with metabolic syndrome. In summary, these recent data suggest that CPAP is able to reduce systemic inflammation, improve endothelial function and restore insulin sensitivity in lean OSA, but has a less significant impact on metabolic dysfunction in obese OSA.

Another intriguing confounding factor relates to sleep duration. There is now substantial evidence linking sleep duration with obesity and diabetes [103–106]. There are also studies

showing a strong relationship between sleep duration and hypertension risk [107, 108]. The mechanisms relating sleep deprivation and both metabolic and cardiovascular morbid conditions may rely on inflammation [109], and these mechanisms are currently under investigation [110]. However, the exact contribution of sleep duration to sleep apnoea comorbidity remains unknown.

The other stimuli occurring during sleep apnoea (*i.e.* sleep fragmentation, repetitive episodes of hypercapnia and respiratory efforts) may also contribute to chronic consequences. Their acute impact on the autonomic nervous system is well established [111]. Whether or not sleep fragmentation or respiratory efforts contribute to chronic morbidity is still poorly understood. Sleep fragmentation seems to be associated with both inflammation and prothrombotic factors at the plasmatic level [112]. This could have an additive effect to the impact of nocturnal hypoxia. With respect to respiratory efforts, as reflected by the changes in intrathoracic pressure occurring during OSA, it might also offset the normal fall in BP that occurs overnight, as evidenced in a community population [113].

CSA SYNDROME WITH CSR

This is a condition including both central apnoeas and hypopnoeas and CSR that is usually associated with an increase in ventilatory response to CO_2, promoting ventilatory and thus sleep instability [1]. The most prevalent condition leading to CSR with CSA (CSR-CSA) is CHF, being both a marker of severity and a factor of aggravation affecting both morbidity and mortality [114].

Prevalence

There is still much debate regarding the prevalence and incidence of CSR-CSA. The reported prevalences of CSR-CSA in CHF patients widely range 30–100%. The first large study included 450 people with CHF, and reported a 38 and 33% prevalence of OSAS and CSA syndrome, respectively, when using an AHI cut-off of 10 events·h^{-1} during sleep [115]. These differences in various CHF populations may be explained by the size of the sample studied, patient selection, the stability of the disease and the criteria used to score hypopnoeas. More recently, JAVAHERI [116] reported on a prospective study of 100 patients out of 114 consecutive eligible patients with heart failure and a left ventricular ejection fraction (LVEF) of <45%. Of these patients, 49% had sleep apnoea, with a mean AHI of 49 events·h^{-1}, 37% had CSR-CSA and 12% had OSA. In this study, the hallmarks of CSR-CSA were New York Heart Association (NYHA) functional class III, atrial fibrillation, frequent nocturnal ventricular arrhythmias, low arterial carbon dioxide tension (Pa,CO_2) and an LVEF of <20% [116]. Finally, the largest study was published in 2007 and included 700 patients. These patients received β-blockers in 85% of cases. SDB was present in 76% of patients, 40% showing CSA and 36% showing OSA. CSR-CSA patients were more symptomatic (NYHA functional class 2.9±0.5 *versus* 2.57±0.5 with no SDB or 2.57±0.5 with OSA; $p<0.05$) and exhibited a lower LVEF than OSA patients (27.4±6.6 *versus* 29.3±2.6%; $p<0.05$) [117].

One critical and highly discussed question is whether or not the high incidence of CSR-CSA persists despite the newest treatments for heart failure. The relationships between β-blocker treatment and CSR-CSA have, for instance, been investigated in terms of SDB severity [118]. Among 45 patients with CHF (NYHA functional class II/III and LVEF of <50%), patients receiving β-blockers showed a lower AHI and central apnoea index than patients not receiving β-blockers. Multiple regression analysis selected no use of β-blockers as an independent factor for central apnoea index. These results suggest that β-blocker therapy may dose-dependently suppress CSR-CSA in patients with CHF [118], although this is not consistent with the latest large studies in the field showing a persistently high prevalence of CSR-CSA despite a high rate of use of β-blockers [117, 119].

Pathophysiology

Heart failure leads to an increased left ventricular filling pressure. The resulting pulmonary congestion activates lung vagal irritant receptors, thus leading to hyperventilation and hypocapnia. Superimposed arousals cause further abrupt increases in ventilation, and drive the Pa,CO_2 below the threshold for ventilation, triggering central events. CSAs are sustained by recurrent arousals resulting from apnoea-induced hypoxia and the increased effort of breathing during the ventilatory phase because of pulmonary congestion and reduced lung compliance. Although central apnoeas exhibit a different pathophysiology from obstructive apnoeas, and are not associated with the generation of exaggerated negative intrathoracic pressure, both acutely increase sympathetic nervous system activity [120]. However, in CHF patients with CSR-CSA, the chronic increase in muscle sympathetic nervous system activity is related more to the severity of heart failure than to the occurrence of CSR-CSA [121].

Consequences

An increase in sympathetic activity occurs during both heart failure and CSR-CSA. The relative contributions of heart failure and CSR-CSA remain the subject of discussion. Overnight sympathetic activity is significantly greater in CHF patients than in OSA patients. The haemodynamic severity of CHF contributes to the elevation of sympathetic activity in CHF patients to a greater degree than the apnoea-related hypoxaemia [122]. In addition, other important biological markers of CHF have been shown to be affected by CSR. This is the case for atrial natriuretic peptide, B-type natriuretic peptide and ET, underlining the complex relationship that exists between the respective mechanisms of CHF and CSR [123–125].

An association between CSR-CSA and ventricular ectopy has also been suggested, and a cause–effect relationship evidenced [126]. Ventricular premature beat frequency was also found to be higher during periods of CSR-CSA than during periods of regular breathing, either occurring spontaneously or induced through inhalation of CO_2. This increase in ventricular premature beats might contribute to the higher mortality rates reported in heart failure patients with CSR-CSA. Atrial fibrillation (AF) has been shown to occur frequently in CHF patients with CSR-CSA [115, 127]. It has been evidenced that AF represents a predictive factor for CSR-CSA and also a risk factor for decreasing cardiac output when treating these subjects with CPAP [128]. LEUNG *et al.* [129] showed a markedly increased prevalence of AF among patients with idiopathic CSA in the absence of CHF. This high AF prevalence

was not explainable by the presence of hypertension or nocturnal oxygen desaturation, since both factors were more strongly associated with OSA. This, therefore, favours a specific role of CSR-CSA in promoting AF independently of CHF, with the mechanisms remaining to be elucidated.

All of these factors, *i.e.* sympathetic activation and other biological changes, ventricular ectopy and AF, may act, in variable part, as deleterious factors regarding cardiac function and contribute to aggravate heat failure. Thus, there is a rationale for viewing CSR-CSA not only as a marker of the severity of CHF but also as a risk factor for heart failure aggravation. Sympathetic activation, in increasing BP and cardiac frequency, increases myocardial oxygen demand in the face of reduced supply. This chain of events contributes to a pathophysiological vicious cycle [130].

CSR-CSA may, for these reasons and independently of other risk factors, elevate the risk of mortality in CHF two- or three-fold [131, 132]. However, there are not many evidence-based studies so this has been challenged. In a recent study of 78 patients aged 53±9 yrs with an LVEF of 19.9±7.2%, 29% had no apnoea, 28% had OSA and 42% had CSR-CSA at baseline. At 52 months, their overall mortality was 40% and the event rate (death or heart transplantation) was 72%. Mortality rates were similar between the three apnoea groups. Moreover, survivors had a similar prevalence of SDB (71%) to non-survivors (70%), and multivariate analysis identified transplantation but not SDB type or severity as a significant predictor of survival [133]. There are very recent data, however, to support a significant impact of CSR-CSA on mortality [132]. Patients with systolic heart failure presenting with or without CSR-CSA (n=88) were followed for 51 months. Their mean AHI was 34±25 events·h^{-1}, with mainly central apnoeas. The median survival of patients with CSR-CSA was 45 months compared with 90 months for those without CSR-CSA. The other two variables that correlated with poor survival were severity of right ventricular systolic dysfunction and low diastolic BP. Overall, there is evidence for increased morbidity and possibly mortality in CHF patients presenting with CSR-CSA. It is, however, mandatory that this be firmly established in large-scale studies. However, another means of demonstrating such a link is to look at CSR-CSA treatment effects.

