DETERMINANTS PHYSIOLOGIQUES DES POTENTIELS EVOQUES RESPIRATOIRES - APPLICATION AU SYNDROME D'APNEES OBSTRUCTIVES DU SOMMEIL

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remerciements

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sommaire

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publications

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résumé

Déterminants physiologiques des potentiels évoqués respiratoires. Application au syndrome d'apnées obstructives du sommeil.

Les potentiels évoqués respiratoires (PER) correspondent aux projections corticales d'afférences mises en jeu lors d'occlusions inspiratoires brèves. Ils pourraient constituer un outil d'étude des voies afférentes et des systèmes d'intégrations cérébraux impliqués dans le contrôle supra-pontique de la ventilation et dans certaines sensations respiratoires. Les travaux présentés dans cette thèse visent à caractériser les déterminants des PER et à étudier leurs éventuelles modifications au cours du syndrome d'apnées obstructives du sommeil sévère.

La première étude montre que la fatigue diaphragmatique ne modifie pas les caractéristiques des PER. La deuxième étude suggère un rôle déterminant des afférences provenant des voies aériennes supérieures dans la constitution des PER. La troisième étude montre que l'anesthésie locale des voies aériennes supérieures n'affecte pas les PER. La quatrième étude révèle que la transmission au cortex cérébral d'informations relatives à l'occlusion inspiratoire des voies aériennes supérieures, est normale au cours du syndrome d'apnées obstructives du sommeil, à l'éveil. Elle met cependant en évidence l'existence d'anomalies du traitement cortical d'informations de source respiratoire. Le rôle de ces anomalies dans une éventuelle prolongation des troubles respiratoires nocturnes, reste à déterminer.

Au terme de ce travail, et aux vues des différentes données de la littérature, il apparaît que les déterminants des PER sont probablement multiples et complexes. La place de cette technique en tant qu'outil d'investigation des sensations respiratoire reste à préciser.

Mots-clefs : potentiels évoqués respiratoires, afférences respiratoires, sensations respiratoires, voies aériennes supérieures, syndrome d'apnées obstructives du sommeil, potentiels évoqués cognitifs

résumé en anglais

Physiological determinants of respiratory-related evoked potentials. Application to the obstructive sleep apnea syndrome.

Respiratory-related evoked potentials (RREP) reflect the activity of cortical neurons in response to occlusions of the airway at the mouth during inspiration. They may provide insights into afferents pathways and cortical processes underlying supra-pontine control of breathing and perception of respiratory sensations. This thesis aimed at clarifying the origin of the RREP and at assessing whether severe obstructive sleep apnea syndrome (OSAS) would be associated to changes in their characteristics, during wakefulness. The first study of this thesis showed that predominant diaphragm fatigue did not affect the RREP. The second study showed that upper airway afferents were a paramount source for the early components of the RREP. The third study showed that upper airway anesthesia did not modify the RREP. The results of the fourth study were consistent with a normal projection to the cortex of sensory inputs related to upper airway occlusion, in severe OSAS patients during wakefulness. However, these results were also consistent with an impairment of the cortical processing of these inputs. The role of this impairment in the pathogenesis of OSAS remains to be assessed.

Together with other published data, the results of this thesis suggest that the sources and the determinants of the RREP may be multiple and complex. Further investigations are therefore needed before clinical applications.

Keywords: respiratory-related evoked potentials, respiratory afferents, upper airway, respiratory sensations, obstructive sleep apnea syndrome, event-related potentials

introduction générale

1. sensations respiratoires

La respiration normale est un acte inconscient ne donnant généralement lieu à aucune sensation intrinsèque (45).

Cependant, une grande variété de sensations respiratoires peut être perçue en physiologie ou en pathologie (perception du mouvement de l'appareil respiratoire, perception d'une irritation des voies aériennes, perception de l'effort respiratoire, impression de soif d'air…).

Pour lever l'ambiguïté entre sensations normales, physiologiques (par exemple à l'exercice) et pathologiques, on utilise généralement le terme de dyspnée qui qualifie la perception d'un "inconfort respiratoire survenant pour un niveau d'activité usuel, n'entraînant normalement aucune gêne" (37). La richesse du vocabulaire utilisé pour qualifier la dyspnée (« gène respiratoire », « suffocation », « manque d'air », « constriction thoracique »…) suggère qu'elle regroupe de multiples combinaisons de sensations respiratoires.

La dyspnée est une perception consciente (réunion de sensations en images mentales) dont l'évaluation est rendue difficile car elle fait appel à des processus multiples, cognitifs, psychoaffectifs, et émotionnels.

Contrairement à la plupart des autres sensations, la nature exacte des stimulus déclenchant la dyspnée, les voies afférentes impliquées, et les mécanismes de contrôle central ne sont pas clairement identifiés. De nombreuses afférences ont été impliquées dans la genèse de la composante sensorielle élémentaire de la dyspnée, en provenance des muscles respiratoires, des récepteurs intra pulmonaires, des chémorécepteurs, des barorécepteurs vasculaires (voir revues dans (52, 58)). Aucune de ces afférences n'est individuellement responsable de la dyspnée. Leur suppression individuelle ne la fait pas disparaître (voir revue dans (52)).

Quelles que soient les afférences impliquées dans la dyspnée, il semble qu'elles donnent naissance à un processus cérébral particulier. Ainsi, l'induction d'une dyspnée en empêchant un sujet d'hyperventiler en réponse à une hypercapnie, entraîne une activation prépondérante de l'insula droite et du cortex

cingulaire, en tomographie par émission de positons (4, 7, 44). Des résultats similaires ont aussi été rapportés avec l'imagerie fonctionnelle par résonance magnétique (23). L'activation de ces régions est retrouvée également lors de l'induction d'une dyspnée par application de charges résistives externes (53).

En tant que symptôme, la dyspnée constitue une source majeure de handicap et d'altération de la qualité de vie, ce qui en fait une cible thérapeutique importante. A l'inverse, la dyspnée peut-être "utile" en tant que signe d'alerte. Ainsi, au cours de l'asthme, la perception insuffisante d'altérations brutales des conditions ventilatoires est un facteur de gravité (36, 14). Pour toutes ces raisons, il apparaît pertinent de chercher à développer des outils d'évaluations des sensations respiratoires.

Des méthodes de psychophysiologie ont été appliquées aux sensations respiratoires afin d'obtenir des outils de mesure qui soient le plus objectif possible. Les techniques ainsi mises au point se heurtent cependant aux limites imposées par le recours au langage et à la subjectivité de l'individu. Il serait intéressant de disposer de moyens d'investigation des afférences respiratoires et de leur traitement cortical, indépendants des limites de l'expression individuelle.

C'est dans cette optique, que des techniques de neurophysiologie ont été appliquées à l'étude de sensations respiratoires, au cours de ses dernières années.

2. potentiels évoqués cérébraux

2.1. potentiels évoqués exogènes

La physiologie des sensations somatiques peut être étudiée chez l'homme par la méthode des potentiels évoqués cérébraux.

Les potentiels évoqués cérébraux « exogènes » correspondent à l'activité électrique enregistrée au niveau du scalp, pendant une période de temps définie, à la suite d'un stimulus spécifique, électrique ou mécanique. Le stimulus est répété, et le signal électroencéphalographique est moyenné pour améliorer le rapport signal/bruit et identifier les potentiels cérébraux spécifiquement évoqués par le stimulus. Ces potentiels évoqués sont définis par la polarité, la latence, et l'amplitude de leurs composantes ainsi que par leur localisation à la surface du

scalp. Les latence et amplitude des différentes composantes sont directement liés aux caractéristiques de la stimulation (type, intensité, durée, fréquence). L'électrode de recueil active étant la cathode, une composante négative est dirigée vers le haut sur les tracés, et notée Nx, x indiquant sa latence au pic ; une composante positive est dirigée vers le bas et notée Px. Dans le domaine des potentiels évoqués exogènes, il est classique de considérer que la première composante positive d'un potentiel reflète l'arrivée au niveau du cortex primaire du signal détecté, alors que les composantes plus tardives sont relatives au traitement de l'information (10).

Les différentes projections corticales des systèmes auditifs, visuels et somesthésiques ont été ainsi largement étudiées.

Les potentiels évoqués apportent des informations précises et fiables concernant la voie neurosensorielle stimulée. Ils peuvent révéler un dysfonctionnement sensoriel non suspecté cliniquement et ils aident à préciser le diagnostic lésionnel (30).

2.2. potentiels évoqués endogènes

Les renseignements apportés par les potentiels évoqués exogènes n'indiquent cependant pas la façon dont le sujet intègre les informations neurosensorielles qui parviennent à son cortex. Les potentiels évoqués tardifs, ou endogènes, ou cognitifs sont modifiés, voire créés, par la manière dont le sujet traite l'information. Les composantes cognitives reflètent la mise en jeu de mécanismes sous-jacents aux activités intellectuelles de perception et de décision.

Ils sont évoqués par la réalisation aussi rapide que possible d'une action en réponse à la présentation du stimulus, alors qu'au contraire dans le cas des potentiels évoqués exogènes, on demande au sujet d'ignorer autant que faire se peut la stimulation. Le potentiel évoqué cognitif dépend non seulement des caractéristiques physiques du stimulus mais aussi de la réaction du sujet face à ce stimulus, et correspond aux différentes étapes du traitement cognitif des informations (30).

Ces potentiels évoqués cognitifs, ou « potentiels liés à des évènements » (Event-Related Potentials, ERPs) permettent d'identifier une activité électrique corticale relative à certaines opérations mentales élémentaires. Il a ainsi été

montré qu'un stimulus identique produit une réponse électro-encéphalographique différente selon que le sujet l'attend à ce moment là ou non.

L'onde P300 est la composante positive des potentiels évoqués qui apparaît lorsqu'une stimulation provoque chez un sujet un effet de surprise auquel il doit répondre. Son amplitude est corrélée avec l'improbabilité du stimulus, avec certains aspects de l'attention sélective, avec le degré de motivation et de vigilance du sujet. La P300 est déterminée non pas par le stimulus, mais est fonction de l'activité cognitive d'identification perceptuelle de la cible. Des stimulus d'intensité très faible peuvent évoquer des P300 de grande amplitude.

3. potentiels évoqués respiratoires

3.1. description

Chez les sujets normaux, il est possible d'évoquer des potentiels cérébraux en rapport avec les muscles respiratoires par la stimulation électrique des nerfs intercostaux (26), et du nerf phrénique (59, 67). Les stimulations électriques du nerf lingual et du nerf palatin permettent d'évoquer des potentiels cérébraux relatifs aux voies aériennes supérieures (46).

Il est également possible d'étudier les projections corticales d'afférences ventilatoires en étudiant les potentiels cérébraux évoqués par l'occlusion inattendue des voies aériennes à la bouche lors de l'inspiration (potentiels évoqués "respiratoires") (15). Compte tenu des récepteurs potentiellement mis en jeu lors d'une telle occlusion (récepteurs pulmonaires, de la paroi thoracique incluant les muscles, des voies aériennes), les potentiels évoqués respiratoires pourraient traduire la projection corticale d'afférences ventilatoires « globales ».

Depuis leur description initiale, différents stimulus respiratoires ont été utilisés pour évoquer de tels potentiels : occlusion complète des voies aériennes à la bouche en début (15) ou en milieu d'inspiration (56), adjonction de résistances inspiratoires (40), ou application d'une pression négative à la bouche, pendant l'inspiration (60). Des potentiels évoqués ont aussi été décrits, soit par occlusions expiratoires des voies aériennes supérieures (31), soit par application d'une pression expiratoire négative (NEP) à la bouche (29).

Les potentiels évoqués respiratoires obtenus lors de l'occlusion des voies aériennes en milieu d'inspiration, sont caractérisés par une première composante positive (P1) dont la latence normale varie entre 34 et 58 ms, suivie par une composante négative (N1), dont la latence normale varie entre 80 et 100 ms, puis par une seconde composante positive (P2) et une seconde composante négative (N2) *(**figure 1**)*. Selon le protocole mis en œuvre et le moment de l'interruption inspiratoire, 32 à 180 occlusions sont nécessaires pour évoquer des potentiels au niveau du cortex cérébral somesthésique (15, 56, 13). Par analogie avec les potentiels évoqués cérébraux, il est admis que la composante P1 correspond aux projections afférentes primaires au niveau du cortex somesthésique, alors que les composantes plus tardives (P2, N2) sont relatives au traitement de l'information. La composante N1 (qui se situe à la limite entre composante précoce et tardive) pourrait représenter déjà une partie du processus de traitement de l'information (33).

S'inspirant des paradigmes utilisés en neurophysiologie pour étudier les perturbations cognitives, Harver et coll. (32), ont enregistré les réponses corticales à des d'occlusions inspiratoires et expiratoires lorsque celles-ci survenaient dans deux conditions, selon que les sujets faisaient attention ou non au stimulus. Il s'agissait donc de potentiels évoqués de type « cognitifs ». Harver et coll. (32) ont ainsi mis en évidence des composantes tardives dont les caractéristiques sont identiques à celles observées lors de paradigme utilisant des stimulations auditives ou visuelles (32), (63). La composante P3 avait une amplitude augmentée lorsque le sujet comptait les occlusions et les latences des composantes N2 et P3 étaient plus longues chez les sujets âgés que chez les sujets jeunes.

3.2. pertinence clinique

Un certain nombre de données de la littérature a laissé espérer que les potentiels évoqués respiratoires pourraient constituer une méthode d'évaluation objective des sensations respiratoires.

Ainsi, les changements d'amplitude de la première composante positive (P1) des potentiels évoqués respiratoires, obtenus lors de l'adjonction de résistances inspiratoires croissantes, étaient corrélés avec la capacité de sujets normaux à détecter des charges ventilatoires (19, 40, 39). Par ailleurs, quand

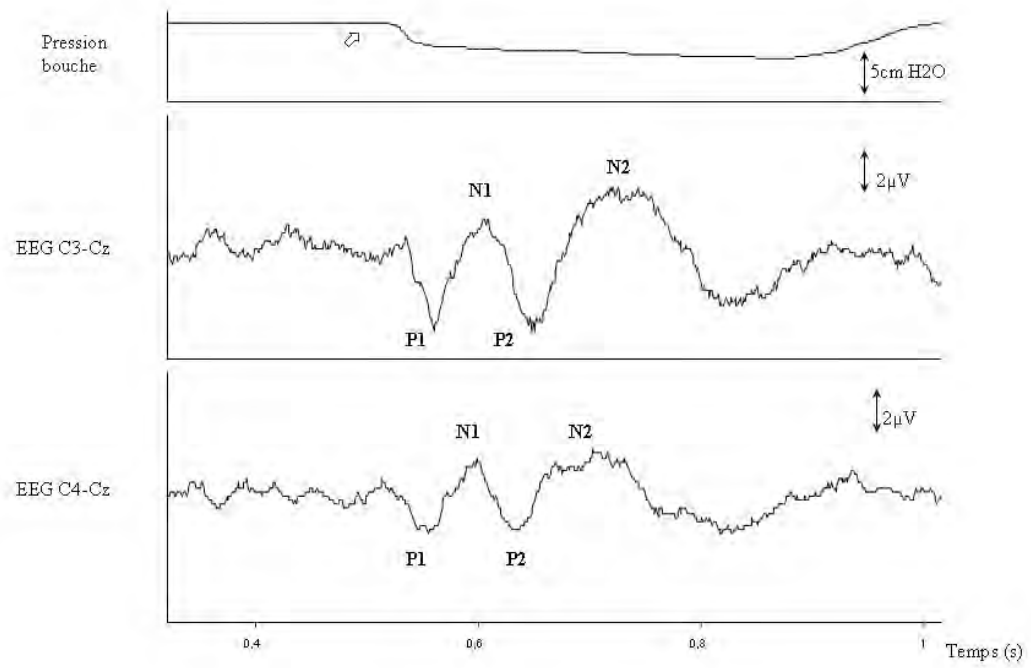

Figure 1. Exemple de potentiels évoqués respiratoires obtenus lors de l'occlusion des voies aériennes en milieu d'inspiration, ici chez un sujet sain respirant par la bouche.

Le tracé du haut représente la pression à la bouche, le tracé du milieu représente le signal électroencéphalographique dans la dérivation C3-Cz (système international 10-20), le tracé du bas représente le signal électroencéphalographique dans la dérivation C4-Cz (système international 10-20) (voir revue dans (42)).

L'ensemble des données présentées correspond au moyennage de 80 segments de cycles ventilatoires, 200 ms avant et 500 ms après l'occlusion qui est identifiée par la chute de pression à la bouche (flèche).