Treatment

Short-term CPAP application, in patients with stable CHF, has been shown to reduce left ventricular afterload [134], increase stroke volume in patients with an elevated left ventricular filling pressure [135] and reduce adrenergic tone [136]. Long-term nightly use of CPAP over 1–3 months has been shown to alleviate CSR-CSA [137, 138], increase LVEF [139] and inspiratory muscle strength [140], and reduce mitral regurgitation, atrial natriuretic peptide levels [123] and adrenergic tone [141]. It has also been shown to improve quality of life [139]. Furthermore, there is evidence, in patients with CHF and CSR-CSA, that nightly administration of CPAP can attenuate CSR-CSA, improve cardiac function and alleviate symptoms of heart failure [139]. It has also been suggested that CPAP can reduce the combined mortality–cardiac transplantation rate in those CHF patients with CSR-CSA who comply with therapy [131]. However, the major limitation of these trials was the inclusion of only small samples. Thus, the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial represented the first large-scale randomised controlled trial performed in the field. The first report did not confirm any reduction in mortality, although there was a significant improvement in heart function. This was related to an initial increase in mortality that remained unexplained in the initial report [142]. However, a complementary analysis has recently been performed, published in 2007, demonstrating that the correction of respiratory events observed in part of this CSR-CSA population under CPAP led to a significant improvement in mortality in the CPAP responders [143]. This finding certainly supports a critical role for CSR-CSA in heart failure outcome, although it needs further confirmation in further randomised controlled trials. Moreover, other modes of positive airway pressure, such as assisted servo-ventilation, being apparently more acceptable to heart failure patients and more effective in CSR-CSA and for heart function [114, 144], are currently under investigation in large multicentric controlled trials.

Establishing the role of hypoxia in this context

Although there are very few specific data, several issues can be raised. There is a contribution of nocturnal hypoxia in promoting sympathetic activity in CSR-CSA. The additive effect of CSR-CSA to sympathetic activity in heart failure has been demonstrated previously [145]. Nocturnal hypoxia is likely to play a role in this context. Indeed, the reversibility of this sympathetic activation during CPAP is also of importance [141]. When applying CPAP, although there is a clear mechanical effect in reducing left ventricular transmural pressure, the beneficial effect on sympathetic activity, cardiac function and overall outcome appears exclusively in heart failure patients with CSR-CSA, when compared with patients without CSR-CSA [131]. Finally, it is of major importance to note that only CPAP-treated heart failure patients being corrected for their respiratory events exhibit a significant improvement in outcome [143]. Thus, although hypoxia is usually moderate and less severe in CSR-CSA compared to OSA, it also seems critical in this context.

OBESITY HYPOVENTILATION SYNDROME

OHS includes both obesity and daytime hypercapnia [1], and involves either hypoventilation, apnoeas or both during sleep. Such patients exhibit undiagnosed daytime hypercapnia [146]. They also frequently present with pulmonary hypertension and cor pulmonale [147]. Use of healthcare resources [148], rates of hospitalisation and early mortality are increased in OHS patients [146]. Noninvasive ventilation (NIV) is the first-line therapy in patients with OHS [149]. Patients show good compliance rates with NIV [150], and the therapy is effective in terms of clinical status and blood gas improvements [149–151].

The pathophysiology of OHS results from complex interactions, among which are increased work of breathing related to obesity, normal or diminished ventilatory drive, various associated SDB (*i.e.* obstructive apnoeas and rapid eye movement sleep hypoventilation) and neurohormonal changes, such as leptin resistance [147]. Leptin is produced primarily by white adipose tissue. This hormone elicits appetite suppression and weight loss. Circulating plasma leptin levels reflect the

amount of energy storage in adipose tissue and increase exponentially with increasing fat mass. Plasma leptin levels also respond to short-term energy imbalance, increasing during periods of overfeeding and decreasing with fasting. The hormone activates specific receptors located at several sites throughout the brain but plays a key role at the hypothalamus, in particular, where it alters the expression of several hypothalamic neuropeptides. One of the most important, neuropeptide Y (NPY), is a potent stimulator of food intake and activator of the hypothalamic-pituitary-gonadal axis. Leptin inhibits synthesis of hypothalamic NPY, and downregulation of NPY is associated with appetite suppression, increased sympathetic nervous system outflow and increased energy expenditure. Increased leptin levels activate the thyroid hormone, gonadal and growth hormone axes and suppress the pituitary-adrenal axis. Circulating leptin levels are typically higher than normal in human obesity, indicating and contributing to a leptin-resistant state. This resistant state is partial, since there is a loss of appetite suppression during which the increase in sympathetic activity is maintained [152].

Apart from its anti-obesity effects, leptin exerts important physiological effects on the control of respiration [153]. Mice lacking the gene responsible for production of leptin (*ob/ob* mice) demonstrate hypoventilation in addition to marked obesity. Furthermore, these animals exhibit an impaired hypercapnic ventilatory response (HCVR) during both wakefulness and sleep [154]. During rapid eye movement sleep, the HCVR is absent in *ob/ob* mice. This HCVR impairment in *ob/ob* relative to wild-type mice cannot be attributed to the mechanical effects of obesity since it precedes the development of the latter. Furthermore, leptin replacement studies in *ob/ob* mice have shown improvements in baseline minute ventilation and HCVR during wakefulness and sleep under experimental conditions that prevented a concomitant weight change in the animal [152, 154]. Most patients with OHS suffer from OSA, and, in many (but not all) cases, treatment of OSA with nasal CPAP restores daytime eucapnia. In some patients, OHS cannot be explained on the basis of OSA, and daytime hypercapnia appears to result from inadequate physiological compensation for the development of obesity alone. Thus leptin may play a central role in OHS pathophysiology with respect to CO_2 response [147, 155–159] and also OHS-associated morbidity. Leptin may be a modulator of respiratory drive in both obese [157] and OHS patients [158]. NIV, the first-line treatment in OHS, results in improvement in daytime and night-time blood gas levels, CO_2 ventilatory response and serum leptin levels [147, 155, 158]. There is also an improvement in vigilance, linked to the CO_2 response changes under NIV [160]. Both vigilance and cardiovascular morbidity may be dependent upon leptin, as well as on other inflammatory cytokines (see later).

Indeed, adipose tissue is able to express numerous other adipokines that are involved in energy homeostasis, as well as in vascular and endothelial physiology (TNF-α, interleukin-6, complement factors, angiotensinogen, resistin, adipocyte differentiation factor and nitric oxide; fig. 3). These adipokines are thought to be the mediators of endothelial injury and atherosclerosis. Although most adipokines promote insulin resistance and endothelial dysfunction, adiponectin protects against these disorders. Adiponectin levels are decreased in

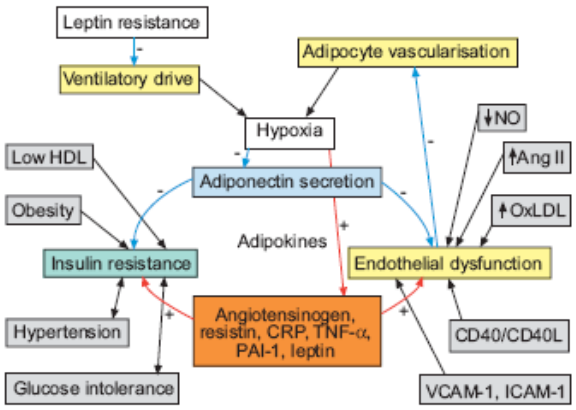

FIGURE 3. Effect of hypoxia on adipokines and their interactions with insulin metabolism and endothelial function. The main factors involved are leptin, angiotensinogen (Ang), resistin, C-reactive protein (CRP), tumour necrosis factor (TNF)-α and plasminogen activator inhibitor-1 (PAI-1). Leptin promotes (red arrows) insulin resistance and endothelial dysfunction, whereas adiponectin is protective (blue arrows). Obesity, a state of leptin resistance and endothelial dysfunction, also exhibits hypoxia, which is known to activate (red arrow) promoting adipokines and inhibit (blue arrows) adiponectin production. In obesity hypoventilation syndrome, obesity and night-time hypoxia and hypercapnia might act synergistically in producing inflammation at the systemic and vascular level, and in promoting metabolic and cardiovascular dysfunction. HDL: high-density lipoprotein; OxLDL: oxidised low-density lipoprotein; CD40L: CD40 ligand; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; +: activation/promotion; -: inhibition/protection; ↓: decrease; ↑: increase. Modified from [161] with permission from the publisher.

obesity [162] and inversely correlate with cardiovascular morbidity. With both systemic hypoxia and tissue ischaemia, adipokine levels are altered, with downregulation of adiponectin expression [163] and upregulation of plasminogen activator inhibitor-1 [164] and leptin through hypoxia-inducible factor 1α activation.

Thus, in obesity hypoventilation, a condition in which resistance to leptin, obesity and, usually, severe nocturnal hypoxia occur, there is possible insulin resistance and endothelial dysfunction resulting from systemic and adipose tissue hypoxia. The role of nocturnal hypoxia resulting from nocturnal hypoventilation and recurrent apnoeas, when present, may be critical. It might explain, at least partly, the excess of morbidity and mortality occurring in OHS.

CONCLUSIONS

The hypoxic insult occurring during sleep-disordered breathing varies from one condition to another. However, there are common cardiovascular and metabolic morbidities in these various conditions. There are major differences with continuous hypoxia, suggesting specific pathways originating from the occurrence of oxidative stress and inflammatory cascade activation. Hypoxia seems to be the major factor in morbidity. Despite the great scientific advances of the past years in this field, the cellular and molecular mechanisms involved during intermittent hypoxia remain to be fully elucidated.

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SLEEP AND NON INVASIVE VENTILATION: MONITORING OF THE PATIENT UNDER HOME VENTILATION

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Sleep and non invasive ventilation: Monitoring of the patient under home ventilation

Running title: Sleep and non invasive ventilation

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Introduction

Sleep is a unique physiological state associated with deep changes in upper airway resistances, respiratory control and lung mechanics. In patients with chronic respiratory diseases, this specific situation induces different categories of consequences. First, as minute ventilation decreases particularly in REM sleep, sleep-related hypoventilation is the first sign of respiratory failure systemically preceding the development of daytime chronic hypercapnic failure. Second, as abnormal respiratory events occur specifically during sleep, non invasive ventilation (NIV) settings which are appropriate for ventilating awake patients may no work appropriately during the night. On the other hand, sleep per se increases non intentional leaks, patient-ventilator asynchrony and periodic breathing or glottic closures, thus justifying a specific monitoring of NIV efficacy during the night.

In this article, we will successively review the overall mechanisms for ventilatory changes occurring during sleep, the ability of NIV to suppress respiratory events during night and improve sleep quality and the tools that can be proposed for monitoring NIV efficacy during sleep. We will cover these topics for patients suffering from chronic respiratory failure, in stable state and home-ventilated by NIV.

During sleep changes in ventilation

There are several mechanisms explaining that, even in normal subjects, ventilation is slightly reduced during sleep. Modifications occur in muscle activity, respiratory drive and lung mechanics. Depending upon the underlying respiratory disease, these different mechanisms isolated or in association may aggravate or reveal respiratory failure during sleep.

1. *Reduction of activity of respiratory muscles:*

During sleep, the loss of the wakefulness stimulus is associated with a decreased activity of the medullary respiratory neurons [1] leading to a reduction of respiratory muscles tonic activity. There is a concomitant fall in ventilation [2]. In normal individuals, $PaCO_2$ rises by 2-8 mm Hg, PaO_2 decreases by 3-10 mmHg and oxygen saturation drops by less than 2% [3-5]. These changes occur despite the reduction in oxygen consumption and CO_2 production during sleep [4]. The decrease in ventilation occurs during all stages of sleep and worsens during REM, particularly during phasic REM sleep [1, 6, 7]. Phasic REM sleep is associated with a dramatic reduction in intercostal muscle phasic and tonic activity and a reduction in diaphragm tonic activity whereas diaphragmatic phasic inspiratory activity is preserved [8, 9]. During this period, breathing is more irregular, rapid and shallow [10] (figure 1).

Diaphragmatic functioning is absolutely critical in REM sleep, because the other respiratory muscles cannot maintain alone a normal alveolar ventilation. Subjects with diaphragmatic weakness as in neuromuscular disorders or breathing with a diaphragm in unfavourable mechanic conditions as in morbid obesity or in COPD with hyperinflated lungs are highly prone to hypoventilate during REM sleep.

2. *Changes in ventilatory control:*

Ventilatory control is physiologically altered during sleep, resulting in a diminished responsiveness to chemical, mechanical and cortical inputs. During REM sleep [8, 9], there is virtually no metabolic control in ventilation. The respiratory muscles also exhibit a diminished response to ventilatory drive during sleep [8]. This reduction in ventilatory responses is particularly deleterious in patients who already have an abnormal chemosensitivity during wakefulness such as patients with myotonic dystrophy or obesity hypoventilation syndrome (OHS). In OHS, daytime ventilatory responses to CO2 are highly related to percentage of REM sleep spent in hypoventilation [11].

3. *Changes in Functional Residual Capacity (FRC):*

In normal subjects, FRC decreases during REM sleep as a result of supine position and atonia of the intercostals muscles [12-14]. This reduction in FRC is particularly marked in morbidly obese subjects and in patients using their accessory muscles to compensate for either a diaphragm weakness or a diaphragm working in an unfavourable geometrical position.

4. *Change in V/Q mismatch:*

Breathing irregularity and rapid shallow breathing during REM sleep [15] also increases the physiologic dead space in COPD patients and thus impairs gas exchange [14, 16-18].

5. Associated sleep-disordered breathing:

The upper airway resistance is increased, secondary to a reduction in tonic and phasic activity of the upper airway (UA) muscles. These UA muscles are both responsible for preventing pharyngeal collapse during the contraction of the diaphragm (phasic activity) and for maintaining the UA tone during sleep (tonic activity) [1, 6, 7]. Obstructive sleep apnea is a common condition and thus its' association with another frequent disease such as COPD is expected. However, sleep apnea is not more prevalent in COPD than in the general population. Conversely, prevalence of sleep apnea seems to be increased in Kyphoscoliosis and in neuromuscular disorders. Finally, severe sleep apnea is almost always present in OHS and is a key factor in the pathophysiology of chronic respiratory failure in these patients.

NIV can suppress or reduce sleep-related hypoventilation, episodes of upper airway collapse and improve sleep quality

To limit its impact on quality of life and to compensate for the physiological decreases in nocturnal ventilation which may be critical in chronic respiratory failure, non-invasive ventilation is mainly applied during night. Efficacy of NIV is mainly assessed by daytime outcome measures such as blood gases, health-related quality of life scores and number of hospitalizations. Surprisingly, there is a limited number

of studies addressing specifically the question of NIV efficacy during the night in terms or improving nocturnal hypoventilation and sleep quality.

In restrictive chronic respiratory failure patients, Schonhofer et al. [19] showed that nocturnal hypoventilation improved and both slow wave sleep and REM sleep increased after one year of home NIV. Interestingly, after six months of treatment, a one night withdrawal of NIV was associated with a significant but lesser degree of sleep hypoventilation compared to baseline. This suggests that long term NIV improved respiratory drive and limited immediate recurrence of severe REM sleep hypoventilation. A recent meta-analysis [20], in neuromuscular and chest wall disorders, found only eight trials (144 participants) eligible. In these studies, alleviation of sleep hypoventilation or correction of sleep-disordered breathing was measured only by nocturnal pulse-oximetry. SaO_2 is however a surrogate marker which cannot clearly discriminate between apneas or hypopneas and episodes of REM sleep hypoventilation. Using NIV, the average increase in mean nocturnal SaO_2 was 5.45% (95% CI 1.47 to 9.44) [20]. In a similar population of neuromuscular and chest wall disorders, Ward et al. [21] noted that patients with nocturnal hypoventilation (nocturnal $PtcCO_2$ > 6.5 Kpa) but with normal daytime $PaCO_2$ at baseline are likely to deteriorate with the development of daytime hypercapnia and/or progressive symptoms within 2 years. Early introduction of nocturnal NIV before occurrence of daytime hypercapnia reduced levels of nocturnal $PtcCO_2$.

O'Donoghue et al. [22] documented sleep hypoventilation in over 43% of a group of hypercapnic COPD. Sleep hypoventilation was associated with significant increases in night-to-morning $PaCO_2$, and proposed as contributing to long-term elevations in $PaCO_2$. Accordingly, in a randomized controlled trial, Meecham-Jones

et al. [23] showed using transcutaneous CO_2 measurements ($PtcCO_2$) that degree of improvement in daytime $PaCO_2$ was correlated with the improvement in mean overnight $PtcCO_2$ by using NIV. A meta-analysis addressing the issue of efficacy of NIV in COPD patients with chronic respiratory failure, suggested a detrimental (although non significant effect) of the device in terms of sleep efficiency [24]. However, the small sample size precludes a definitive statement regarding the clinical implications of such a result. In another systematic review of NIV in COPD, sleep-related difficulties were reported in 4 of the 15 included studies [25].

In OHS patients, NIV treats associated sleep apnea syndrome, improves ventilatory responses and sleep quality and suppresses REM sleep hypoventilation [11]. Conversely, in a percentage of extremely obese subjects, CPAP alone corrected upper airway collapse but severe oxygen desaturation persisted and NIV was required [26] in this situation to treat sleep-related hypoventilation.

Thus, in different diseases associated with chronic respiratory failure, NIV is capable of counteracting the different mechanisms associated with sleep-related hypoventilation. Even though robust data are lacking, it is generally accepted that sleep quality is improved. However, in the real life of home ventilated patients, the situation appears more problematic and sleep hypoventilation or sleep fragmentation is far from being perfectly corrected [27-29].

Potential undesirable respiratory events and sleep fragmentation induced by NIV

Non intentional leaks, around the mask or through the mouth are common during sleep [27-30] and remain one of the main events which impair effectiveness of ventilatory support. Leaks can either alter functioning of the NIV apparatus (i.e

triggering, pressurisation delay) [31, 32] or directly decrease level of ventilation [33] inducing recurrent episodes of hypoventilation and oxygen desaturations. Gonzalez et al. demonstrated a significant relationship between air leaks and persistent hypercapnia [34]. Moreover, by increasing microarousals related to leaks, sleep efficiency can be significantly altered [27, 29, 30].