Conformément aux conventions électroencéphalographiques usuelles, les déflexions dirigées vers le bas sont considérées positives et notées "P", les déflexions dirigées vers le haut sont considérées négatives et notées "N" (30)]. La première composante positive (P1) du potentiel évoqué par l'occlusion des voies aériennes survient typiquement 34 à 58 ms après la chute de pression dans les voies aériennes. Elle est suivie par une composante négative (N1), dont la latence normale varie entre 80 et 100 ms, puis par une seconde composante positive (P2) et une seconde composante négative (N2).

l'inspiration était interrompue par une charge dont le niveau était inférieur au seuil de détection perceptible par le sujet, il n'était pas possible de mettre en évidence un potentiel cortical (12).

Récemment, Eckert et coll. ont montré que l'hypoxie aiguë altérait la perception de charges inspiratoires (22). La diminution de cette perception s'accompagnait d'une diminution des amplitudes des composantes P1 et P2 des potentiels évoqués respiratoires, ce qui suggérait que la transmission au cortex d'afférences respiratoires était perturbée dans cette condition.

Des anomalies des potentiels évoqués respiratoires ont aussi été mises en évidence au cours de l'asthme. Davenport et coll. ont montré que la composante P1 était absente dans une sous-population d'enfants asthmatiques ayant présenté un asthme aigu grave, alors qu'elle était présente dans un groupe contrôle d'enfants non asthmatiques ainsi que dans un groupe contrôle d'enfants asthmatiques sans passé de crise grave (14). Dans une autre étude, Davenport et coll., ont mis en évidence des altérations de la détection et de l'estimation de charges inspiratoires chez dix patients aux antécédents d'asthme aigu grave (17). Un enregistrement des potentiels évoqués respiratoires a été réalisé chez trois de ces dix patients. La composante P1 des potentiels évoqués respiratoires était absente chez ces trois patients ce qui suggère que les anomalies de perception des charges inspiratoires pourraient être objectivées par l'enregistrement des potentiels évoqués respiratoires (17).

Peu d'études se sont intéressées aux éventuelles modifications des composantes endogènes, cognitives, des potentiels évoqués respiratoires en pathologie. Webster et Colrain ont mis en évidence une diminution de l'amplitude de la composante P3 des potentiels évoqués respiratoires chez des patients asthmatiques (62). La signification physiologique de ce résultat est cependant peu claire puisqu'une diminution d'amplitude était également retrouvée chez les patients asthmatiques pour la composante P3 de potentiels évoqués auditifs.

3.3. origine des potentiels évoqués respiratoires

Avant que les potentiels puissent être utilisés comme outils d'évaluation des sensations respiratoires et plus spécifiquement de la dyspnée, il est indispensable d'élucider les mécanismes qui les sous-tendent. La source précise de ces

potentiels n'est pas connue et de nombreuses afférences sont susceptibles d'être en cause (voies aériennes supérieures et inférieures, poumons, paroi thoracique et muscles respiratoires).

Plusieurs études ont été menées afin de préciser l'origine des potentiels évoqués respiratoires. Aucune d'entre elles ne permet de conclure définitivement. Il est possible (sinon probable) qu'il y ait des afférences redondantes et que la source des potentiels évoqués respiratoires ne soit pas univoque.

3.3.1. voies aériennes supérieures

Dans un travail réalisé par Daubenspeck et coll., les potentiels évoqués par l'application d'une pression négative étaient enregistrés lors de la ventilation au travers d'un masque laryngé ce qui excluait le pharynx et une partie du larynx (11). Avec ce paradigme expérimental, les afférences des voies aériennes glottiques et sous glottiques, des muscles inspiratoires et de la paroi thoracique étaient potentiellement mises en jeu. Les potentiels évoqués respiratoires enregistrés lors de la ventilation sur masque laryngé avaient une amplitude significativement réduite par rapport à ceux enregistrés lors de la ventilation sur embout buccal. Ceci suggérait que les mécanorécepteurs des voies aériennes supra glottiques contribuaient pour une plus grande part aux potentiels évoqués respiratoires que les récepteurs glottiques, sous glottiques, des muscles inspiratoires et de la paroi thoracique.

3.3.2. voies aériennes inférieures

La similitude de potentiels évoqués respiratoires chez des patients transplantés bi- pulmonaires (chez lesquels les afférences vagales provenant des voies aériennes inférieures sont supprimées) et chez des sujets témoins plaidait en faveur du rôle mineur de telles afférences dans la constitution des potentiels évoqués respiratoire (66).

3.3.3. muscles inspiratoires

Knafelc et Davenport ont rapporté que l'amplitude de la première composante positive (P1) des potentiels évoqués respiratoires, obtenus lors de l'adjonction de

résistances inspiratoires croissantes, augmentait avec l'intensité de l'effort requis pour vaincre la charge (39). Ce résultat suggérait que les variations « aigues » de charge imposées aux muscles respiratoires modifiaient les caractéristiques des potentiels évoqués respiratoires.

Huang et coll. n'ont pas mis en évidence de différence significative de latence et d'amplitude des composantes précoces (P1 et N1) des potentiels évoqués respiratoires avant et après quatre semaines d'entraînement musculaire inspiratoire bien que la course inspiratoire, mesurée par la $P_{0,1}$**,** soit diminuée (33). Dans cette étude, il existait cependant une tendance à la diminution de l'amplitude de la composante P1 après entraînement musculaire inspiratoire.

objectifs du travail

Le but de ce travail de thèse a été de rechercher l'origine des potentiels évoqués respiratoires, leurs déterminants (et donc leur signification physiologique) et, par conséquent, de préciser leur valeur en tant qu'outil d'investigation des sensations respiratoires au sens large.

Ce travail de thèse s'est décomposé en quatre étapes. La première étape a consisté à évaluer l'effet de la fatigue diaphragmatique sur les caractéristiques des potentiels évoqués respiratoires de sujets sains (étude n°1). La deuxième étape a consisté à étudier la contribution des voies aériennes supérieures aux potentiels évoqués respiratoires (étude n°2). La troisième étape a consisté à déterminer l'effet de l'anesthésie des voies aériennes supérieures sur les caractéristiques des potentiels évoqués respiratoires (étude n°3). La quatrième étape a consisté en l'étude des potentiels évoqués respiratoires, à l'éveil, au cours du syndrome d'apnées obstructives du sommeil sévère (étude n°4).

méthodes

Cette recherche a été conduite dans le cadre de la loi sur la protection des personnes se prêtant à des recherches biomédicales, dite loi Huriet. Ces études ont été soumises à l'approbation préalable d'un Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale (CCPPRB). L'information des participants aux études a été assurée oralement et par écrit. Leurs consentements libres et éclairés ont été recueillis par écrit.

1. enregistrement de la ventilation

Les patients et sujets étaient confortablement installés dans un fauteuil légèrement incliné de manière à ce que la tête, le dos et le cou soient parfaitement relâchés ***(figure 2).*** Il leur était spécifiquement demandé de relâcher au maximum les muscles de la face et en particulier de ne pas serrer l'embout buccal afin de ne pas produire de signaux myogéniques pouvant induire des artefacts au niveau du signal électroencéphalographique. Pendant la durée de l'enregistrement, les patients et sujets ventilaient au travers d'un circuit comportant en série un pneumotachographe chauffé (Hans Rudolf, série 3700, linéaire de 0 à 160 l.min, Kansas City, MO, USA), puis une valve unidirectionnelle (Hans Rudolf 2600 medium, Kansas City, MO, USA), permettant de séparer les voies inspiratoire et expiratoire ***(figure 3).***

La pression était mesurée au niveau de la voie inspiratoire à l'aide d'un capteur de pression différentiel**,** linéaire de 0 à 150 cm H2O (DP15-32, Validyne, Northridge, CA, USA). Le signal de pression était numérisé à une fréquence d'échantillonnage de 100 Hz, (MacLab/16, AD Instruments, Castle Hill Australie) puis stockée sous forme électronique (logiciel Chart v3.6.1/s®, AD Instruments, Castle Hill Australie) dans un ordinateur Power Macintosh G4 (Apple computer, Cupertino, CA, USA) pour analyse ultérieure ***(figure 4).***

Le capteur de pression était calibré avant chaque enregistrement à l'aide d'une colonne d'eau. Il était relié à la voie inspiratoire par un tuyau non compliant d'un diamètre interne de 2 mm.

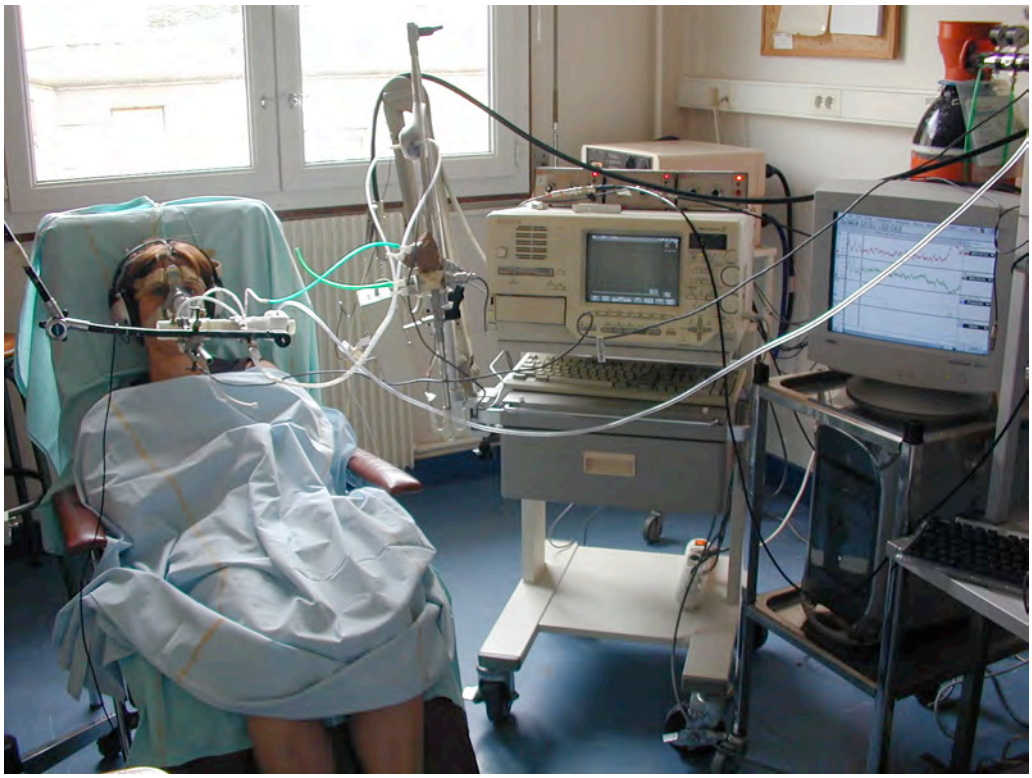

Figure 2. Vue générale de la technique d'enregistrement des potentiels évoqués respiratoires chez un sujet sain. Le sujet est confortablement installé dans un fauteuil légèrement incliné. Les différents signaux sont filtrés, amplifiés, numérisés puis stockée sous forme électronique dans un ordinateur.

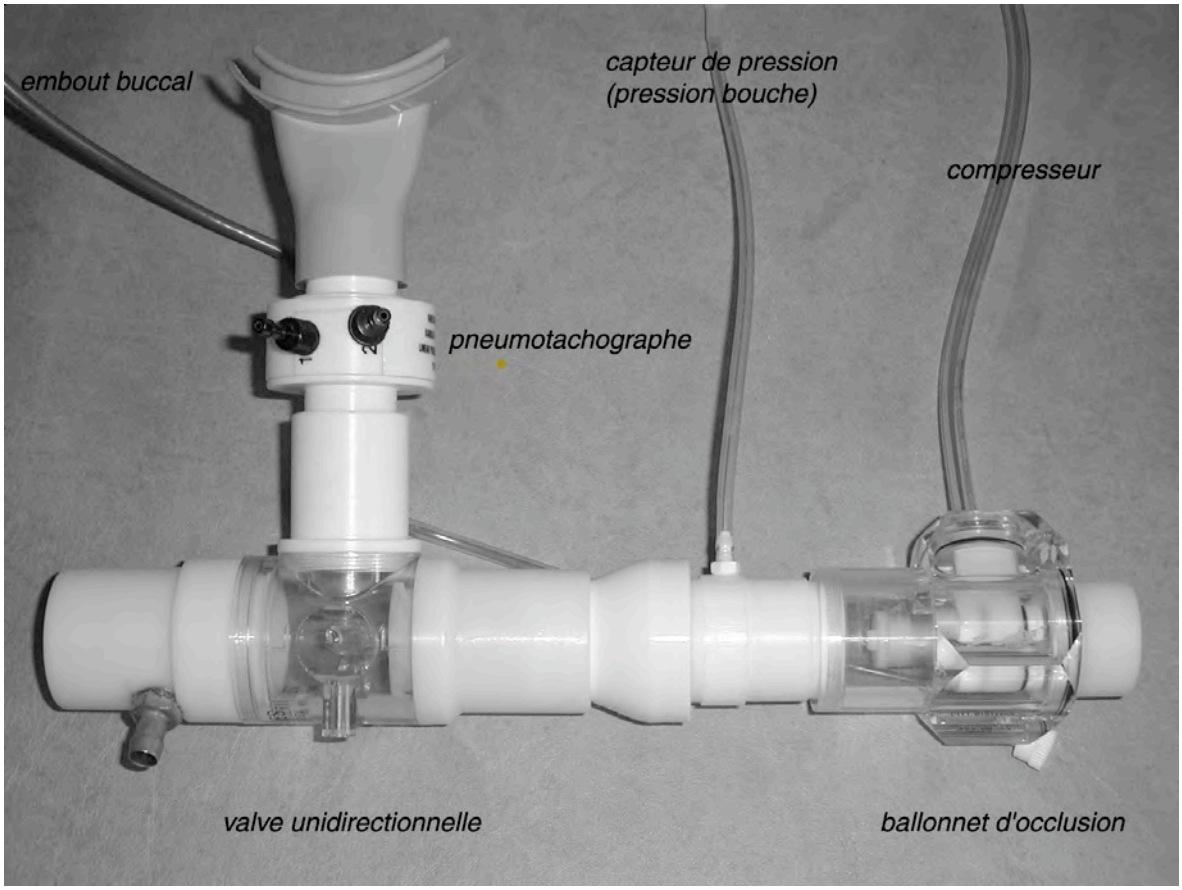

Figure 3. Photographie de l'ensemble du dispositif à travers lequel les sujets ventilaient pour l'enregistrement des potentiels évoqués soit par l'intermédiaire d'une pièce buccale, soit par l'intermédiaire d'un masque nasal, comportant de bas en haut et de gauche à droite un pneumotachographe chauffé et une valve unidirectionnelle sur la voie inspiratoire de laquelle était insérée un ballonnet d'occlusion relié à un compresseur.

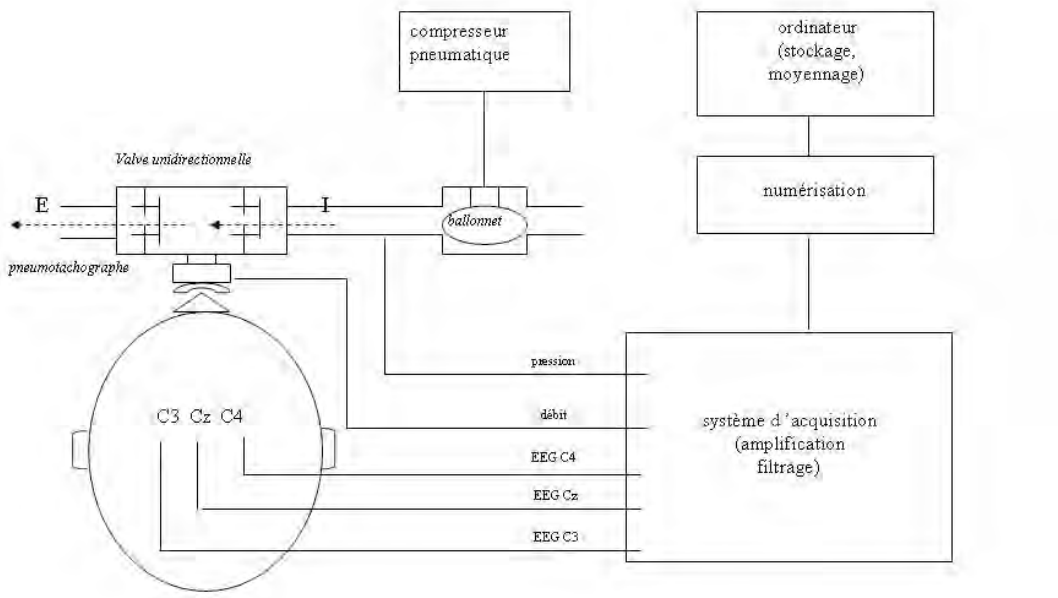

Figure 4. Représentation schématique du dispositif d'enregistrement des potentiels évoqués respiratoires.