Although non intentional leaks may lead to inappropriate ventilatory support, other patterns of sleep-disordered breathing (i.e periodic breathing, closure of the glottis and patient/ventilator asynchrony) may be induced by the ventilatory support itself [35-37] independently of leaks.

NIV has the potential to induce *periodic breathing during sleep*. In a recent polysomnography study, 40% of obese using NIV showed a high index of periodic breathing, mostly occurring in light sleep and associated with severe nocturnal hypoxemia [36]. A $PaCO_2$ apneic threshold exists during sleep at 1.5–5.8 Torr below eupneic $PaCO_2$ [38]. If NIV settings lead to hyperventilation, bursts of central apneas or hypopneas can occur particularly during transitions between sleep onset and wakefulness. The susceptibility to periodic breathing varies considerably among subjects; its occurrence under NIV is thus difficult to predict and needs to be specifically monitored (Figure 2). High levels of pressure support are more frequently associated with this abnormality.

Hyperventilation associated with NIV use can also lead to *glottis narrowing and closures* [37, 39]. Glottis narrowing seems more related to a controlled mode (both in volumetric and barometric support). In spontaneous cycles, initiation of inspiration by the patient may allow an activation of the inspiratory glottis abductors inducing vocal cord abduction [40]. High levels of ventilation and hypocapnia are more frequently associated with these adverse events. During NIV, ventilatory

responses to hypoxia are highly dependent on CO_2 levels and can be definitely abolished by severe hypocapnia ($PaCO_2$<27mmHg) [41]. This means that glottis closures can be associated with severe desaturations before reopening of the glottis and resumption of effective ventilation.

Profound modifications in the recruitment of the respiratory muscles may occur during the various stages of sleep potentially leading to inappropriate triggering. *Patient–ventilator dyssynchrony* may be a cause of suboptimal ventilation and sleep fragmentation [42] (Figure 3). In a systematic polysomnographic study in OHS, 55% of the patients exhibited desynchronization occurring mostly in slow-wave sleep and REM sleep and associated with arousals [36]. Auto-triggering was more sporadic and usually limited to one or two breaths [36]. Similarly, Fanfulla et al. [43], including 48 patients enrolled in a long term home NIV program found a mean of 48±37 ineffective efforts per hour during sleep compared to none during wakefulness.

How should one monitor NIV during sleep?

During sleep, specific respiratory events result both from physiological changes and use of NIV. An appropriate strategy for monitoring these respiratory events should be proposed. Monitoring tools can be limited to the recognition of consequences such as oxygen desaturation or increases in $PtcCO_2$. More complex and complete evaluations can be done by polygraphic or polysomnographic recordings. These assessments provide more insights as to the mechanisms involved but are more costly and less available. Finally, manufacturers have developed softwares using signals included in NIV devices that provide interesting

information. The following chapter aims to describe the different techniques and their respective contribution for assessing home ventilated patients during sleep.

Nocturnal pulse-oximetry

The amount of nocturnal oxygen desaturation is considered as one of the major determinants of adverse neurocognitive and cardiovascular consequences occurring during chronic respiratory failure and sleep apnea syndrome [44, 45]. It is obviously an important item to monitor in home ventilated patients. It has been suggested that the morphological pattern of SaO_2 desaturation could be specific of the different mechanisms explaining their occurrence [46]. When SaO_2 measurements are performed in spontaneous breathing, repetitive episodes of brief desaturation/ reoxygenation sequences with simultaneous acceleration/ deceleration of heart frequency (figure 4-A) are generally accepted as being associated with obstructive or central apneas. However, overnight nocturnal pulse-oximetry cannot distinguish central vs. obstructive events [47]. In patients using NIV at night, repetitive oscillations in SaO_2 should be interpreted more cautiously as they may reflect central events (Figure 2), residual obstructive events (Figure 5), patient-ventilator asynchrony (Figure 3) or repetitive leaks interrupted by microarousals. Another characteristic pattern of SaO_2 recordings in spontaneous breathing is a prolonged desaturation (10 to 30 minutes) with concurrent acceleration of heart frequency, occurring approximately every 90-120 minutes during the night. This is a typical of pattern of REM sleep hypoventilation (figure 4-B). In ventilated patients however, the same aspect can result not only from persistant REM sleep hypoventilation (Figure 6), but also from prolonged leaks or insufficient pressure support irrespective of sleep stage.

In summary, the occurrence of desaturations is highly sensitive to detect breathing abnormalities in NIV users but the different patterns are difficult to interpret. When abnormalities are present, a polygraphy or polysomnography is required for understanding the relevant mechanisms and adjusting ventilator settings and/or interfaces.

Trancutaneous CO_2 tension monitoring:

Assessing $PaCO_2$ overnight is essential for evaluating efficacy of NIV during sleep. The simplest approach is to measure $PaCO_2$ by arterial puncture at the end of the night to document night-to-morning increases in $PaCO_2$ [22]. However, blood is most often sampled after arousal and thus after a short period of appropriate ventilation. In this condition a normal morning $PaCO_2$ actually does not reflect the abnormal time course of $PaCO_2$ during the night. Repeated sampling of arterial blood from a catheter in the radial artery remains the "gold standard" for estimating PaCO2 changes but is not conceivable for routine assessment in stable state patients. $ETCO_2$ is unreliable in patients with chronic respiratory failure, particularly in COPD, and is technically difficult to measure with the continuous flow related to bi-level pressure support. Continuous transcutaneous recordings ($PtcCO_2$) (figure 7) show good agreement with arterial measurements [48-50] even if high levels of $PaCO_2$ may increase $PaCO_2$ / $PtcCO_2$ bias [48]. Importantly, further studies [48-53] have reported that the good agreement between $PtcCO_2$ and $PaCO_2$ is preserved when patients are treated by CPAP or pressure support. A limitation of the technique is the requirement for periodic calibration and changes of membrane in order to ensuring sufficient precision of transcutaneous measurements. Despite these precautions, $PtcCO_2$ sensor drift has been reported during overnight recordings [22].

Compensation of this drift has been proposed by using linear interpolation, but actually requires two arterial measures of $PaCO_2$ (at the beginning and at the end of $PtcCO_2$ recording) [22]. One study however showed that, in 28 subjects under NIV, $PtcCO_2$ recordings could be performed continuously for 8 hours at a probe temperature of 43°C, without any local discomfort or significant signal drift [51]. More recent devices, combining $PtcCO_2$ and SpO_2 earlobe sensors, have been validated in acute care and chronic clinical settings, are designed for continuous recording over 8 hour periods without requiring recalibration, and are feasible for routine use [53-55]. All $PtcCO_2$ sensors have a lag-time (approximately 2 min) which precludes monitoring of rapid changes of $PaCO_2$ such as those which could be associated with recurrent apneas, hypopneas, or brief leaks [49].

In summary, nocturnal $PtcCO_2$ should be considered as a reliable non-invasive tool to monitor nocturnal $PaCO_2$ for patients treated with NIV on a long term basis. Limitations of the technique are the cost of the devices, the increase in bias between arterial and transcutaneous values at high $PaCO_2$ values [48], and the occasional occurrence of unexplained errand values. Recent devices are however easy to use with user-friendly softwares, and can be connected to polysomnography software. Finally, nocturnal $PtcCO_2$ reveals the occurrence of episodes hypoventilation but provides no information as to their cause (inappropriate settings, leaks…).

Data available from NIV machines:

The majority of industrial companies have designed NIV devices including flow and pressure sensors and storing raw data of these parameters on a long term

basis. Specific softwares allow home care providers or clinicians to download these data on a personal computer.

Downloaded data can be separated in three categories. The first is a *"synthesis report"* (i.e a trend of each parameter recorded during a given period) (figure 8). Depending on the manufacturers and the machines (Table1), compliance, settings, mean level of leaks, tidal volume, respiratory frequency, minute ventilation could be provided. The second category is a *"detailed data analysis"*. Raw data of a given parameter could be analysed cycle by cycle (figure 9). The third category provides *"polygraphic data analysis"*. In this situation by adding an external module connected to the machine (Reslink, RESMED™ or Stardust, RESPIRONICS™) physiological parameters such as oxygen saturation, heart rate and respiratory effort can be recorded and displayed in addition to the signals already stored by the device (figure 10).

There are large discrepancies in parameters provided by the different softwares. This reflects the fact that relevant parameters for monitoring NIV have not been yet clearly defined by clinicians and that recommendations in this field should be proposed by scientific societies. Second, the validity of several parameters estimated by the NIV devices (minute ventilation, tidal volume, apnea-hyponea index) is questionable, and must be validated by independent clinical and/or bench test studies. As for pulse-oximetry, these data should be used as screening tools for identifying, in a large population of home ventilated patients, those requiring further investigations.