I, inspiration ; E, expiration.

L'ensemble du dispositif était maintenu à l'aide d'un bras articulé de manière à ce que les patients et sujets n'aient aucun effort à fournir pour maintenir le dispositif en place et puissent se détendre au mieux *(**figure 5**)*..

Les patients et les sujets écoutaient une musique de leur choix grâce à un casque audio phonique ce qui leur permettait d'être isolés de l'ambiance sonore du laboratoire et en particulier de ne pas entendre le bruit produit par le gonflement du ballonnet d'occlusion.

L'inspiration était en effet interrompue en actionnant manuellement un compresseur pneumatique (Hans Rudolf 9330 series, Kansas City, MO, USA) relié à un ballonnet placé dans la voie inspiratoire de la valve unidirectionnelle (Hans Rudolf 9340 series, Kansas City, MO, USA) *(**figures 3 et 4**)*. Chaque occlusion commençait 200 à 700 ms après le début d'une inspiration, repéré sur l'annulation du débit ventilatoire, et durait 400 à 700 ms. Les occlusions inspiratoires étaient séparées par 2 à 5 cycles respiratoires et répétées 100 fois.

Deux séries consécutives d'enregistrements étaient réalisées afin de vérifier l'obtention d'un signal reproductible.

2. électroencéphalogramme

2.1. recueil des signaux

Le signal électroencéphalographique était recueilli selon la technique initialement décrite pour l'obtention des potentiels évoqués respiratoires (15). L'électroencéphalogramme était enregistré au niveau des dérivations C3-Cz, C4-Cz (système international 10-20) (voir revue dans (42)) *(**figure 6**)* à l'aide d'électrodes de surface en cupule d'argent recouvertes de pâte conductrice (Elefix, Nihon-Kohden, Tokyo, Japon) posées sur le scalp abrasé et dégraissé et fixées avec du collodion (procédure standard d'exploration fonctionnelle neurophysiologique). L'électrode de terre était collée sur le front et fixée avec du sparadrap hypoallergénique.

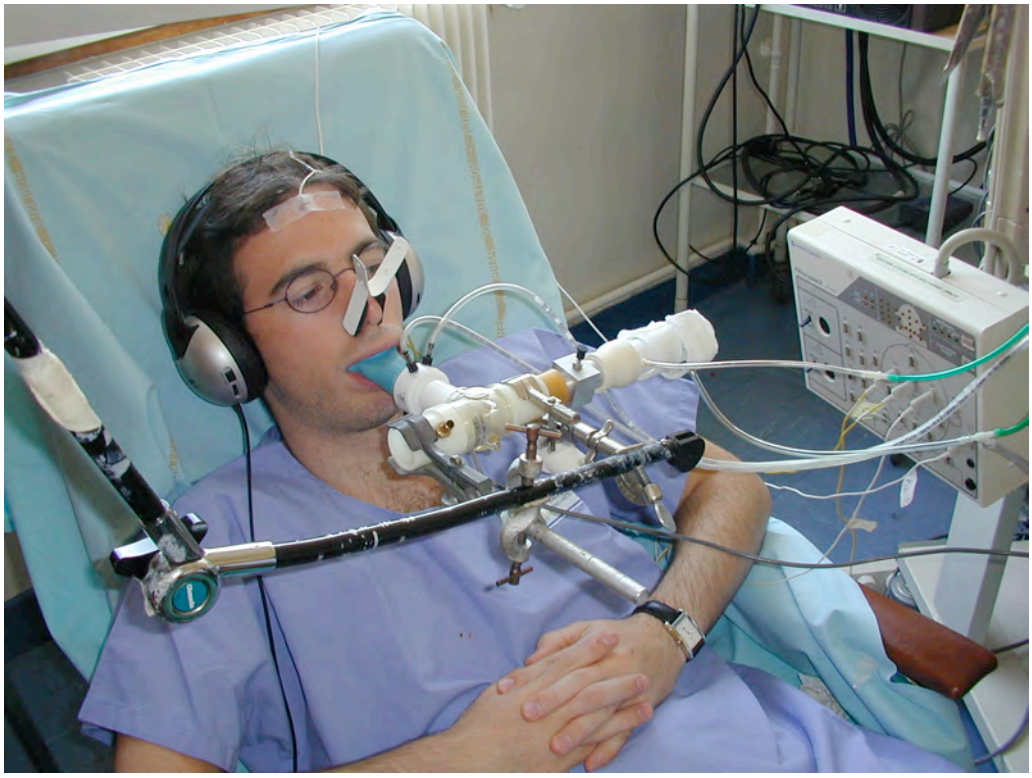

Figure 5. Vue générale de la technique d'enregistrement des potentiels évoqués respiratoires lors de la ventilation sur un embout buccal chez un sujet sain. L'ensemble du dispositif est maintenu à l'aide d'un bras articulé. Le nez est maintenu fermé à l'aide d'un pince-nez.

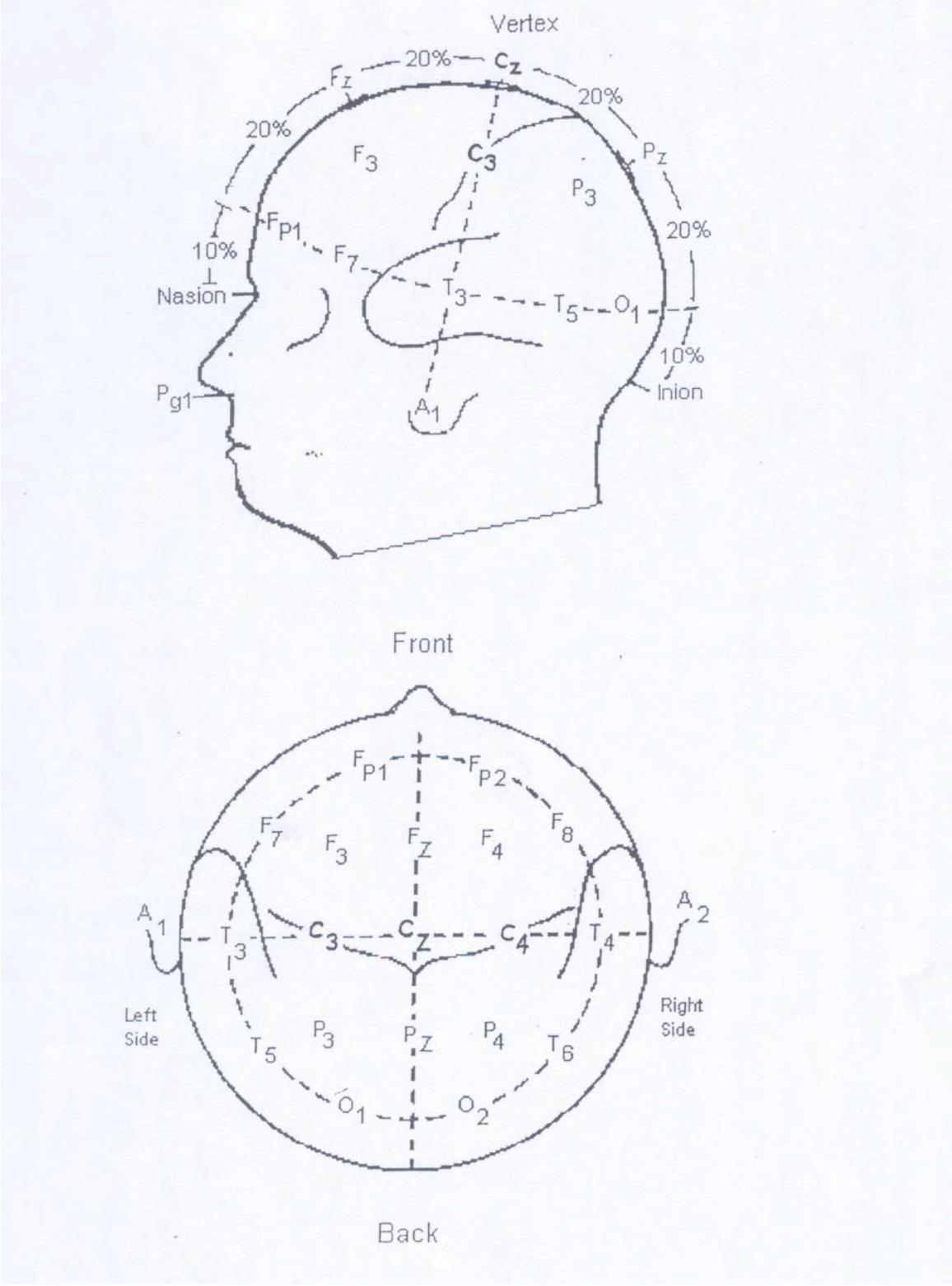

Figure 6. Représentation schématique de l'emplacement des électrodes de recueil de l'électroencéphalogramme selon le système international 10-20 (voir revue dans (42).

Pour l'étude des potentiels évoqués respiratoires, l'électroencéphalogramme était recueilli au niveau des dérivations C3 et C4 en référence à Cz selon la technique initialement décrite par Davenport et coll. (15).

L'impédance de chaque électrode était contrôlée avant chaque cycle d'enregistrement et maintenue inférieure à 5 KiloOhm.

L'activité électroencéphalographique était filtrée (0,5-500Hz) et amplifiée (Neuropack Sigma, Nihon-Kohden, Tokyo, Japon). Les signaux électroencéphalographiques étaient recueillis et numérisés à une fréquence d'échantillonnage de 1000 Hz (MacLab/16, AD Instruments, Castle Hill Australie) puis stockés sous forme électronique (logiciel Chart v3.6.1/s®, AD Instruments, Castle Hill Australie) dans un ordinateur Power Macintosh G4 (Apple Computer, Cupertino, CA, USA) pour analyse ultérieure *(**figure 4**)*.

2.2. moyennage du signal électroencéphalographique

Pour extraire les potentiels évoqués respiratoires du signal électroencéphalographique (EEG) brut, un minimum de 60 époques d'EEG, s'étendant de 200 ms avant et 1000 ms après une occlusion, étaient sélectionnées manuellement à partir du signal de pression à la bouche. Un cycle "occlus" donné était retenu pour le moyennage si la ligne de base EEG précédant l'occlusion était stable et dépourvue de signaux parasites de haute fréquence *(**figure 7**)*. Les signaux EEG et de pression à la bouche étaient ensuite moyennés grâce aux logiciels Chartv3.6.1/S® (AD Instruments, Castle Hill, Australie) et Microsoft® Excel 98. A titre de contrôle, la même procédure était répétée en utilisant un nombre égal de cycles respiratoires non occlus**.**

2.3. analyse

Deux séries d'occlusions étaient réalisées et les résultats des moyennages de l'EEG étaient superposés *(**figure 8**)* afin de vérifier la reproductibilité intra séance des signaux obtenus. Les deux cycles étaient ensuite analysés séparément. L'amplitude des composantes était mesurée entre la ligne de base du signal EEG et leur pic.

Pour mesurer la latence des composantes des potentiels évoqués respiratoires, un point "zéro" correspondant au début vraisemblable du stimulus était déterminé sur le signal de pression moyenné, selon la méthode décrite par Davenport et coll. (16). Ce point correspondait à l'intersection d'une droite

extrapolée de la ligne de base et d'une droite extrapolée de la droite de régression correspondant à la chute de pression brutale suivant l'occlusion *(**figure 9**)*. Il était déterminé à l'aide du logiciel Matlab5.3® (The Math Works, Natick, MA, USA). La latence d'une composante donnée était définie comme le temps écoulé entre ce "point zéro" et le pic de la composante. La valeur de la chute de pression dans les voies aériennes 30 ms après le « point zéro » était également mesurée.

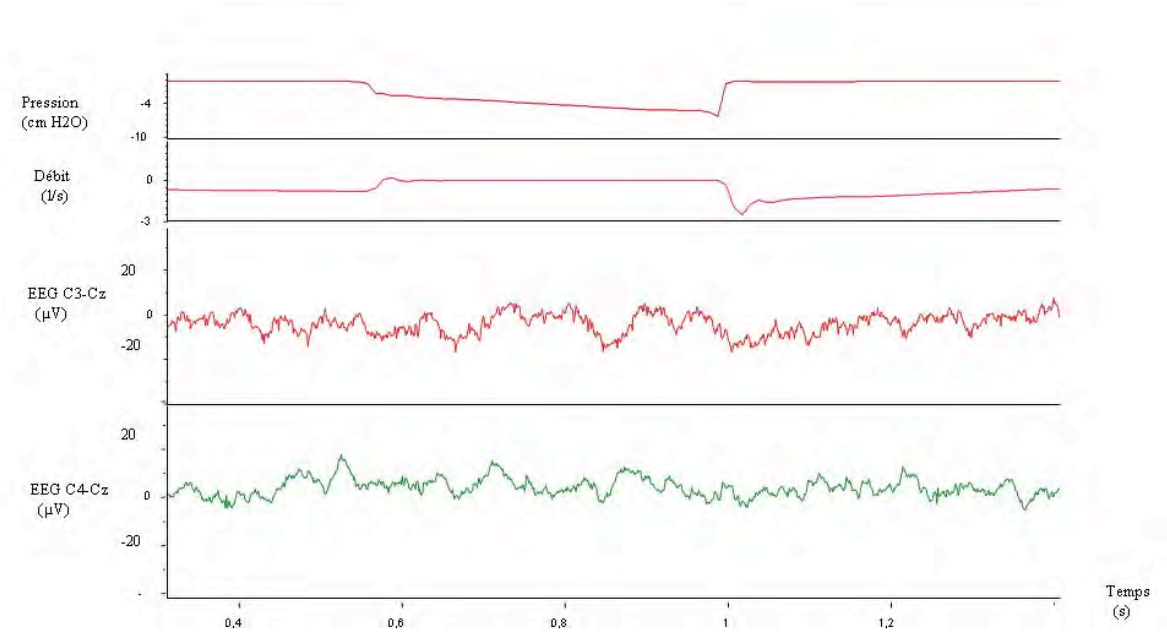

Figure 7. Exemple de cycle inspiratoire avec occlusion, retenu pour le moyennage permettant l'extraction des potentiels évoqués respiratoires.

Le tracé du haut représente la pression à la bouche. Le second tracé représente le débit ventilatoire. Le troisième tracé représente le signal brut, non moyenné, de l'enregistrement électroencéphalographique dans la dérivation C3-Cz (système international 10-20). Le tracé du bas représente le signal brut, non moyenné, de l'enregistrement électroencéphalographique dans la dérivation C4-Cz (système international 10-20).

La chute de pression au niveau des voies aériennes et l'annulation du débit inspiratoire sont les témoins de l'occlusion. Les tracés électroencéphalographiques sont dépourvus d'artéfacts et d'ondes lentes.

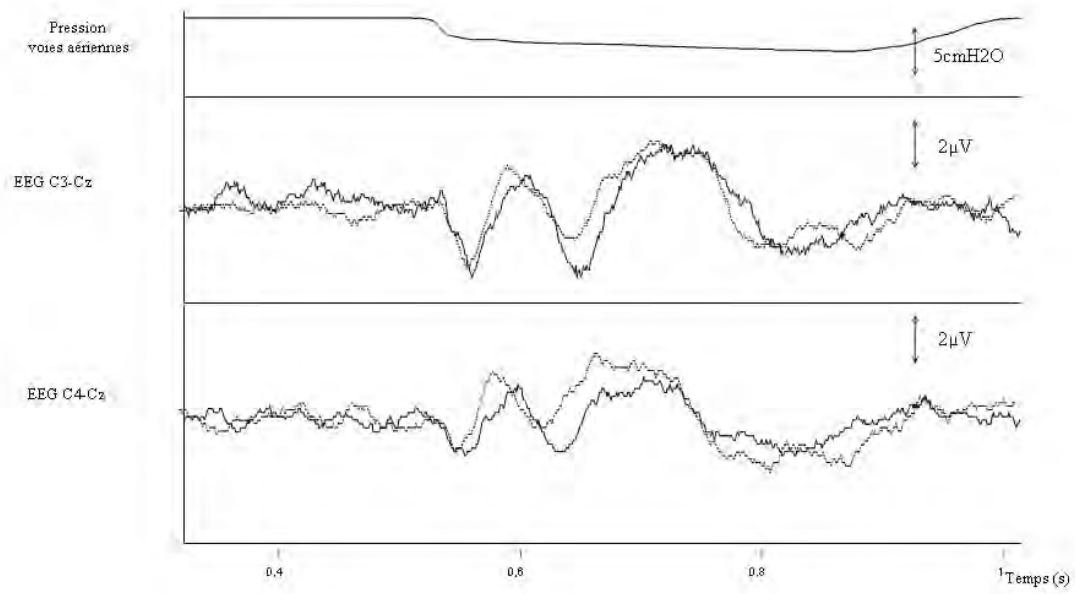

Figure 8. Exemple de superposition de 2 enregistrements séquentiels de potentiels évoqués respiratoires chez un sujet sain, lors de la même session expérimentale.