Polygraphy and Polysomnography

As illustrated by figures 1 to 7, polysomnography is the most integrative assessment of NIV during sleep, allowing in most circumstances a precise description of the different mechanisms involved in desaturations, episodes of hypoventilation, or disrupted sleep structure. Identifying the mechanisms involved in these respiratory events is crucial for adapting NIV settings or interfaces. Thus, documenting residual obstructive events in an obese patient will lead to an increase in positive expiratory pressure. Persistent hypoventilation during REM sleep may warrant either increasing level of pressure support or implementing a volume-targeting mode which has been shown to decrease more efficiently $PtcCO_2$ during sleep [56]. Periodic breathing and glottis closure as frequently associated with hypocapnia and hyperventilation might be diminished by reducing the levels of ventilation and increasing inspiratory trigger sensitivity then favouring spontaneous cycles. Finally, patients-ventilator asynchrony may require adjusting inspiratory and expiratory triggers and reducing non-intentional leaks when present. Leaks increase the probability of most abnormal respiratory events under NIV, thus reducing the efficacy of ventilatory support. It must be kept in mind that relationships between these events and quality of sleep are extremely complex. For example, volume targeting may improve ventilation but seems to be associated with increased sleep fragmentation (Janssens, Respiratory Med 2008, In press). Moreover, increasing ventilation to correct residual REM sleep hypoventilation can favour the emergence of periodic breathing particularly in Non REM sleep.

An important contribution of polysomnography is to document sleep fragmentation and to relate microarousals to their cause. Microarousals related to leaks should be managed by improving the interface or using a mouth strip [28, 29, 57]. Conversely, microarousals related to other above-mentioned respiratory events

require adapting NIV settings. Guo et al. [36] reported that patient ventilator asynchrony is usually not associated with significant changes in PtcCO2 or oxygen saturation (SpO2) and thus a polysomnography was necessary to identify these respiratory events and improve NIV settings.

For all these reasons, periodic polysomnography is recommended by experts in the follow-up of home ventilated patients [57, 58]. However, in the field of sleep medicine, interpreting polysomnography under NIV is probably one of the most difficult tasks. Resulting flow and pressure signals are influenced not only by the patients' ventilation but also by the technical specifications of the device and the ventilatory mode. Specific recommendations regarding the channels that need to be recorded and consensus criteria for scoring are highly desirable.

Polygraphy is easier to perform in an outpatient setting, and clearly useful for identifying events such as patient-ventilator asynchrony, periodic breathing, auto-triggering, and their impact on SpO_2. Obviously, impact on sleep structure of these events will not be detected, although integration of signs of "autonomic arousals" in portable polygraphy recordings may be useful in a near future.

Conclusions

Overall sleep and breathing during NIV are far from ideal. Screening studies using ventilator softwares and/or nocturnal pulse-oximetry are useful for identifying patients with significant problems, but these tools may not suffice. Polysomnography (or polygraphy) under NIV, interpreted by trained specialists, may allow improving ventilator settings, respiration during sleep and hopefully sleep quality. Future studies are needed to establish whether recognition and correction of these

abnormalities during sleep positively impact either on long term efficacy of NIV, compliance or quality of life.

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Legends

Figure 1: Irregular, rapid and shallow breathing during phasic REM sleep

Decrease in ventilation during phasic REM sleep episodes: a sustained reduction in flow and thoracic and abdominal movements occurs concurrently with rapid eye movements. This occurs to various degrees in normal subjects and is aggravated or revealing in patients with respiratory failure.

Tho: Thoracic movements; Abd: Abdominal movements; Flo: Flow signal; PTT: Pulse transit time; BP: arterial blood pressure; EM: eye movements.

Figure 2: 5 minutes epoch of polysomnography with central events induced by NIV

SpO_2 oscillations related to central events occurring in stage 1 sleep. Note the decrease in respiratory effort during events as identified by pulse transit time.

Tho: Thoracic movements; Abd: Abdominal movements; Flo: Flow signal measured using a pneumotachograph; PTT: Pulse transit time; Pre: Pressure.

Figure 3: 5 minutes epoch of polysomnography with patient-ventilator asynchrony

See ineffective efforts (arrows) and SaO2 oscillations related to patient-ventilator asynchrony.

Tho: Thoracic movements; Abd: Abdominal movements; Flo: Flow signal measured using a pneumotachograph; PTT: Pulse transit time; Pre: Pressure.

Figure 4: Four hours recordings of SaO2 in spontaneous breathing

A- Repetitive episodes of brief desaturation/ reoxygenation sequences with simultaneous acceleration/ deceleration of heart frequency generally accepted as associated with obstructive or central apneas.

B- Persistent desaturation (10 to 30 minutes) with concurrent acceleration of the heart frequency and occurring approximately every 90-120 minutes during the night. This corresponds to a typical of pattern of REM sleep hypoventilation

Figure 5: 5 minutes epoch of polysomnography with residual obstructive events

Tho: Thoracic movements, Abd: Abdominal movements, Flo: Flow signal measured using a pneumotachograph, PTT: Pulse transit time, Pre: Pressure.

Figure 6: 5 minutes epoch of polysomnography in a NIV user with a transition from persistent hypoventilation during REM sleep and awakening

See flow reduction during REM sleep with sustained desaturation.

Tho: Thoracic movements; Abd: Abdominal movements; Flo: Flow signal measured using a pneumotachograph; PTT: Pulse transit time; Pre: Pressure.

Figure 7: During night evolution of PtcCO2

Note the systematic increase in PtcCO2 concurrently with REM sleep. Arrows depict significant increase in arterial carbon dioxide tension night-to-morning (adapted from O'Donoghue Eur Respir J 2003).

Figure 8: Synthesis data analysis downloaded from NIV device softwares

Example of data downloaded from GK 425 Tyco Healthcare™ using silverlining 3.0 software. Compliance data but also mean respiratory rate and percentage of spontaneous cycles are available.

Figure 9: Detailed data analysis downloaded from NIV device softwares (5 min epoch)

Pressure, flow, leaks monitored respiratory cycle by respiratory cycle (download from Ventimotion Weinmann™ using ventisupport 1.01 software).

Owing to the increase of leaks, pressure support move to back up frequency (spontaneous cycles are replaced by controlled cycles (widening of inspiratory pressure delay).

Figure 10: polygraphic data by using the NIV device associated with an external module (2 hours epoch)

Combination of data usually provided by the NIV machine and physiological data (SpO2 and heart rate); download from VPAP 3 ST RESMED™ using Rescan 5.3 software). Note oxygen desaturation explained by a huge increase in leaks levels.

Table 1: Specifications of software's from NIV devices allowing to download data

Figure 1

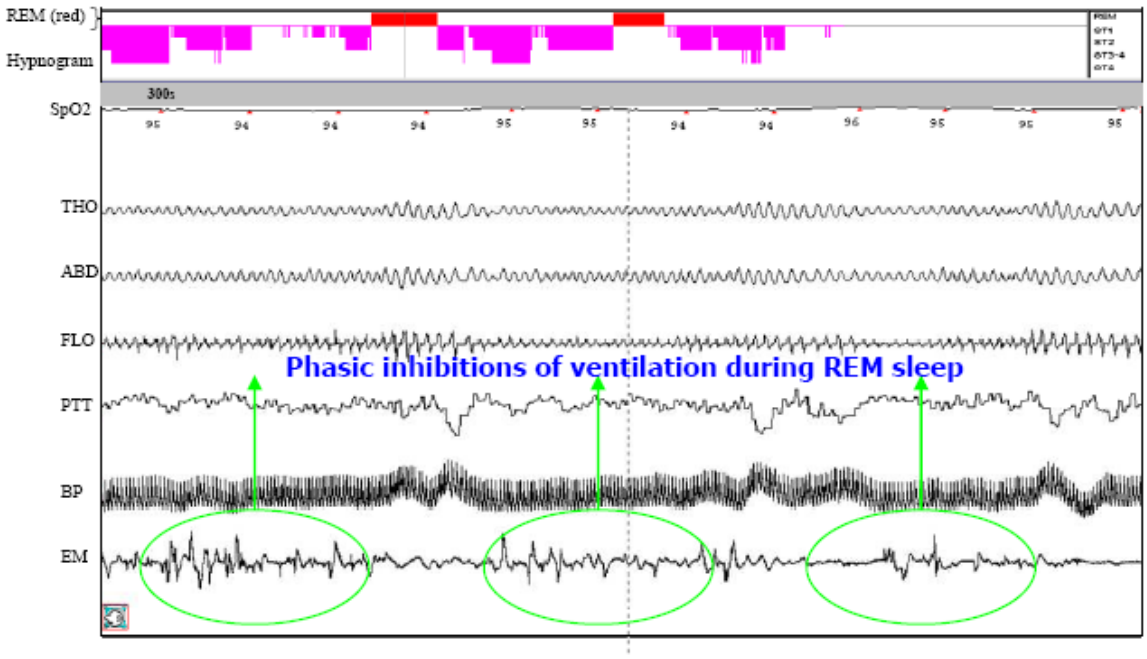

REM (red)
Hypnogram
300s
SpO2
95
94
94
94
95
95
94
94
96
95
95
95
THO
ABD
FLO
Phasic inhibitions of ventilation during REM sleep
PTT
BP
EM

Figure 2

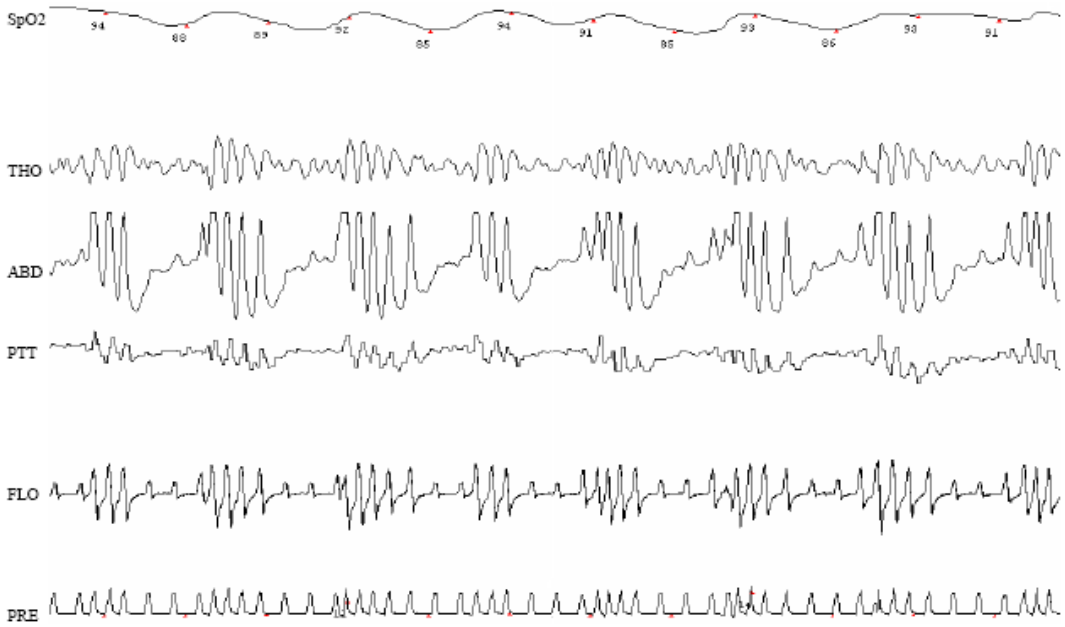


Figure 3

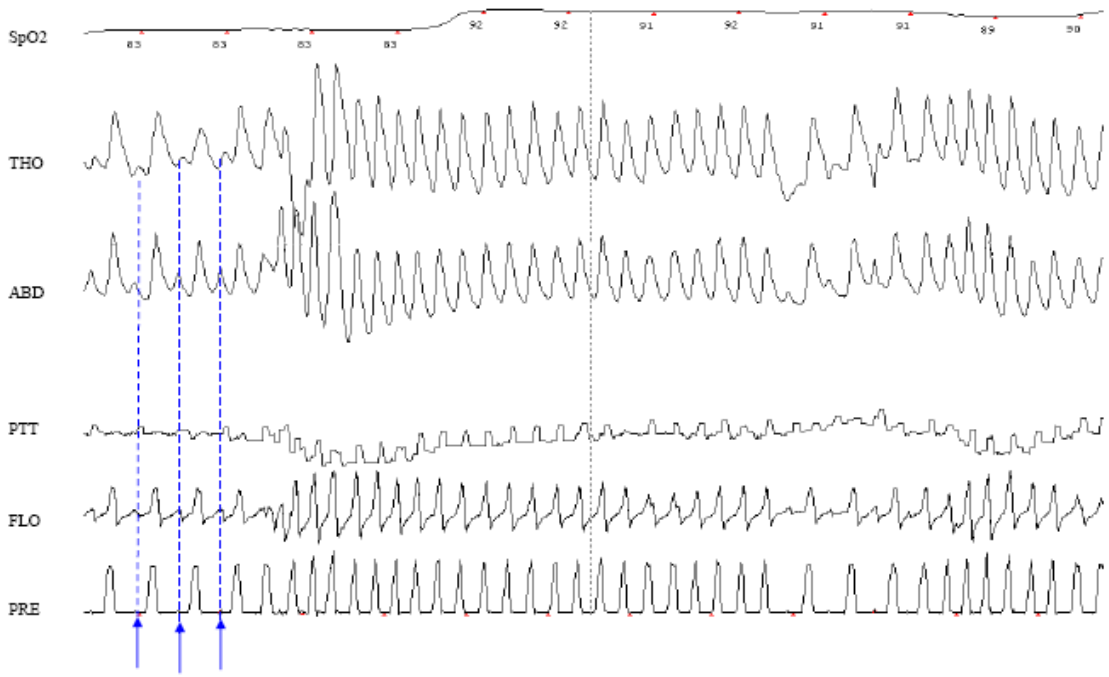
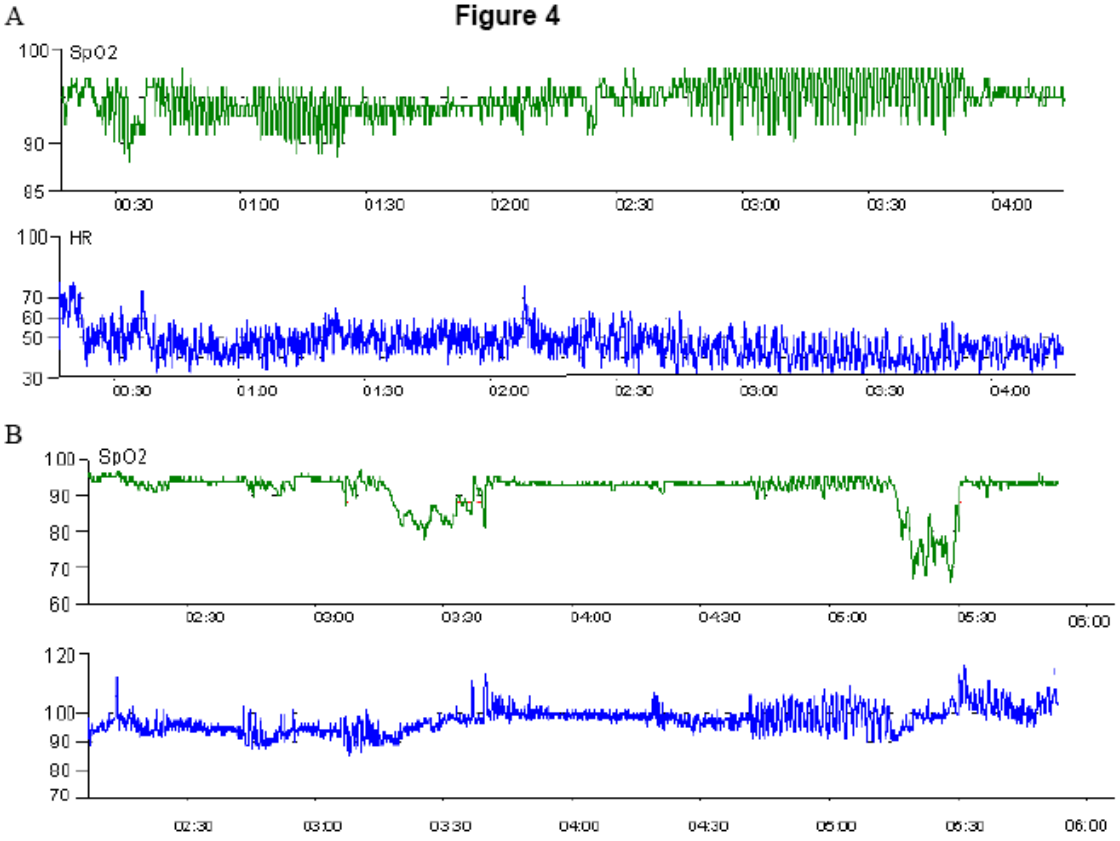


Figure 4


A
100
SpO2
90
85
00:30
01:00
01:30
02:00
02:30
03:00
03:30
04:00
100
HR
70
60
50
30
00:30
01:00
01:30
02:00
02:30
03:00
03:30
04:00
B
100
SpO2
90
80
70
60
02:30
03:00
03:30
04:00
04:30
05:00
05:30
05:00
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04:00
04:30
05:00
05:30
06:00