Le tracé du haut représente la pression à la bouche, le tracé du milieu le représente signal électroencéphalographique dans la dérivation C3-Cz (système international 10-20), le tracé du bas représente le signal électroencéphalographique dans la dérivation C4-Cz (système international 10-20).

Chaque tracé correspond au moyennage de 80 segments de cycles ventilatoires, 200 ms avant et 500 ms après l'occlusion qui est identifiée par la chute de pression.

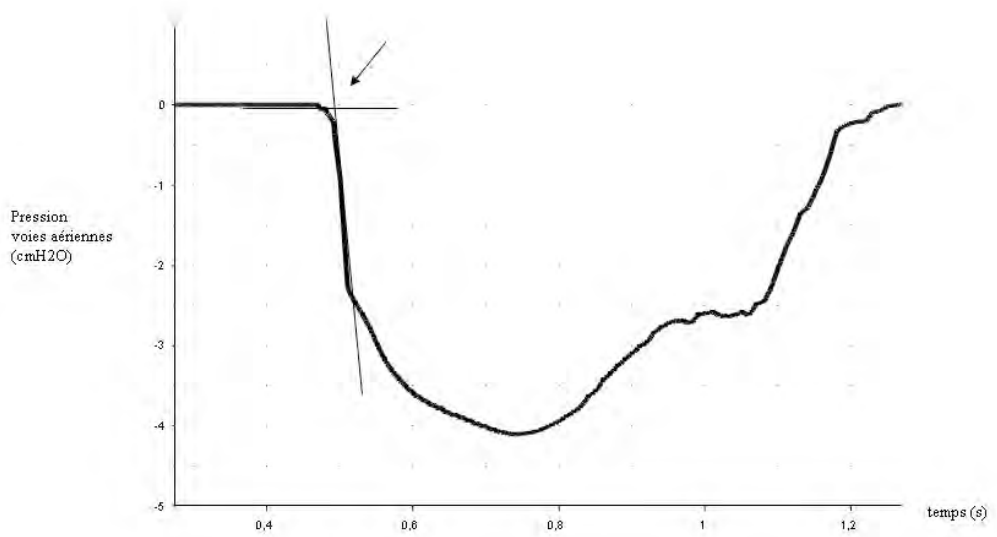

Figure 9. Principe de détermination du point de référence pour la mesure de la latence des composantes des potentiels évoqués respiratoires.

Le tracé représente l'onde de pression obtenue par moyennage des cycles comportant une occlusion respiratoire retenus pour l'extraction des potentiels. Le point de référence est défini comme l'intersection de l'extrapolation d'une droite de régression calculée sur la ligne de base et de l'extrapolation d'une droite de régression calculée sur le segment de pression de plus grande pente après l'occlusion. D'après Davenport et coll. (16).

étude 1

Effet de la fatigue diaphragmatique sur les caractéristiques des potentiels évoqués respiratoires.

Bezzi M, Donzel-Raynaud C, Straus C, Tantucci C, Zelter M, Derenne J-Ph, Similowski T.

Unaltered respiratory-related evoked potentials after acute diaphragm dysfunction in humans

Eur Respir J 2003 ; 22:625-30

1. objectif de l'étude

La première étape de cette thèse a consisté en l'étude de l'effet de la fatigue diaphragmatique sur les composantes des potentiels évoqués respiratoires.

De nombreux arguments expérimentaux plaident en faveur d'un rôle important des muscles respiratoires dans la genèse des sensations respiratoires (37, 35, 25, 9). L'existence de potentiels cérébraux évoqués par la stimulation des nerfs phréniques (67, 59) et intercostaux (26), témoigne de la réalité de projections corticales d'afférences provenant des muscles respiratoires chez l'homme. Or, il a été montré chez le chat que la fatigue diaphragmatique altérait les potentiels cérébraux évoqués par la stimulation des nerfs phréniques (3).

L'hypothèse fondatrice de cette étude a donc été qu'une fatigue diaphragmatique chez l'homme pourrait induire des modifications des potentiels évoqués respiratoires. La vérification de cette hypothèse aurait constitué un argument en faveur d'une origine musculaire des afférences responsables de ces potentiels.

2. méthodes

Une fatigue diaphragmatique aiguë a été induite chez neuf sujets sains par l'imposition d'une résistance inspiratoire contre laquelle ils devaient produire au moins 60% de leur pression transdiaphragmatique maximale jusqu'à « épuisement ».

L'apparition d'une fatigue était définie par une chute de plus de 10% de la pression trans-diaphragmatique en réponse à une stimulation magnétique cervicale, sans modification ou augmentation du rapport pression oesophagienne sur pression gastrique.

Deux sujets ont été exclus car les critères de fatigue n'ont pas pu être remplis. Les potentiels évoqués respiratoires ont été enregistrés avant et après l'induction de la fatigue.

3. résultats

Les caractéristiques des potentiels évoqués respiratoires n'ont pas été modifiées par la fatigue diaphragmatique malgré l'obtention d'une fatigue

musculaire objectivée par la chute des pressions intra thoraciques en réponse à la stimulation phrénique.

4. conclusion

Cette étude a montré que les caractéristiques des potentiels évoqués respiratoires n'étaient pas modifiées lorsque l'aptitude du diaphragme à produire une dépression inspiratoire était diminuée.

A première vue, ce résultat peut paraître surprenant puisque plusieurs études ont montré que des variations « aigues » de charge imposées aux muscles respiratoires modifiaient les caractéristiques des potentiels évoqués respiratoires (39, 40). Il nous amène à formuler l'hypothèse que la corrélation entre l'amplitude de la composante P1 et l'importance de la charge inspiratoire retrouvée dans ces études puisse être liée uniquement à l'augmentation de l'intensité du stimulus respiratoire lors de l'adjonction de charges croissantes.

Notre résultat est à mettre en parallèle avec l'absence de modification significative des latences et amplitudes des composantes précoces (P1 et N1) des potentiels évoqués respiratoires après plusieurs semaines d'entraînement musculaire inspiratoire (33). Il n'exclut pas que le diaphragme soit une source d'information sensorielle mais suggère que les mécanorécepteurs du diaphragme ne contribuent pas de manière déterminante à la constitution des potentiels évoqués respiratoires.

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Unaltered respiratory-related evoked potentials after acute diaphragm dysfunction in humans

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Unaltered respiratory-related evoked potentials after acute diaphragm dysfunction in humans. M. Bezzi, C. Donzel-Raynaud, C. Straus, C. Tantucci, M. Zelter, J-P. Derenne, T. Similowski. ©ERS Journals Ltd 2003.

ABSTRACT: Respiratory muscles play an important role in the origin of respiratory sensations. Data dissecting the role of the diaphragm and other inspiratory muscles are scarce. This study aimed to determine the impact of diaphragm dysfunction following inspiratory resistive loading on respiratory-related evoked potentials considered as a neurophysiological substrate of certain types of respiratory sensations.

Altogether, nine subjects aged 25–50 yrs (six females) participated in the study. Transdiaphragmatic pressure output of cervical magnetic stimulation (with subdivision in oesophageal and gastric component), and respiratory-related evoked potentials (C3 and C4 derivations in the international 10–20 system) following mid-inspiratory occlusions were studied before and after an inspiratory-resistive loading challenge.

Predominant diaphragm dysfunction was observed in seven subjects (average 28% reduction in transdiaphragmatic pressure, from 27.25–19.91 cmH_20, with increased oesophageal-to-gastric pressure ratio). The latencies and amplitudes of all the components of the respiratory-related evoked potentials were unchanged.

The study concluded that predominant diaphragm fatigue does not affect respiratory-related evoked potentials.

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Respiratory sensations are commonly considered to result from the balance between the central ventilatory drive, the corresponding production of force by ventilatory muscles, and a complex afferent feedback [1]. The neural processing of changes associated with inspiratory loads allows normal humans to detect them, identify their nature (*e.g.* resistive *versus* elastic), estimate their magnitude, and in turn to adapt to their presence. The corresponding sensations provide an alarm system of which the deficiency can be a relevant pathophysiological determinant of respiratory diseases (*e.g.* certain severe forms of asthma are associated with a blunted perception of inspiratory loads [2]).

There is considerable evidence documenting the role of inspiratory muscles and the rib cage in the detection of added inspiratory loads [3]. Respiratory muscle function also modulates respiratory sensations. Inspiratory strength training does not alter load detection but reduces the perceived magnitude of both resistive and elastic loads [4]. Conversely, globally weakening inspiratory muscle exacerbates the sense of inspiratory efforts [5, 6]. This is similar to that occurring in upper limb muscles where the development of fatigue increases the perceived heaviness of a lifted object [7], and illustrates the role of respiratory muscle afferents in the genesis of respiratory sensations. Another illustration of this contribution is provided by the neurophysiological evidence of a cortical processing of respiratory muscle afferents. The stimulation of intercostal [8] and phrenic [9, 10] afferents indeed evoke cerebral potentials in humans. Coherently, diaphragm fatigue has been shown to alter phrenic cortical potentials in the cat [11]. However, in man such changes do not seem to have been reported.

A simple means to study the cortical processing of respiratory afferents is to record the brain activity following repeated inspiratory occlusions at the airway opening (respiratory-related evoked potentials (RREP)), even though the exact source of this activity is not precisely known. The amplitude of the first positive component of the RREP varies with the intensity of the inspiratory effort required to overcome a resistive inspiratory load [12]. It is related to both the corresponding transdiaphragmatic pressure and subjective magnitude estimation [12, 13]. It is thus possible that respiratory muscle afferents participate in the genesis of the RREP. In this case, observing changes in the amplitude of the somatosensory component of the RREP in response to

acute inspiratory muscle dysfunction would substantiate the corresponding changes in the sensory processing of inspiratory muscle information.

The contribution of the diaphragm and of extradiaphragmatic inspiratory muscles to respiratory sensations appears to be different [14, 15]. The present study aimed at examining the effects of experimentally reducing the pressure generation ability of the diaphragm, while sparing rib cage muscle as much as possible [16], on the characteristics of RREP.

Materials and methods

Subjects

After completion of the French legal procedure for biomedical research in human volunteers, nine White subjects participated in the study (six females, three males; aged 25–50 yrs; height 159–192 cm; weight 48–100 kg). They were informed in detail of the purpose of the study and methods used, and gave written consent. The subjects were instructed to avoid sleep deprivation during the 48 h preceding the experiments, to refrain from any consumption of alcohol and psychotropic substances, and to eat lightly on the day of the study.

Measurements and procedures

Breathing circuit. The subjects, wearing a noseclip, breathed room air through a flanged mouthpiece and a heated Hans-Rudolph pneumotachograph (3700 series; Hans Rudolph, Kansas City, MO, USA) connected to a ± 2 cmH_2O linear differential pressure transducer (Validyne, Northridge, CA, USA) in order to measure the ventilatory flow. The pneumotachograph was assembled in series to a nonrebreathing two-way valve (2600 series; Hans Rudolph) of which the inspiratory port could be occluded by an inflatable balloon (Hans-Rudolf 9340 series occlusion valve and 9330 series compressor; Hans Rudolph). Mouth pressure was measured from a side port of the mouthpiece, using a differential pressure transducer (DP 15–32; Validyne).

Abdominal displacements. Changes in abdominal circumference were monitored with a mechanical strain gauge (Nihon Kohden, Tokyo, Japan) attached to an elastic belt placed at the level of the umbilicus.

Pressures. Oesophageal pressure (Pes) and gastric pressure (Pga) were measured with two balloon-tipped catheters (thin-walled balloon sealed over a polyethylene catheter with distal side holes, 60 cm length, 1.7 mm inside diameter) connected to two Validyne MP45 linear differential pressure transducers (Validyne, Northridge, CA, USA). Transdiaphragmatic pressure (Pdi) was obtained on-line by connecting the Pes and Pga catheters to a third transducer of the same type. Pdi was continuously displayed to the subjects on a computer screen.

Surface diaphragm electromyograms. Surface recordings of the right and left costal diaphragmatic electromyographical activity were obtained using disposable silver cup electrodes taped to the skin [17], in order to assess the validity and reproducibility of phrenic nerve stimulation [18]. The signals were fed to amplifiers (Nihon Kohden), with a 10 kHz sampling rate and a 20 Hz–5 kHz bandwidth.

Cervical magnetic stimulation. Cervical magnetic stimulation (CMS) was carried out according to the previously described technique [19, 20], using a Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK) equipped with a 90 mm circular coil (peak magnetic field 2.5 Teslas). All the stimulations were delivered at relaxed end-expiration as judged from the abdominal circumference trace, as well as the Pes and Pdi traces, with the glottis closed. The maximal stimulation intensity of the stimulator was systematically used, after verifying from a simplified recruitment curve (amplitude of diaphragm quasi-synchronised action potentials *versus* stimulation intensity) that it corresponded to a supramaximal response. Diaphragm twitches were retained for analysis only if the amplitude of the corresponding electromyographic responses to CMS matched the previously determined maximum amplitude, before and after fatigue. The amplitude of the oesophageal, gastric, and transdiaphragmatic pressures swings produced by the CMS-induced diaphragm twitches (Pes,tw, Pga,tw, and Pdi,tw, respectively) were measured from baseline to peak.

Respiratory-related evoked potentials. The electroencephalographic activity (EEG) was recorded using standard surface electrodes placed at the scalp positions C_Z, C_3, C_4 on the basis of the international 10–20 system [21]. C_3 and C_4 were referenced to C_Z to record the left and right activity, respectively. The ground electrode was placed on the left earlobe. Electrode impedances were monitored and maintained at <5 kOhms. The EEG electrodes were connected to a standard amplifier system (Nihon Kohden). The signal was sampled at a 1 kHz rate over a 0.5–500 Hz bandwidth. Respiratory-related potentials were evoked by mid-inspiratory occlusions [22]. To ensure immediate reproducibility of the signals, two separate averagings of 80 occluded breaths were systematically performed in each studied condition and the resulting traces superimposed. Control signals were obtained by averaging the same number of unoccluded breaths. The peak latencies of the first positive (P1), first negative (N1), second positive (P2) and second negative (N2) components of the RREP were measured from the onset of inspiration determined on the averaged mouth pressure trace according to DAVENPORT *et al.* [23]. The amplitude of the P1 component of the RREP was measured from baseline to peak. The amplitudes of the N1, P2 and N2 components were measured from peak to peak (P1-N1, N1-P2, and P2-N2, respectively).

Maximal static transdiaphragmatic pressure. Maximal static Pdi (Pdi,max) was determined by asking the subjects to perform inspiratory efforts from functional residual capacity against the occluded airway, with visual feedback of the Pdi signal. No instruction was given as to the type of manoeuvre to perform. The best of three attempts was retained.

Diaphragm challenge. To acutely modify diaphragm function, the subjects were asked to breathe against an inspiratory resistance while targeting an inspiratory Pdi amounting to 60% of Pdi,max with an inspiratory time of ~50% of the ventilatory period, until task failure with strong verbal coaching. This protocol was chosen according to in-house observations showing that, in subjects without prior experience of inspiratory loading, it tends to produce changes in inspiratory muscle output predominantly due to a diaphragmatic contribution. In the authors experience, this result is achieved with no need to standardise the reference Pdi,max manoeuvre and the pattern of muscle recruitment used during the loading procedure. The authors considered predominant diaphragm dysfunction present when a reduction in Pdi,tw of $\geqslant 10$ % was observed, with a Pes,tw:Pga,tw unchanged or increased [16].