Figure 5

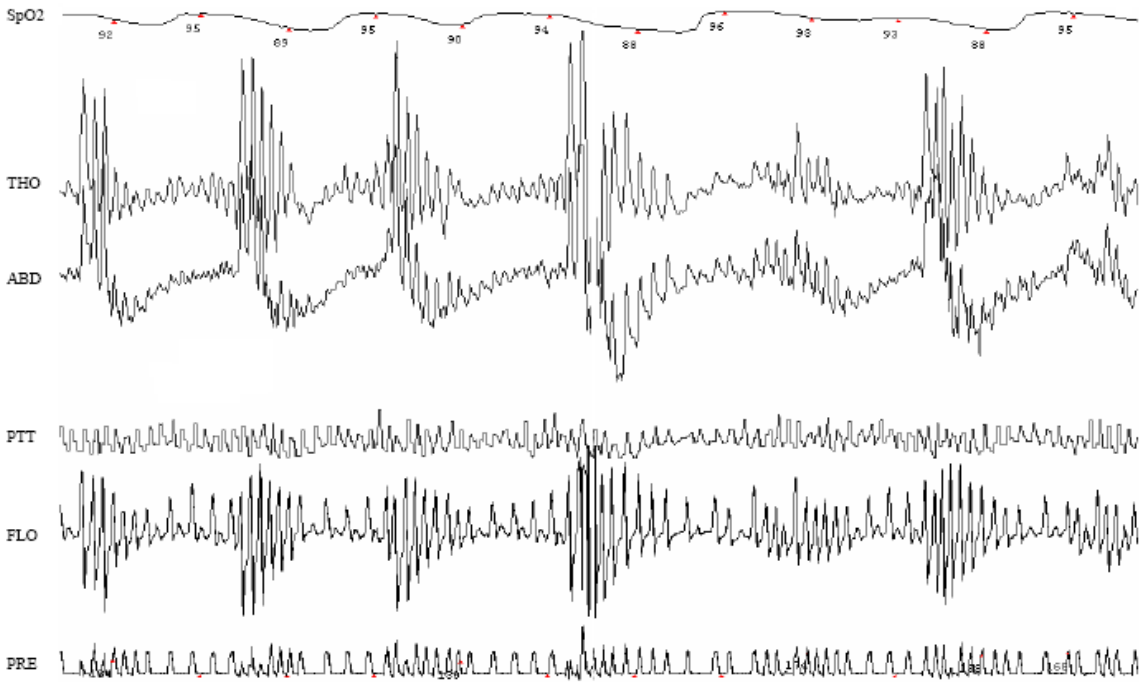


Figure 6

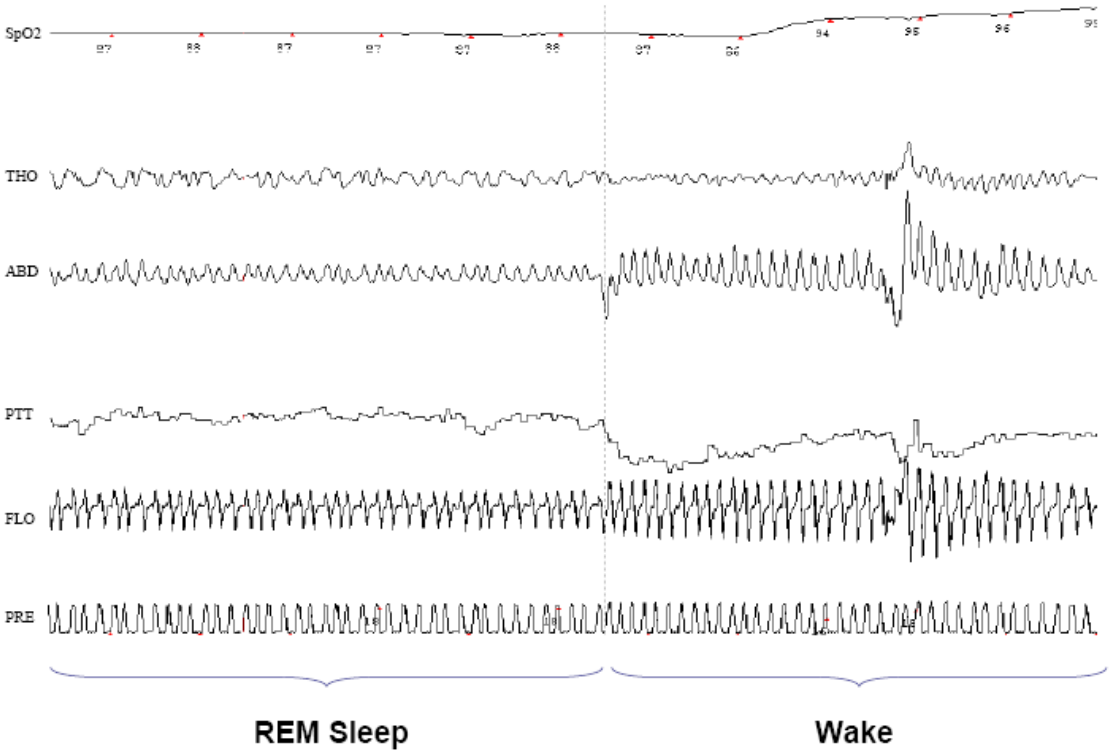


Figure 7

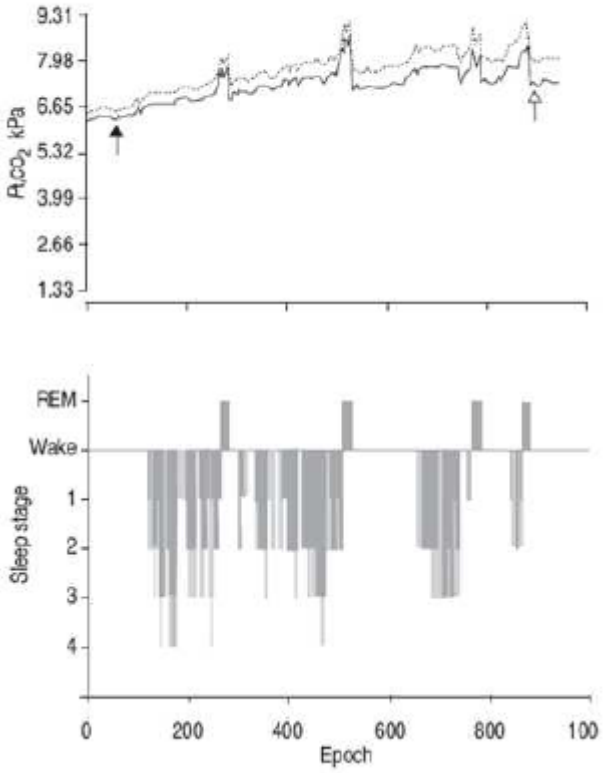

9.31
7.98
6.65
5.32
3.99
2.66
1.33
$P_{A}CO_2$, kPa
REM
Wake
1
2
3
4
Sleep stage
0
200
400
600
800
100
Epoch