Experimental conditions and sequence. The subjects were studied sitting (respiratory pressure measurements and fatigue

protocol) or semireclined (respiratory related evoked potentials), abdomen unbound, on a lounge chair with the back, neck and head comfortably supported. They were instructed to relax but to keep their eyes open in order to avoid any risk of falling asleep or producing slow brain waves. During the experimental sequence, the subjects wore earplugs and headphones through which they listened to a quiet musical piece of their choice, in order to mask the auditory ambiance of the laboratory.

After completion of the experimental setup, baseline RREP were gathered and $P_{di,max}$ was determined. Baseline diaphragm twitches were then collected, and the acute loading procedure was performed. Immediately after task failure, RREP were gathered again, after which diaphragm twitches were again obtained.

Statistical analysis

Data are described as mean±SD. Given the small size of the sample, and to avoid making assumptions on the distribution of the characteristics of the RREP, the analysis was conducted in a nonparametric way. The effects of inspiratory loading on twitch pressures were tested using the Wilcoxon test. Regarding the RREP, two steps were taken. First, when the number of observations of a given component in a given derivation differed before and after loading, a Chi-squared test with correction for small sample size was conducted to test the difference in a dichotomic manner. Secondly, the amplitude and latency of the various peaks in the C3 and C4 derivations before and after loading were compared using a nonparametric Kruskall-Wallis analysis of variance. Differences were considered significant when the probability of a type I error was <5%.

Results

Diaphragm function

Before loading, the $P_{di,max}$ values in the nine subjects ranged 50–160 cmH_2O (88±35 cmH_2O), and the $P_{di,tw}$ values were 27.25±5.52 cmH_2O, within the normal range [18]. The time to task failure ranged 12–34 min. In one subject, $P_{di,tw}$ was unaffected by the procedure. This subject was therefore excluded from the analysis. In one additional subject, $P_{di,tw}$ decreased by >10% but the $P_{es,tw}$:$P_{ga,tw}$ also decreased. This individual was also excluded from the analysis, which was therefore conducted in seven subjects who met the predefined criteria for a predominant diaphragmatic change ($P_{es,tw}$: $P_{ga,tw}$ increased in six cases, unchanged in one). The average $P_{di,tw}$ after loading was 19.91±6.46 cmH^2O, namely a 28±13% reduction (fig. 1) (p=0.018, power 85% for an alpha value of 0.05). The average reductions in $P_{es,tw}$ and $P_{ga,tw}$ were 14±8% (p=0.009) and 51±25% (p=0.002), respectively. The amplitudes of the electromyographical responses to phrenic stimulation were unaffected by the loading protocol (see Materials and methods).

Respiratory-related evoked potentials

Averaging the EEG signal corresponding to unoccluded breaths did not yield any potential. At baseline, RREP were identified in all subjects (table 1, table 2, and fig. 2). The P1, N1 and P2 components were present in either C_3 or C_4 in the seven cases, and bilaterally in four. The N2 component was present in either C3 or C4 in six cases, and again bilaterally in four. After acute loading, the P1 and N1 components were also present in either C3 or C4 in the seven cases (always homolaterally as compared with baseline condition), and bilaterally in four. The P2 and the N2 components were present in either C3 or C4 in five cases, and bilaterally in four. There was no statistically significant difference regarding the number of occurrences of the components before and after fatigue (Chi-squared test, see methods). Among the seven subjects, the comparison of the amplitudes and latencies of the components before and after fatigue did not yield any significant difference (Kruskall-Wallis test, see Materials and methods).

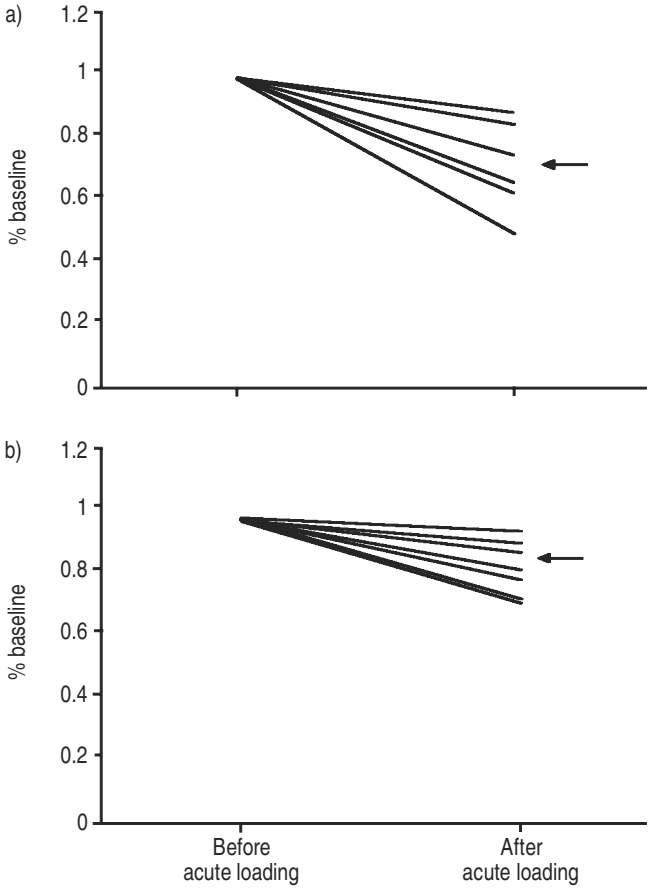

Fig. 1.–The effects of the acute inspiratory resistive loading protocol on the capacity of the diaphragm to produce a) transdiaphragmatic pressure and b) oesophageal pressure in the seven subjects retained for analysis. The "after" values are expressed in percentage of the "before" ones. The horizontal arrows indicate the mean of the "after" values.

Discussion

In this study, the characteristics of RREP were unaffected by an inspiratory resistive challenge imposed on healthy subjects to the point of task failure. This challenge resulted in an overt reduction of the transdiaphragmatic pressure produced in response to phrenic stimulation (28±13%). The pattern of this reduction suggested a predominant impact on the diaphragm, rather than on extradiaphragmatic inspiratory muscles (although some degree of rib cage muscle dysfunction cannot be completely excluded in the absence of comparison of CMS with electrical phrenic nerve stimulation) [16].

Of note, the effects of loading on the response to phrenic stimulation were assessed after the collection of the RREP data, namely ~15 min after task failure. The observed lack of

Table 1. – Latencies of the components of the respiratory-related evoked potentials (RREP) before and after inspiratory loading in the C_Z-C3 and C_Z-C4 scalp positions

	C_Z-C3				C_Z-C4			
	Before fatigue	n#	After fatigue	n#	Before fatigue	n#	After fatigue	n#
P1	38.30±5.96	5	38.80±3.90	5	38.00±3.32	5	37.83±3.13	6
N1	91.42±19.39	6	96.25±18.08	6	88.83±21.55	6	94.30±16.36	5
P2	144.83±23.15	6	146.70±22.04	5	129.67±18.00	6	131.50±23.98	4
N2	219.10±8.65	5	209.10±9.79	5	198.80±16.16	5	191.00±18.50	4

Data are presented as mean±SD ms. The peak latencies of the first positive (P1) and first negative (N1) components of the RREP were present at least unilaterally in the seven cases, both before and after fatigue, in a homolateral manner. P2: peak latency of second positive component of the RREP; N2: peak latency of the second negative component of the RREP. #: indicates the number of occurrences of the different components in the seven subjects retained for analysis.

Table 2. – Amplitudes of the components of the respiratory-related evoked potentials (RREP) before and after inspiratory loading in the C_Z-C3 and C_Z-C4 scalp positions

	C_Z-C3				C_Z-C4			
	Before fatigue	n#	After fatigue	n#	Before fatigue	n#	After fatigue	n#
P1	2.88±1.55	5	2.80±0.84	5	2.44±0.95	5	2.25±0.94	6
N1	-4.15±2.00	6	-4.62±1.08	6	-3.62±0.94	6	-3.76±0.74	5
P2	2.77±1.15	6	2.94±0.66	5	2.35±0.72	6	1.90±0.67	4
N2	-3.36±0.76	5	-2.94±0.57	5	-3.32±0.69	5	-2.80±0.57	4

Data are presented as mean±SD μV. The peak latencies of the first positive (P1) and first negative (N1) components of the RREP were present at least unilaterally in the seven cases, both before and after fatigue, in a homolateral manner. P2: peak latency of second positive component of the RREP; N2: peak latency of the second negative component of the RREP. #: indicates the number of occurrences of the different components in the seven subjects retained for analysis.

change in these variables is thus not likely to be due to the effects of loading on inspiratory muscle function having waned between task failure and data collection.

RREP represent the respiratory counterpart of somatosensory evoked potentials. They correspond to the activity of cortical neurons in response to a mechanical inspiratory stimulus. Their first positive component, P1, is considered to reflect the cortical arrival of the afferent stimulus [24]. Their later components are considered to reflect the cortical processing of the afferent information. Identifying the determinants of the RREP is important, because this could provide a means to objectively quantify some aspects of respiratory sensations, and to assign objective numerical values to their changes after an intervention. In this view, the

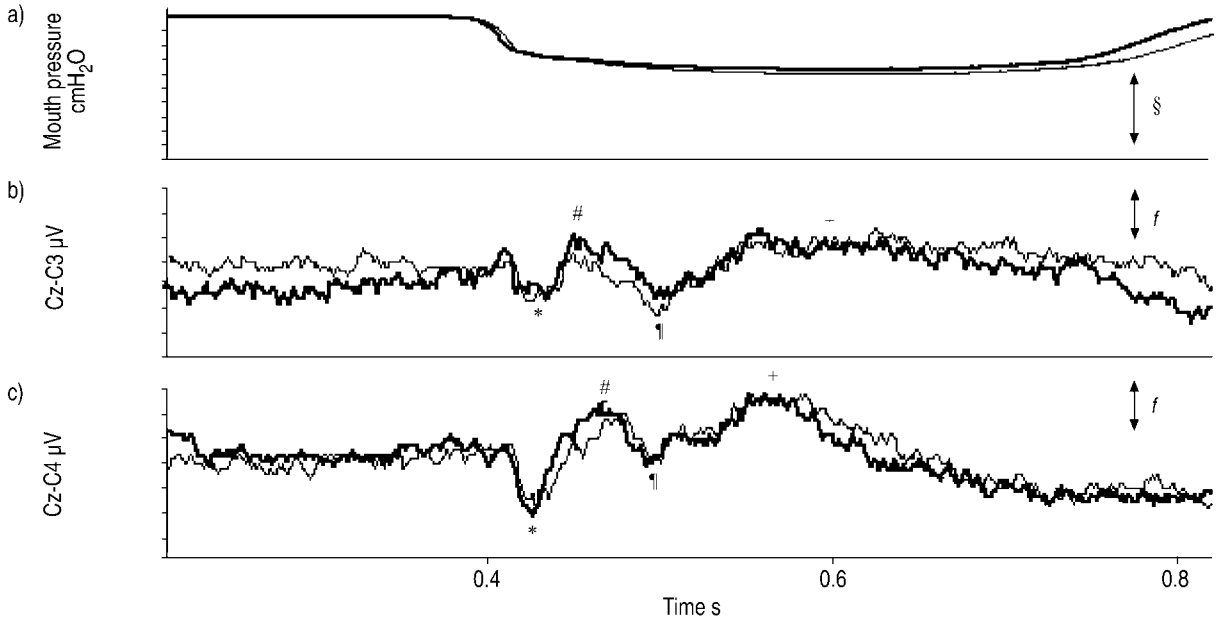

Fig. 2. – Example, in one subject, of respiratory-related evoked potentials including a) mouth pressure, b) C_Z-C3 and c) C_Z-C4, before (–) and after (–) the acute loading protocol. Each trace in b) and c) corresponds to the ensemble averaging of two separate superimposable traces obtained from 80 mid-inspiratory occlusions. *: first positive; #: first negative; ¶; second positive; +: second negative; §: 5 cmH_20; f: 2 μV.

P1 component appears particularly important. Its latency relates to the intensity of the inspiratory motor drive [23]. Its amplitude increases with the level of inspiratory effort developed to overcome a load [13]. The estimated magnitude of an inspiratory load relates to the amplitude of P1 [12, 13]. In children having suffered near-fatal attacks of asthma (as opposed to "normal" asthmatic children and controls) [25], it has been shown that the RREP could lack the P1 peak, a finding that fits with the blunted perception of loads featured by severe asthmatics [2].

Many structures throughout the respiratory system can theoretically give rise to the afferent information underlying the RREP, but their location and nature are not precisely known. Data in lung transplant recipients suggest that vagally mediated afferents do not play a significant role [26]. Conversely, the role of the supraglottic receptors located in the upper airway is probably major [27], but currently available data leave open the possibility of downstream sources. These include the respiratory muscles. KNAFELC and DAVENPORT [13] indeed reported that the P1 peak amplitude increased in relation to the intensity of the inspiratory effort required to overcome a load. From another point of view, HUANG *et al.* [28] studied RREP in healthy subjects before and after inspiratory muscle training. In this study, inspiratory muscle strengthening, as ascertained by an increase in the subjects′ ability to develop static inspiratory pressures, was associated with a significantly decreased motor drive to breathe. Globally, this study did not evidence statistically significant changes in the RREP. However, restricting the analysis to the somatosensory electrodes, the authors noted a significant reduction in the amplitude of the P1 component after training. It thus appears that acutely modifying the load imposed on inspiratory muscles [13] or chronically modifying their ability to develop inspiratory pressures [28] can change at least the characteristics of the P1 peak of the RREP. How the various inspiratory muscle groups (including the diaphragm) contribute to these changes is not known. Indeed, in the study by KNAFELC and DAVENPORT [13], the relationship between the amplitude of P1 and the inspiratory effort was present when the inspiratory effort was judged in terms of transdiaphragmatic pressure, but also in terms of the non-specific oesophageal and mouth pressures. The training protocol used by HUANG *et al.* [28] did not put emphasis on any particular inspiratory muscle group. However, elucidating the respective contribution of afferents from the diaphragm and from other inspiratory muscles is of pathophysiological relevance because load-related dyspnoeic sensations differ when extradiaphragmatic inspiratory muscles, rather than the diaphragm, are predominantly involved in the load response [14, 15]. This could influence the determinants of dyspnoea in diseases affecting inspiratory muscle groups differentially.

In subjects in the current study, modifying the ability of the diaphragm to produce inspiratory pressures did not result in significant changes in the characteristics of the various components of the RREP. In the hypothesis of an actual contribution of respiratory muscles to RREP, this does not exclude the diaphragm as a sensory information source, but suggests that the sensory processing arises from more than just the diaphragm and involves several inspiratory muscle groups. This result is in line with various types of data relating respiratory muscle function and respiratory sensations. Indeed, global inspiratory muscle dysfunction or fatigue, as induced by partial curarisation [6] and exhaustion following repeated maximal static inspiratory efforts [5] lead to the overestimation of inspiratory loads. Conversely, respiratory sensations seem preserved in situations where inspiratory muscle groups are altered separately. BRADLEY *et al.* [29], producing shifts in the high-to-low ratio of the frequency content of the diaphragmatic electromyographical signals through a loading protocol similar to that used in the current study, reported that the sense of inspiratory effort was independent of diaphragm fatigue. FITTING *et al.* [15] reported that the perceived magnitude of an inspiratory effort exerted against a load was independent of the emphasis put on the diaphragm. FRANKEL *et al.* [30] described the case of a tetraplegic patient with diaphragm atrophy but preserved inspiratory neck muscles in whom the perception and magnitude estimation of inspiratory loads were normal. Conversely, SINDERBY *et al.* [31] established a link between respiratory effort sensation and the frequency content of diaphragm electrical activity, but their loading protocol might however have led to global inspiratory fatigue.

In the above paragraphs, it was assumed that inspiratory muscle afferents contribute directly to the origin of the RREP, and therefore that inducing a predominant diaphragm dysfunction did not suffice to suppress this contribution. Alternatively, the generation of the airway occlusion-related evoked potentials measured in unloaded conditions could be independent from the strength of the inspiratory muscles. This hypothesis could be tested by studying the changes in the amplitude of P1 elicited by graded inspiratory resistances (instead of complete occlusions) before and after inspiratory fatigue. Of note, the results from the current study do not exclude modifications of the RREP as they would be measured during the loading challenge itself rather than after task failure. Indeed, diaphragm fatigue activates type IV afferents originating in respiratory muscles [32], which could account for the diaphragm-fatigue related changes in cortical potentials that have been described in the cat [11]. Finally, the contribution of respiratory muscle afferents to the RREP (a plausible possibility in view of intercostal and phrenic source of evoked potentials) [8–10] could be either inexistent or extremely small. In support of the latter idea, bypassing most of the upper airway with a laryngeal mask dramatically reduces the amplitude of the various components of the RREP [27].

In part, because of the relatively small size of the population studied, further studies are needed to clarify several issues raised from the current study. It would, in particular, be useful to correlate, in the same subjects and at the same time, the evolution of RREP and load detection and estimation after various types of interventions. However, the results support the notion, apparent in the literature, that an acute decrease in diaphragm function does not suffice to modify the sensory processing of inspiratory loads. Thus, there could be a redundancy between afferents from the diaphragm and afferents from other inspiratory muscles, which, considering respiratory sensations as an alarm system, could serve a safety purpose (this is similar to the notion that diaphragm fatigue does not prevent the inspiratory muscle system as a whole to adequately respond to hypercapnia [33]). This could have implications in the understanding of the mechanisms of dyspnoea during various types of respiratory disease.

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étude 2

Contribution des voies aériennes supérieures aux potentiels évoqués respiratoires

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Upper airway afferents are sufficient to evoke the early components of respiratory-related cortical potentials in humans.

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1. objectif

De nombreuses afférences pourraient, à priori, être à l'origine des potentiels évoqués respiratoires. Cependant, Daubenspeck et coll. ont montré que la ventilation à travers un masque laryngé, créant ainsi un court-circuit des voies aériennes supra-glottiques, réduisait considérablement l'amplitude des potentiels évoqués respiratoires (11). Ce résultat suggérait que les mécanorécepteurs des voies aériennes supra glottiques exerçaient une fonction déterminante dans la constitution des potentiels évoqués respiratoires.

Le but de notre étude a été de préciser le rôle des voies aériennes supérieures dans l'origine des potentiels évoqués respiratoires, grâce à l'étude de potentiels évoqués respiratoires chez des patients trachéotomisés.

2. méthodes

Nous avons comparé les potentiels évoqués respiratoires obtenus lors de la ventilation par les voies aériennes « naturelles » (au travers un embout buccal) aux potentiels évoqués respiratoires obtenus lors de la ventilation au travers de la canule de trachéotomie chez huit patients. Quatre de ces patients étaient tétraplégiques. Ils ventilaient grâce à un stimulateur phrénique implanté. Leur inspiration résultait donc de la production d'une pression intra-thoracique négative, comme l'inspiration physiologique.

3. résultats

Des potentiels évoqués ont été mis en évidence chez tous les patients lors de la ventilation sur embout buccal, au moins dans l'une des dérivations de recueil, C3-Cz ou C4-Cz.

Les occlusions réalisées lors de la ventilation par la canule de trachéotomie, voies aériennes supérieures exclues, n'ont évoqué de potentiel chez aucun patient.

4. conclusions

Chez les patients trachéotomisés non tétraplégiques, l'absence de potentiels évoqués respiratoires lorsque les voies aériennes supra-glottiques sont exclues, suggère que la source principale de ces potentiels ne réside pas au niveau des voies aériennes sous-glottiques, des muscles inspiratoires ou de la paroi thoracique.

Chez les patients tétraplégiques, les afférences provenant de la paroi thoracique et des muscles intra thoraciques sont interrompues. La présence de la composante P1 lorsque les occlusions sont réalisées à la bouche de ces patients, montre donc que les afférences provenant des voies aériennes ou des poumons suffisent à l'obtention de cette composante. Les occlusions inspiratoires lors de la ventilation sur canule de trachéotomie, en revanche, n'étaient susceptibles de stimuler que des afférences sous-glottiques véhiculées par le nerf vague. Comme ce type d'occlusion n'a pas évoqué de potentiels, notre étude est en faveur d'un rôle minime voire nul de telles afférences dans la constitution des potentiels évoqués respiratoires. Cependant, il demeure impossible d'exclure formellement la présence de potentiels évoqués corticaux dont l'amplitude serait minime et qui seraient masqués, chez ces patients, par le bruit électrique du stimulateur phrénique.

Dans une étude récente, Davenport et coll., ont mis en évidence des potentiels évoqués respiratoires, lors d'occlusions sur canule de trachéotomie chez deux patients ayant bénéficié d'une transplantation bi-pulmonaire (18). Les conditions d'enregistrement de l'électroencéphalogramme étaient différentes de celles utilisées dans nos études puisque cette équipe a utilisé une référence extra céphalique (oreilles jointes). Les auteurs de ce travail soulignent par ailleurs que les patients étudiés ne présentaient pas de pathologie neuromusculaire ou respiratoire, à la différence de ceux de notre étude. Cependant, les amplitudes des potentiels évoqués lors des occlusions sur canule de trachéotomie semblaient nettement diminuées par rapport aux amplitudes des potentiels évoqués lors des occlusions à la bouche, ce qui rend ces résultats compatibles avec les nôtres.

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Upper airway afferents are sufficient to evoke the early components of respiratory-related cortical potentials in humans

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Donzel-Raynaud, Christine, Christian Straus, Michela Bezzi, Stefania Redolfi, Mathieu Raux, Marc Zelter, Jean-Philippe Derenne, and Thomas Similowski. Upper airway afferents are sufficient to evoke the early components of respiratory-related cortical potentials in humans. *J Appl Physiol* 97: 1874–1879, 2004. First published June 25, 2004; doi:10.1152/japplphysiol.01381.2003.—Repeated inspiratory occlusions in humans elicit respiratory-related cortical potentials, the respiratory counterpart of somatosensory-evoked potentials. These potentials comprise early components (stimulus detection) and late components (cognitive processing). They are considered as the summation of several afferent activities from various part of the respiratory system. This study assesses the role of the upper airway as a determinant of the early and late components of the potentials, taking advantage of the presence of a tracheotomy in patients totally or partially deafferented. Eight patients who could breathe either through the mouth or through a tracheotomy orifice (whole upper airway bypassed) were studied (4 quadriplegic patients with phrenic pacing, 4 patients with various sources of inspiratory pump dysfunction). Respiratory-related evoked potentials were recorded in C_Z-C_3 and C_Z-C_4. They were consistently present after mouth occlusions, with a first positive P1 and a first negative N1 components of normal latencies (P1: 40.4 ± 6.1 ms in C_Z-C_3 and 47.6 ± 7.6 ms in C_Z-C_4; N1: 84.4 ± 27.1 ms in C_Z-C_3 and 90.2 ± 17.4 ms in C_Z-C_4) and amplitudes. Tracheal occlusions did not evoke any cortical activity. Therefore, in patients with inspiratory pump dysfunction, the activation of upper airway afferents is sufficient to produce the early components of the respiratory-related evoked cortical potentials. Per contra, in this setting, pulmonary afferents do not suffice to evoke these components.

somatosensory evoked potentials; visceral afferents; respiratory sensations; dyspnea

RESPIRATORY-RELATED EVOKED potentials reflect the activity of cortical neurons in response to occlusions of the airway at the mouth during inspiration (4). They represent the respiratory counterpart of somatosensory evoked potentials. Typically, they begin with a first positive component (P1, 40–60 ms after the beginning of the load-related change in mouth pressure), considered to reflect the cortical arrival of the afferent message (6). It is at times referred to as "exogenous." P1 is followed by a negative component N1 and by later components positive and negative again (P2 and N2). P2 and N2 are considered to reflect the cognitive processing of the sensory information (6), as do further components occurring ~300 ms after the stimulus, e.g., the P3 component discussed by Zhao et al. (18). Indeed, the late components (at times referred to as "endogenous") are influenced by attention. N1 may have an intermediate status between exo- and endogenous (precognitive processing). Respiratory-related evoked potentials are considered to be the neurophysiological substrates of certain types of respiratory sensations. In support of this contention, the amplitude of their P1 peak increases with the level of inspiratory pressures developed to overcome a load (12, 13), and this increase parallels the magnitude estimation of the corresponding load (12, 13). In children having suffered near-fatal attacks of asthma (as opposed to other asthmatic children and to controls) (3), the respiratory-related evoked potentials can lack a feature that is consistent with the blunted perception of loads featured by severe asthmatic patients (11). Respiratory-related evoked potentials may provide insights into the cortical processes underlying perception of respiratory sensations and thus could lead to better understanding of dyspnea, hence the physiological and clinical relevance of studying their determinants.

The respiratory afferent system is inherently and necessarily redundant, and many structures can contribute to the respiratory-related evoked potentials. These potentials are thus considered to represent the summation of several afferent activities, possibly arising from the upper airway (2) and from downstream sources such as the bronchi, the lungs, the respiratory muscles, or the chest wall. In support of this contention, studies of double-lung transplantation patients have shown that elimination of pulmonary afferents slows down the late components of the cortical potentials after an inspiratory occlusion and decreases their amplitude (18). This is interpreted as an impairment of the cognitive processing of the stimulus due to an impoverishment of its sources (18). However, selective deafferentation does not significantly alter the early cortical components after an inspiratory occlusion (18). This could indicate that pulmonary afferents play no role in the origin of these components or that this role is considerably less important than that of other structures, including the upper airway. This would be in line with the results reported by Daubenspeck et al. (2), who, studying the respiratory-related evoked potentials in terms of global field power, described major alterations

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in both the early and late activity evoked by brief negative pressure pulses applied through a laryngeal mask. With this technique, most of the upper airway is bypassed, but laryngeal afferents, which are very dense (16), are still apt to contribute to the cortical responses to respiratory stimuli. The present study was designed to determine whether the upper airways are sufficient for these responses to occur: in patients in whom the upper airway could be completely bypassed owing to the presence of a tracheotomy, the cortical responses to inspiratory occlusions applied at the mouth were compared with the cortical responses to occlusions applied at the tracheotomy orifice.

METHODS

After completion of the French legal procedure for human biomedical research, eight tracheotomized patients were enrolled (2 women, 6 men; 48 ± 19 yr). They were informed in detail of the purpose of the study and methods used and gave written consent. The tracheotomy had been performed because of chronic respiratory failure in four cases (chronic obstructive pulmonary disease, $n = 2$; kyphoscoliosis, $n = 1$; diaphragmatic dysfunction, $n = 1$) and because of respiratory paralysis after high cervical spinal lesions in four patients in whom negative-pressure breathing was provided by phrenic nerve pacing. The quadriplegic patients suffered from C_1 to C_3 complete spinal section, documented by magnetic resonance imaging and leading to complete paralysis and sensory deafferentation below the lesion. The quadriplegic patients breathed permanently through their tracheotomy. The nonquadriplegic ones also breathed permanently through their tracheotomy, using a positive-pressure ventilator during the night and breathing spontaneously during the day.

The patients were studied seated in a reclining lounge chair or semireclined in bed, with the back, neck, and head comfortably supported. They were instructed to relax but to keep their eyes open to avoid any risk of falling asleep or producing slow brain waves. They wore earplugs and headphones through which they listened to a quiet musical piece of their choice to mask auditory cues. The breathing circuit was firmly held by a metallic frame at the level of the mouth to minimize artifacts due to the activity of facial muscles. Three of the quadriplegic patients received baclofen orally, against spasticity. One of the nonquadriplegic patients received inhaled bronchodilators. None of the patients was under psychotropic or sedative medication at the time of the study.

The patients breathed alternatively through a mouthpiece (wearing a nose clip) or through their tracheal cannula (tracheal cuff inflated). In both cases, the airway opening was connected to a heated pneumotachometer (Hans Rudolf 3700, Kansas City, MO) combined with a ±2-cmH_2O linear differential pressure transducer (Validyne, Northridge, CA) to measure ventilatory flow and connected to a nonrebreathing valve (Hans Rudolf 2600) of which the inspiratory port could be occluded by an inflatable balloon (Hans-Rudolf 9340 occlusion valve and 9330 compressor). Airway opening pressure was measured from a side port of the valve proximal chamber.

The electroencephalographic activity (EEG) was recorded by using standard surface electrodes placed at C_Z, C_3, and C_4 on the basis of the international 10–20 system. C_3 and C_4 were referenced to C_Z to record the left and right activity, respectively. Electrode impedances were maintained below 5 kΩ. Respiratory-related potentials were evoked by 400- to 500-ms midinspiratory occlusions (15), randomly presented every two to four breaths. Two series of 100 occlusions were presented in each of the mouth and trachea conditions (order of conditions randomized among subjects) interspaced by rest periods. The signals were sampled at 1 kHz over a 0.5- to 500-Hz bandwidth, digitized 100 ms before and 2 s after the inspiratory onset determined from the flow trace, and stored on an Apple MacIntosh computer.

Data analysis was performed offline. The individual presentations for a given trial were recalled from computer memory and displayed onscreen. The occluded inspirations were then selected by using the airway opening pressure signal. A given occluded breath was retained for averaging only in the presence of a stable EEG signal baseline and in the absence of obviously aberrant accidents. In addition, "control" trials were obtained by averaging the same number of unoccluded breaths. Four peaks were defined: P1, first positive deflection, 35–60 ms after the stimulus; N1, next negative deflection; P2 and N2, subsequent positive and negative deflections. For the mouth and the trachea conditions, the averaged tracings of the two series of occlusions performed were first superimposed to assess reproducibility. Then all the mouth occlusions were pooled together, and, on the other hand, all the trachea occlusions were pooled separately to obtain one set of measurements per patient. The latencies of the components were measured according to Davenport et al. (5). Amplitudes were measured from baseline to peak. Latencies and amplitudes were determined separately for each component at each site. Additionally, the occluded breaths retained for analysis in the eight patients were pooled together for each conditions (mouth and trachea). This grand averaging procedure was also applied separately to the four quadriplegic and the four nonquadriplegic patients.

The results are expressed as means ± SD. The comparison between the mouth and tracheal pressure drops after the inspiratory occlusions was conducted by using a paired *t*-test. A right-to-left comparison of the latencies and amplitudes of the potentials was conducted by using a paired *t*-test. The comparison between the mouth and trachea conditions was planned with the Fischer's exact test but finally was not performed in the absence of any potentials in the trachea condition (see RESULTS).

RESULTS

The number of averaged epochs was similar in both conditions (mouth: 151 ± 35, trachea: 166 ± 30).

The inspiratory occlusion related decreases in mouth pressure and in tracheal pressure were similar (7 ± 4 vs. 9 ± 6 cmH_2O, respectively, $P = 0{,}31$). This was true both in the quadriplegic patients (9 ± 4 vs. 11 ± 7 cmH_2O) and in the nonquadriplegic ones (5 ± 2 vs. 6 ± 2 cmH_2O).

An evoked activity was present at least in C_Z-C_3 or in C_Z-C_4 in all the patients in the mouth condition (Table 1, Figs. 1–3). This activity consisted of a P1 component in all cases (bilateral in 4 patients, unilateral in 1 of the nonquadriplegic patients and in 3 of the quadriplegic patients) with an average latency of 40.4 ± 6.1 ms in C_Z-C_3 and 47.6 ± 7.6 ms in C_Z-C_4, and with an average amplitude of 2.1 ± 1 μV in C_Z-C_3 and 2.6 ± 1.6 μV in C_Z-C_4. An N1 component was visible in seven cases, with an average latency of 84.4 ± 27.1 ms in C_Z-C_3 and 90.2 ± 17.4 ms in C_Z-C_4, and with an average amplitude of 3.1 ± 1.4 μV in C_Z-C_3 and a 3.1 ± 1.4 μV in C_Z-C_4. There was no significant right-to-left difference. In two quadriplegic patients, the first visible component in C_4 was N1 rather than P1. Table 2 shows that the characteristics of P1 and N1, when present, were roughly similar in the quadriplegic and nonquadriplegic patients. Overall, the full P1-N1-P2-N2 sequence was present bilaterally in only two cases and unilaterally in one case (the patient with chronic obstructive lung disease). The P2 and N2 components lacked bilaterally in all the quadriplegic patients and in one of the nonquadriplegic patients (the one suffering from diaphragmatic dysfunction).