Figure 8

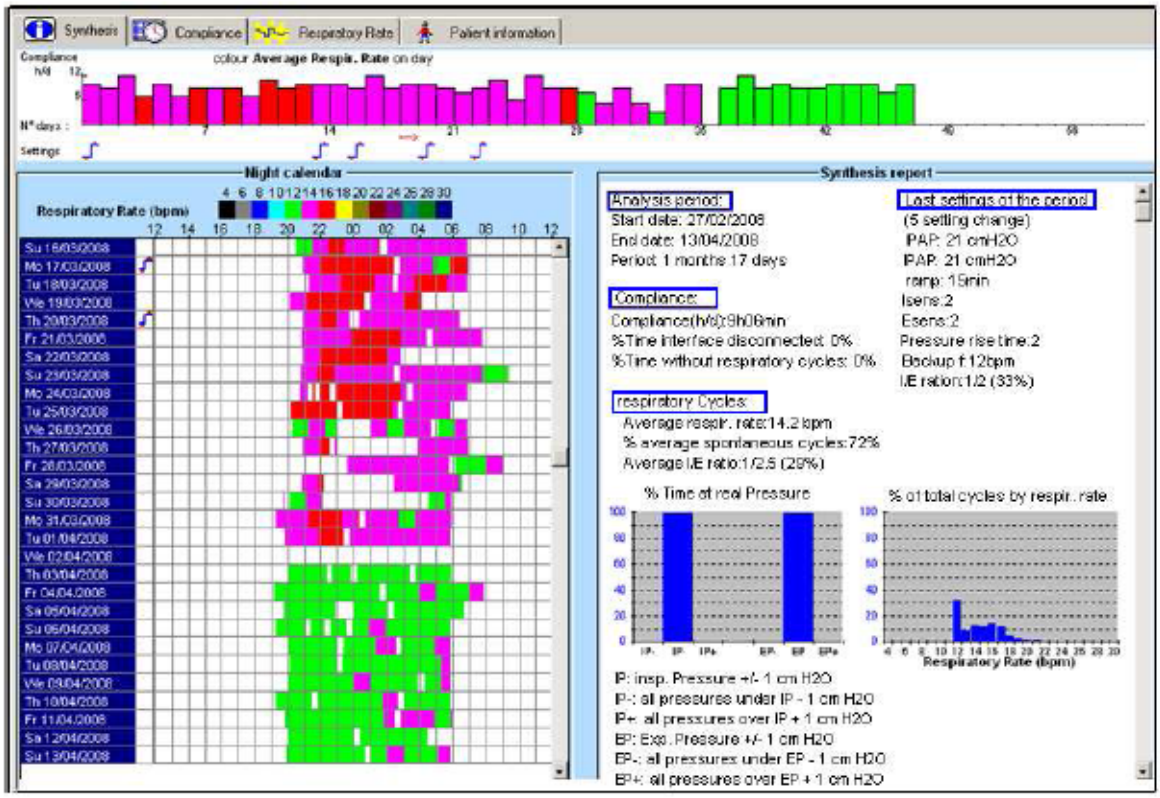

Synthesis
Compliance
Respiratory Rate
Patient information
colour Average Respir. Rate on day
Night calendar
Respiratory Rate (bpm)
Synthesis report
Analysis period:
Start date: 27/02/2008
End date: 13/04/2008
Period: 1 months 17 days
Compliance:
Compliance(h/d):9h08min
%Time interface disconnected: 0%
%Time without respiratory cycles: 0%
respiratory Cycles:
Average respir. rate:14.2 bpm
% average spontaneous cycles:72%
Average I/E ratio:1/2.5 (28%)
Last settings of the period
(5 setting change)
IPAP: 21 cmH2O
EPAP: 21 cmH2O
ramp: 15min
Isens:2
Esens:2
Pressure rise time:2
Backup f:12bpm
I/E ration:1/2 (33%)
% Time at real Pressure
% of total cycles by respir. rate
Respiratory Rate (bpm)
IP: insp. Pressure +/- 1 cm H2O
IP-: all pressures under IP - 1 cm H2O
IP+: all pressures over IP + 1 cm H2O
EP: Exp. Pressure +/- 1 cm H2O
EP-: all pressures under EP - 1 cm H2O
EP+: all pressures over EP + 1 cm H2O

Figure 9

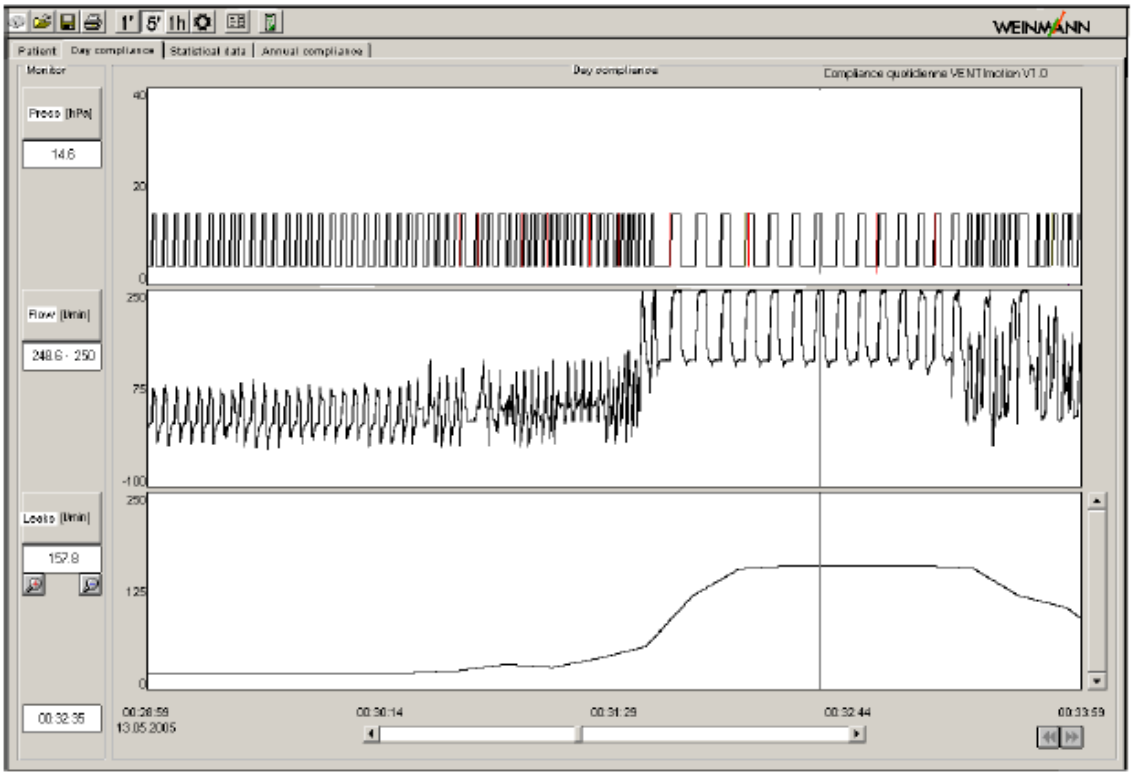
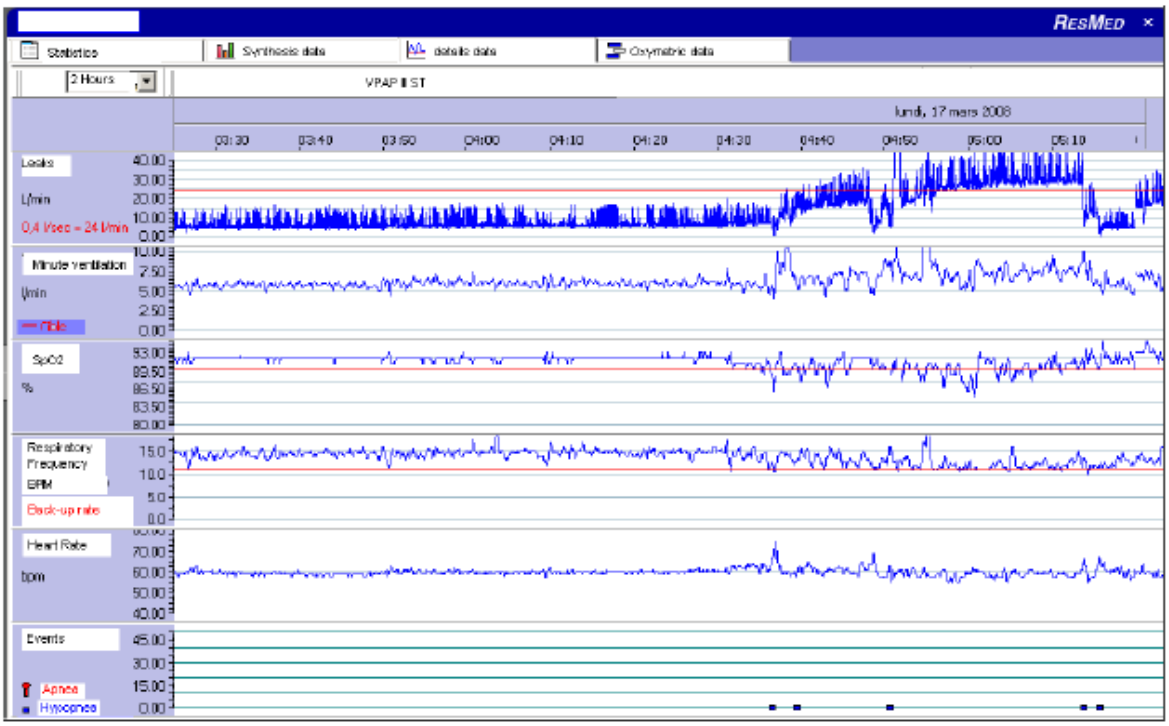

WEINMANN
Patient
Day compliance
Statistical data
Annual compliance
Monitor
Day compliance
Compliance quotidienne VENTImotion V1.0
Press [hPa]
14.6
Flow [l/min]
248.6 - 250
Leaks [l/min]
157.8
00:32:35
00:28:59
13.05.2005
00:30:14
00:31:29
00:32:44
00:33:59

Figure 10


ResMed
Statistics
Synthesis data
details data
Asymetric data
2 Hours
VPAP II ST
lundi, 17 mars 2008
03:30
03:40
03:50
04:00
04:10
04:20
04:30
04:40
04:50
05:00
05:10
Leaks
L/min
0,4 l/sec = 24 l/min
40.00
30.00
20.00
10.00
0.00
Minute ventilation
l/min
10.00
7.50
5.00
2.50
0.00
SpO2
%
93.00
90.50
88.50
85.50
83.50
80.00
Respiratory Frequency
BPM
Back-up rate
15.0
10.0
5.0
0.0
Heart Rate
bpm
70.00
60.00
50.00
40.00
Events
Apnea
Hypopnea
45.00
30.00
15.00
0.00