Conversely, in the trachea condition, the inspiratory occlusions never evoked any identifiable EEG components, neither

Table 1. *Localization and occurrence of the various components of the respiratory-related evoked potentials elicited by inspiratory occlusions at the mouth in the eight patients (inspiratory occlusions at the tracheotomy orifice never elicited respiratory-related evoked potentials)*

	P1	N1	P2	N2
Quadriplegic patients				
Patient 1	C_4	C_3 and C_4	No	No
Patient 2	C_4	No	No	No
Patient 3	C_4	C_3 and C_4	No	No
Patient 4	C_3 and C_4	C_3 and C_4	No	No
Nonquadriplegic patients				
Patient 5	C_3 and C_4	C_3 and C_4	C_3 and C_4	C_3 and C_4
Patient 6	C_3 and C_4	C_3 and C_4	No	No
Patient 7	C_3 and C_4	C_3 and C_4	C_3 and C_4	C_3 and C_4
Patient 8	C_3	C_3	C_3	C_3

P1, first positive peak. N1, first negative peak. P2, second positive peak. N2, second negative peak. C_3, C_4, scalp positions for electroencephalogram.

early nor late (Figs. 1–3). This was the case in all the patients, quadriplegic and nonquadriplegic.

Averaging the data from the four quadriplegic patients (Fig. 2) showed the presence of the P1 component in response to mouth occlusions (but the averaging procedure suppressed the N1 response) and the absence of any cortical response after tracheal occlusions. Averaging the data from the four nonquadriplegic patients showed the same pattern with, in addition, the presence of the P2 and N2 components in the mouth condition (Fig. 3). Again, no cortical response was visible in response to tracheal occlusions.

DISCUSSION

This study demonstrates that, in patients with inspiratory pump dysfunction, the activation of upper airway afferents by inspiratory occlusions is sufficient to produce the early components of the respiratory-related evoked potentials.

Methodological considerations. Our study population is peculiar by its nature and its duality (cervical cord lesions in the 4 quadriplegic patients, marked respiratory abnormalities in the 4 nonquadriplegic ones). This implies that the interpretation of our data must be done carefully. In particular, it is not possible, from this study, to state that the upper airways are the sole source of the respiratory-related evoked potentials as a whole in normal humans. However, in our patients, inspiratory occlusions applied at the mouth consistently evoked cortical potentials resembling the respiratory-related evoked potentials observed in normal subjects or in other types of patients with the same technique. The latencies and amplitudes of the P1 and N1 components of these potentials were similar to values previously reported [P1 latencies of 48 ± 8 ms in C_Z-C_3 and of 46 ± 12 ms in C_Z-C_4, and N1 latencies of 86 ± 11 ms in C_Z-C_3 and of 87 ± 12 ms in C_Z-C_4 (15); comparable figures in asthmatic children (3)]. We feel that this permits the use of our data to discuss some of the mechanisms underlying the respiratory-related evoked potentials.

The lack of evoked activity in response to tracheal occlusions could be a function of the signal-to-noise ratio, P1 being reduced rather than suppressed in the trachea condition, and particularly so in the phrenic pacing patients in whom electronic noise could not always be suppressed (Fig. 2); however, we consistently failed to observe responses after tracheal occlusions, even in the best-quality tracings. Such an explanation would not, in view of the mouth-trachea differences, drastically change the interpretation of the results.

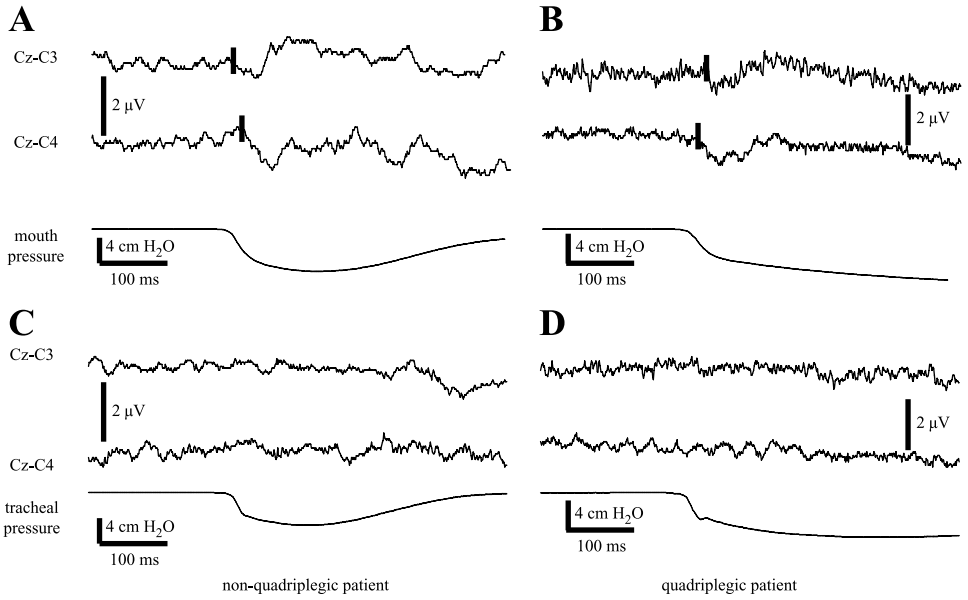

Fig. 1. Individual examples of the cortical responses after airway occlusions in 1 nonquadriplegic patient (*A* and *C*) and 1 quadriplegic one (*B* and *D*). *A* and *B*: application of the occlusions at the mouth. *C* and *D*: application of the occlusions at the trachea. The vertical marks denote the beginning of the respiratory evoked potentials.

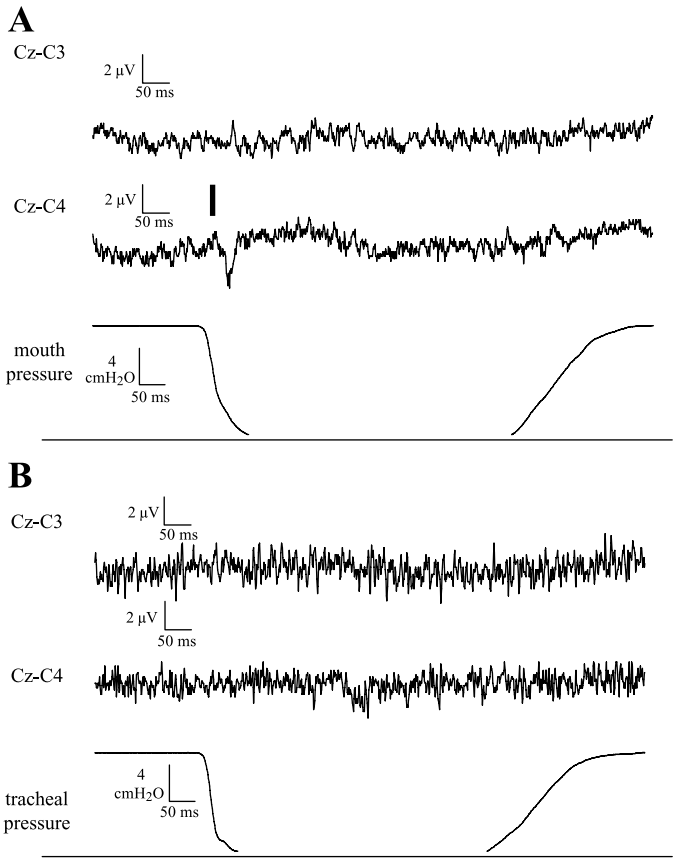

Fig. 2. Grand averaging of the cortical responses after airway occlusions in the subset of 4 quadriplegic patients with phrenic nerve pacing. *A*: application of the occlusions at the mouth (from *top* to *bottom*, averaged C_Z-C_3 electroencephalogram activity, averaged C_Z-C_4 electroencephalogram activity, and averaged mouth pressure). Vertical lines denote the beginning of the respiratory evoked potentials. *B*: application of the occlusions at the trachea (upper airway fully bypassed) (from *top* to *bottom*, averaged C_Z-C_3 electroencephalogram activity, averaged C_Z-C_4 electroencephalogram activity, and averaged tracheal pressure). No potential is discernible.

Information derived from the quadriplegic patients. In these patients, potential sources of respiratory-related evoked potentials only include the upper airway and lung vagal afferents, because the pathways from the rib cage and respiratory muscles are interrupted. The disappearance of the potentials after fully bypassing the airway implies that that vagal afferents do not constitute a sufficient source to the early components of the respiratory-related evoked potentials. This is consistent with the lack of change in these components reported by Zhao et al. (18) in double-lung transplant recipients. The persistence of P1 in response to mouth occlusions in quadriplegic patients indicates that such a response can be observed in the absence of any chest wall afferent information. Of note, P1 was present only unilaterally (right side) in three of these patients (Table 1). Numbers are far too small to draw conclusions at this stage, but if confirmed this observation could support the lateralization of certain of the mechanisms involved in respiratory sensations (see Ref. 14).

Information derived from the nonquadriplegic patients. In these patients, the compromise of the respiratory motor pump activity was not severe enough for inspiratory occlusion evoked potentials to be absent in the mouth study condition. The pressure drops observed after inspiratory occlusions at the trachea were of similar magnitude as those observed after inspiratory occlusions at the mouth (5 ± 2 vs. 6 ± 2 cmH_2O, respectively) and were above the threshold value needed to evoke respiratory-related potentials (13). Thus it does not seem possible to attribute the differences between the mouth and the trachea conditions in this subset of our study population to a decreased output of the respiratory muscles. This confirms that upper airway afferents are sufficient for the early components of the respiratory-related evoked potentials to form.

Nevertheless, the afferent information from the chest wall was probably not normal in these patients. This may account for the fact that the respiratory-related potentials evoked by mouth occlusions were different from what would have been expected in normal subjects. The full P1-N1-P2-N2 sequence indeed lacked in six of eight cases (the four quadriplegic patients, plus the patient with a documented severe diaphragmatic dysfunction and the patient with chronic obstructive lung disease). This could indicate that respiratory muscle and chest wall afferents are necessary for the late components of the respiratory-related evoked potentials to occur after the early one.

Role of upper airway and nonupper airway afferents. Our study shows that in patients breathing through a tracheotomy, namely with the whole upper airway fully bypassed, there is a

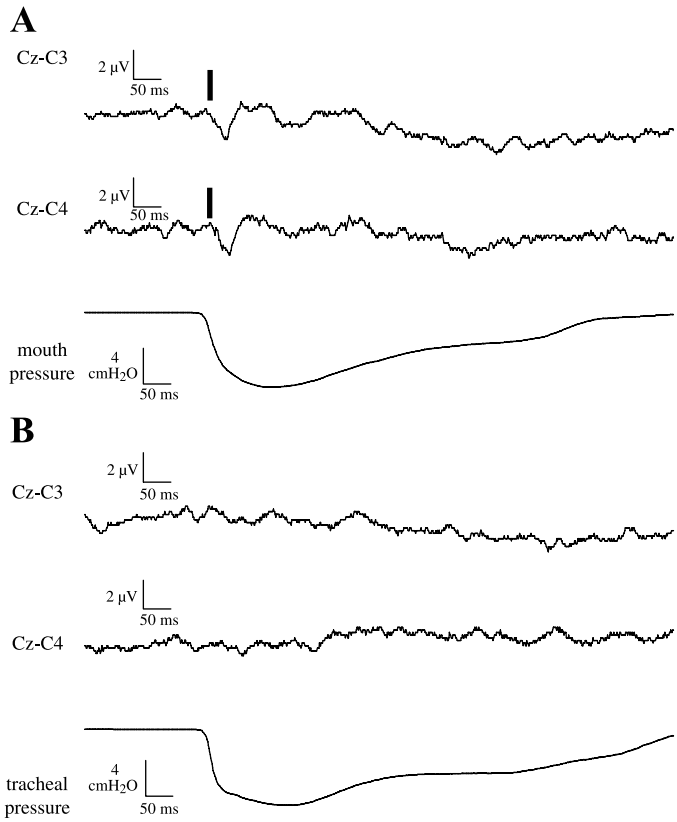

Fig. 3. Grand averaging of the cortical responses after airway occlusions in the subset of 4 nonquadriplegic patients. *A*: application of the occlusions at the mouth (from *top* to *bottom*, averaged C_Z-C_3 electroencephalogram activity, averaged C_Z-C_4 electroencephalogram activity, and averaged mouth pressure). Vertical lines denote the beginning of the respiratory evoked potentials. *B*: application of the occlusions at the trachea (upper airway fully bypassed) (from *top* to *bottom*, averaged C_Z-C_3 electroencephalogram activity, averaged C_Z-C_4 electroencephalogram activity, and averaged tracheal pressure). No potential is discernible.

Table 2. *Latencies and amplitudes of the various components of the respiratory-related evoked potentials elicited by inspiratory occlusions at the mouth in the four quadriplegic and the four nonquadriplegic patients*

	Quadriplegic Patients (n = 4)				Nonquadriplegic Patients (n = 4)			
	P1	N1	P2	N2	P1	N1	P2	N2
Cz-C3	48	73±30			39±5	93±25	124±34	214±74
Latency, ms	(n=1)	(n=3)			(n=4)	(n=4)	(n=3)	(n=3)
Cz-C3	2.2	−3.8±1.9			1.9±1.3	−1.7±0.5	2.3±1.3	−2.4±1.8
Amplitude, μV	(n=1)	(n=3)			(n=4)	(n=4)	(n=3)	(n=3)
Cz-C4	49±6	87±20			45±10	91±14	163±3	227±26
Latency, ms	(n=4)	(n=3)			(n=3)	(n=3)	(n=2)	(n=2)
Cz-C4	3.5±1.7				2.6±0.7	−2.3±1.9	1.4±0.6	−1.6±1.4
Amplitude, μV	(n=4)	−4.7±4			(n=3)	(n=3)	(n=2)	(n=2)

Values are means ± SD; *n*, no. of subjects.

complete abolition of the cortical activity in response to inspiratory occlusions as recorded on the scalp with our montage. The contribution of the upper airway to respiratory-related evoked potentials has been established before by Daubenspeck et al. (2), who showed that bypassing most of the upper airway with a laryngeal mask dramatically modified the cortical potentials evoked by negative pressure pulses (17). In this study, subglottal receptors contributed <40% to the global field power of these potentials. However, Daubenspeck et al. did not observe an eradication of the response. This can be interpreted as reflecting a contribution of downstream afferents (namely from the lungs, bronchi, respiratory muscle, or chest wall) to the cortical potentials. This can also be due to the fact that a laryngeal mask, by definition, does not bypass the entire upper airway. With such a device in place, the vocal cords and the larynx would still be exposed to the stimulus arising from an inspiratory occlusion or a negative pressure pulse. These structures having a very rich somatosensory innervation (the larynx is the most densely innervated region of the upper airway; see Ref. 16) could account for the persistence of the cortical activity described by Daubenspeck et al. It should be noted that the pressure drops after inspiratory occlusions tended to be greater in our quadriplegic patients than in the nonquadriplegic patients (Figs. 2 and 3). The amplitude of the P1 component also tended to be greater in the quadriplegic patients than in the nonquadriplegic ones (Figs. 2 and 3, Table 2). Although caution is needed because of small numbers and a different experimental paradigm, this is consistent with the data reported by Knafelc and Davenport (12), suggesting a relationship between the magnitude of the somatosensory dipole (amplitude of P1) and the magnitude of the afferent activation (airway pressure).

Our study also confirms that vagally mediated afferents and chest wall afferent have little role if any in the constitution of the P1 component of the respiratory-related evoked potentials. This does not contradict the current knowledge on the topic. Regarding respiratory muscle afferents, Huang et al. (9) observed some changes in the early components of the respiratory-related evoked potentials after inspiratory muscle training. These changes were not statistically significant, perhaps because of a very conservative statistical treatment. However, Bezzi et al. (1) failed to observe any difference in the amplitudes and latencies of P1 after an experimentally induced acute diaphragm dysfunction. Regarding vagally mediated afferents, Zhao et al. (18), studying double-lung transplant recipients, found that these patients did not differ from controls in terms of the P1 and N1 components. In the presence of the P1 component (namely after stimulation of upper airway afferents), the lack of later components in most of our patients suggests that chest wall afferents could contribute to the constitution of the typical P1-N1-P2-N2 sequence that is normally observed in response to an inspiratory occlusions and perhaps also to the further components of the response (P3, which our experimental montage was not apt at detecting). The same reasoning applies to vagally mediated afferents. Indeed, Zhao et al., if they did not observe modifications of P1 in the lung transplant recipients that they studied (see above), showed that these patients differed from the controls by a prolonged central processing time (defined as the difference in latency between P1 and P3) and by a reduced amplitude of P3 (18).

The differential contributions of the various afferents to the successive components of the respiratory-related evoked potentials could perhaps be explained by difference in the time variance of signals. An occlusion applied at midinspiration will cause a sharp change in extrathoracic airway transmural pressure likely to cause a sharp volley in mechanoreceptor action potentials, lending itself to generation of evoked potentials. Conversely, there will be no sharp change in transpulmonary pressure, only a leveling off. Lung receptors will thus be weakly stimulated. Chest wall receptors are also likely to be weakly stimulated, and less synchronously so with mouth pressure than with upper airway afferents.

Nature of the stimulus. Somatosensory potentials are elicited by a stimulation that is external to the subject. Conversely, inspiratory occlusion-related potentials arise from a negative pressure stimulus built up by the inspiratory activity of the subject. However, upper airway pressure changes can give rise to cortical potentials independently of any active behavior [namely, protoinspiratory negative pressure pulses (17), negative expiratory pressure time locked to expiration (7), or respiratory occlusions performed during tidal (hence passive) expiration (8)]. From these results and from our observations, it can be postulated that the upper airway serves as a "transducer" relaying the pressure prevailing within the respiratory system to the brain. This is compatible with the observation by Grippo et al. (7) of a relationship between the amplitude of the cortical response and the level of expiratory transmural pressure applied to the airway. This is also compatible with the observations of Peiffer et al. (14), who found a positive correlation between the amplitude of mouth pressure swings during inspiratory resistive breathing and the regional cerebral blood flow in the right anterior insula, cerebellar vermis, and

medial pons. The regional cerebral blood flow in these brain regions was also correlated with the perceived intensity of respiratory discomfort. Isaev et al. (10) confirmed the idea of a relationship between airway pressure, cerebral activation, and respiratory sensations. They observed that the sudden application of an inspiratory resistive load to normal subjects induced significant activations in inferior parietal cortex, prefrontal cortex, midbrain, basal ganglia, and multiple cerebellar sites (but no activations in the primary sensorimotor cortex). They postulated that there is a pattern of motor behavioral response to the uncomfortable sensation that inspiration is impeded, which results in breathing pattern modifications reducing the degree of discomfort, presumably because of the reduction of mean negative pressure in the airways. This hypothesis (upper airway as a relay between inspiratory pressures and the brain) fits with the link between the amplitude of the P1 peak of the respiratory-related evoked potentials and the magnitude of an inspiratory effort that has been reported by Knafelc and Davenport (13).

In conclusion, data available from the literature and the present study suggest that *1*) removal of the whole airway in patients with inspiratory pump dysfunction makes the cortical response to inspiratory occlusions undetectable, because this prevents the initial component of this response to occur or dramatically reduces it; and *2*) multiple afferent sources, including the upper airway, vagally mediated afferents, and respiratory pump afferents, are necessary for the "normal" cortical response to inspiratory occlusion to fully develop (P1-N1-P2-N2 sequence and later components). Although they should be confirmed in normal subjects, our results should help interpretation of respiratory-related evoked potentials and possibly contribute to a better understanding of respiratory sensations in patients with known upper airway diseases or abnormalities.

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étude 3

Effet de l'anesthésie des voies aériennes supérieures sur les caractéristiques des potentiels évoqués respiratoires

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1. objectif

L'étude précédente, portant sur la contribution des voies aériennes supérieures aux potentiels évoqués respiratoires (étude 2), était en faveur d'un rôle important des afférences provenant des voies aériennes supérieures supra-glottiques et glottiques dans la constitution des potentiels évoqués respiratoires.

Les afférences des voies aériennes supérieures naissent de différents types de récepteurs (récepteurs sensibles à l'irritation, au débit, à la pression) qui peuvent être situés à plusieurs niveaux : muqueux, sous muqueux, intramusculaire ou articulaire (57, 64).

L'objectif de ce travail a donc été d'étudier l'effet de l'anesthésie locale des voies aériennes supérieures sur les composantes des potentiels évoqués respiratoires afin de tenter d'identifier les récepteurs jouant les rôles prépondérants.

2. méthodes

L'impact de l'anesthésie locale des voies aériennes supérieures sur les potentiels évoqués respiratoires a été étudié chez vingt-et-un sujets sains.

L'anesthésie locale était réalisée en appliquant une solution d'hydrochloride de lidocaïne 5% au niveau des fosses nasales, de la bouche et du pharynx jusqu'à abolition du réflexe nauséeux et insensibilité au toucher.

Chez six sujets, l'effet de la stimulation des récepteurs au froid par le menthol a également été étudié.

Enfin, les potentiels évoqués par des occlusions inspiratoires lors de la ventilation buccale, à travers un embout, et lors de la ventilation nasale, à travers un masque nasal, ont été comparés chez quinze sujets.

3. résultats

Les caractéristiques des potentiels évoqués respiratoires n'étaient pas différentes avant et après anesthésie locale des voies aériennes supérieures à la

lidocaïne que les occlusions soient réalisées lors de la ventilation sur embout buccal ou sur masque nasal.

L'inhalation de menthol n'entraînait pas non plus de modification des caractéristiques des composantes des potentiels évoqués respiratoires.

4. conclusions

Cette étude montre que l'anesthésie locale des voies aériennes supérieures n'affecte pas les potentiels corticaux évoqués par des occlusions en milieu d'inspiration appliquées lors de la ventilation au travers d'un embout buccal ou d'un masque nasal.

L'innervation des voies aériennes supérieures est très riche, comprenant différents types de récepteurs localisés au niveau muqueux, sous muqueux, musculaires et articulaires.

Nos résultats suggèrent donc que les afférences provenant des récepteurs sensibles à l'anesthésie locale ne contribuent pas de manière significative aux potentiels évoqués respiratoires. Par conséquent, la source des potentiels évoqués respiratoires ne réside probablement pas dans les récepteurs muqueux ou sous-muqueux des voies aériennes supérieures mais plutôt dans des récepteurs plus profonds, jonctionnels ou musculaires.

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Effects of upper airway anaesthesia on respiratory-related evoked potentials in humans

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ABSTRACT: Cortical potentials evoked by mid-inspiratory occlusion arise from numerous receptors, many of which are probably within the upper airway. Their precise nature is not known. The aim of the current study was to improve knowledge of this by studying the effects of topical upper airway anaesthesia on respiratory-related evoked potentials.

Respiratory-related evoked potentials were described through the averaging of electroencephalogram (EEG) epochs following mid-inspiratory occlusions (C_3–Cz; C_4–Cz). A total of 21 healthy volunteers (13 male, aged 22–52 yrs) were studied during mouth breathing, before and after topical upper airway anaesthesia (lidocaine). Moreover, 15 subjects were studied during nose breathing with and without anaesthesia. Six subjects were studied whilst inhaling L-menthol.

Typical potentials were present in all the subjects, their components featuring normal amplitudes and latencies. The route of breathing and upper airway anaesthesia did not modify the EEG responses to inspiratory occlusions, qualitatively or quantitatively, during mouth or nose breathing. L-menthol had no effect.

Upper airway receptors sensitive to topical anaesthesia are unlikely to contribute significantly to mid-inspiratory occlusion-evoked potentials. On the contrary, deeper receptors, such as joint and muscle receptors, could contribute dominantly to these potentials.

KEYWORDS: Dyspnoea, L-menthol inhalation, respiratory-related evoked potentials, upper airway, upper airway anaesthesia

Various respiratory stimuli can evoke cortical potentials in humans. These include direct stimulation of intercostal muscles [1] or phrenic nerve stimulation [2, 3]. Sudden pressure changes within the airway appear particularly apt at evoking cortical responses. These can be induced by: 1) occlusion of the airway at the mouth at the beginning of inspiration [4] or during it [5]; 2) occlusion of the airway at the mouth during expiration [6]; 3) the sudden application of inspiratory resistances [7]; and 4) the application of negative pressure pulses to the airways during inspiration [8] or expiration [9].

The study of the cortical activity in response to respiratory events is a powerful means to improve the physiological knowledge of the relationship between the respiratory system and the brain. By extension, this type of research could lead to a better understanding of the mechanisms underlying certain respiratory sensations through the establishment of the corresponding neurophysiological substrates. Examples of such perspectives are given in the study by KNAFELC *et al.* [10] relating some characteristics of respiratory-related evoked potentials to the magnitude estimation of mechanical loads, or in the study by DAVENPORT *et al.* [11] identifying, in asthmatic children, an association between the lack of the early component of the respiratory-related evoked potentials and a past history of life-threatening asthma. Within this frame, understanding the very determinants of respiratory-related evoked potentials is an important prerequisite.

Although the cortical responses to pressure changes applied at the airway opening can reflect the activation of afferent pathways from various components of the respiratory system, several lines of evidence point to the upper airway as one of their major determinants. Indeed, DAUBENSPECK *et al.* [12], studying the potentials evoked by brief negative pressure pulses in terms of global field power, described major alterations in both the early and late cortical activity when the stimuli

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were applied through a laryngeal mask (that bypasses most of the upper airway but not laryngeal afferents). In tracheotomised patients suffering from inspiratory muscle pump dysfunction, DONZEL-RAYNAUD *et al.* [13] showed that applying mid-inspiratory occlusions to the trachea suppressed responses that were consistently present when occlusions were applied to the mouth.

The upper airway contains several types of receptors, including irritant receptors, and flow, pressure and ''drive'' receptors [14, 15], sensing changes in the prevailing status of the respiratory system. The location of these receptors range from mucosal or submucosal (*e.g.* the cold receptors activated by changes in flow, or laryngeal irritant receptors) to intramuscular and articular (*e.g.* the spindles and tendon organs of the numerous upper airway muscles, or joint receptors). Whether the cortical responses to airway pressure changes involve the stimulation of an array of these receptors or of one category preferentially is unknown. The present study was designed in an attempt to provide some answers to this question. Its aim was to take advantage of the different sensitivities of upper airway receptors to topical anaesthesia [14, 15] to better understand their respective contributions to the cortical responses following mid-inspiratory occlusions.

MATERIAL AND METHODS

Subjects and study conditions

A total of 21 healthy volunteers (13 male, eight female, aged 22–52 yrs, body mass index 19–30 $kg \cdot m^{-2}$) participated in the study after completion of the French legal procedure for human biomedical research. They received detailed information on the study and gave written consent.

The subjects were studied semi-reclined in a comfortable lounge chair with their back, neck and head comfortably supported. They were instructed to relax but to keep their eyes open in order to avoid any risk of falling asleep or producing slow brain waves. They wore earplugs and headphones through which they listened to a quiet musical piece of their choice, in order to mask auditory cues. The breathing circuit was firmly held by a metallic frame at the level of their mouth, in order to minimise artefacts due to the activity of facial muscles.

Measurements and procedures

Breathing apparatus

During the experiments involving mouth breathing (see later) the subjects, wearing a nose clip, breathed room air through a flanged mouthpiece attached to a heated pneumotachometer (Hans-Rudolf 3700; Hans-Rudolf, Kansas City, MO, USA) combined with a ± 2 cmH_2O linear differential pressure transducer (Validyne, Northridge, CA, USA) to measure ventilatory flow, and connected to a nonrebreathing valve (Hans-Rudolf 2600; Hans-Rudolf) of which the inspiratory port could be occluded by an inflatable balloon (Hans-Rudolf 9340 occlusion valve and 9330 compressor; Hans-Rudolf). Mouth pressure (P_m) was measured from a side port of the mouthpiece (DP 15–32 transducer, ± 50 cmH_2O; Validyne, Northridge, CA, USA). Of note, the inspiratory limb of the circuit was also equipped with a small reservoir in which it was possible to deposit L-menthol crystals (see later). During the experiments involving nose breathing (see later), the same apparatus was used, but the subjects breathed through an airtight nasal mask (Comfort Classic; Respironics, Nantes, France) to which the pneumotachometer was connected and within which mask pressure (P_{mask}) could be measured. Subjects were instructed to keep their mouth tightly closed.

Respiratory-related evoked potentials

Surface electrodes were placed over the somatosensory region of the cerebral cortex at CZ, C3, C4 on the basis of the international 10–20 system. C3 and C4 were referenced to CZ to record the left and right activity, respectively. Electrode impedances were maintained below 5 kΩ. Respiratory-related potentials were evoked by 400–500 ms mid-inspiratory occlusions [5], randomly presented every three to six breaths (mid-inspiratory occlusions were chosen, as in previous studies by the present authors [13, 16], because they give potentials ''sharper'' than those elicited by onset-inspiratory occlusions [5]). The signals were sampled at 1 kHz over a 0.5 Hz–500 Hz bandwidth (Neuropack Sigma®; Nihon Kohden, Tokyo, Japan), digitised 100 ms before and 2 s after the inspiratory onset determined from the flow trace, and stored on an Apple Macintosh computer for subsequent analysis (PowerLab®; AD instruments, Hastings, UK). Data analysis was performed off-line. The individual presentations for a given trial were recalled from computer memory and displayed on screen. The occluded inspirations were then selected using the P_m signal. A given occluded breath was retained for averaging only in the presence of a stable electroencephalogram (EEG) signal baseline and in the absence of obviously aberrant accidents. In addition, ''control'' trials were obtained by averaging the same number of unoccluded breaths. To ensure the immediate reproducibility of the signals, two separate averagings of 80 occluded breaths were systematically performed in each of the study conditions and the resulting traces superimposed. Ensemble averaging of all the traces was then performed.

The peak latencies of the first positive (P1), first negative (N1), second positive (P2) and second negative (N2) components of the respiratory-related evoked potentials were measured according to DAVENPORT *et al.* [17], from a ''zero'' point determined on the averaged P_m trace as the point of intersection of a line drawn through the P_m baseline with a second line drawn through the steepest portion of the P_m swing (MatLab5.3®; The Math Works, Natick, MA, USA). The amplitude of all the components was measured from baseline to peak.

Upper airway anaesthesia

A 5% lidocaine hydrochloride solution was sprayed in the nasal and buccal cavities until they were anaesthetised to touch. Subjects were asked to swallow the anaesthetic in order to achieve anaesthesia of the posterior pharynx. If necessary, additional xylocaine was administered up to the suppression of the gag reflex and then further sprayed as distally as possible from the posterior oropharynx. The total lidocaine dose necessary to achieve this result never exceeded 400 mg. All the subjects reported swallowing difficulties at the end of the procedure. Local sensitivity was tested during the interval between the two experimental runs performed under topical

anaesthesia (see later). To do this, the subjects were asked whether their bucco-pharyngeal sensations had changed and if the swallowing difficulties initially reported persisted. In addition, the posterior part of the pharynx was probed with a spatula and the subjects were asked if they felt the touch or felt nausea. If the answer was ''yes'' to any of these questions, additional lidocaine was administered.

Experimental design

Each experimental session consisted of a baseline evaluation made up of two separate series of inspiratory occlusions, followed by a ''test'' evaluation also made up of two separate series of inspiratory occlusions. Three sets of experiments were conducted, listed as follows. 1) Effects of upper airway anaesthesia on the cortical potentials evoked by inspiratory occlusions performed during mouth breathing. All 21 subjects participated in the current study. In six cases, additional recordings were made after a 90-min washout following anaesthesia. 2) Effects of upper airway anaesthesia on the cortical potentials evoked by inspiratory occlusions performed during nose breathing. A subset of 15 subjects participated in the present study, which was conducted on a separate day. 3) Effects of cold receptor stimulation on the cortical potentials evoked by inspiratory occlusions performed during mouth breathing. In six subjects, the inhalation of L-menthol (300 mg of L-menthol crystals deposited in the reservoir connected to the inspiratory limb of the breathing circuit) was used to stimulate upper airway flow receptors. A specific experimental session was performed according to the same design and procedures on a separate day. The effect of L-menthol was considered complete 5 min after the beginning of inhalation [18].

In addition, the effects of upper airway anaesthesia on the sensations associated with the inhalation of L-menthol were evaluated during mouth breathing in 18 subjects and during nose breathing in 15 subjects.

Statistical analysis

Data are presented as mean±SD. After checking for the normality and homoscedasticity of the data sets, the right-to-left comparison of the latencies and amplitudes of the potentials was conducted using a paired t-test, as were the comparisons between the results obtained with the oral and nasal routes of breathing and between the baseline and test conditions. In the six subjects in whom washout measurements were made, the three conditions were compared with a linear ANOVA with the Tukey *post hoc* test. Differences were considered significant when the probability of a type I error was $<5\%$.

RESULTS

Typical respiratory-related evoked potentials (figs 1–3) were present bilaterally in all the subjects at baseline.

Under baseline conditions, the average latencies and amplitude of the components were within the normal range (Before columns in tables 1 and 2). There was no significant right-to-left difference. The latencies and amplitudes measured during mouth and nose breathing were also not significantly different from one another (fig. 1).

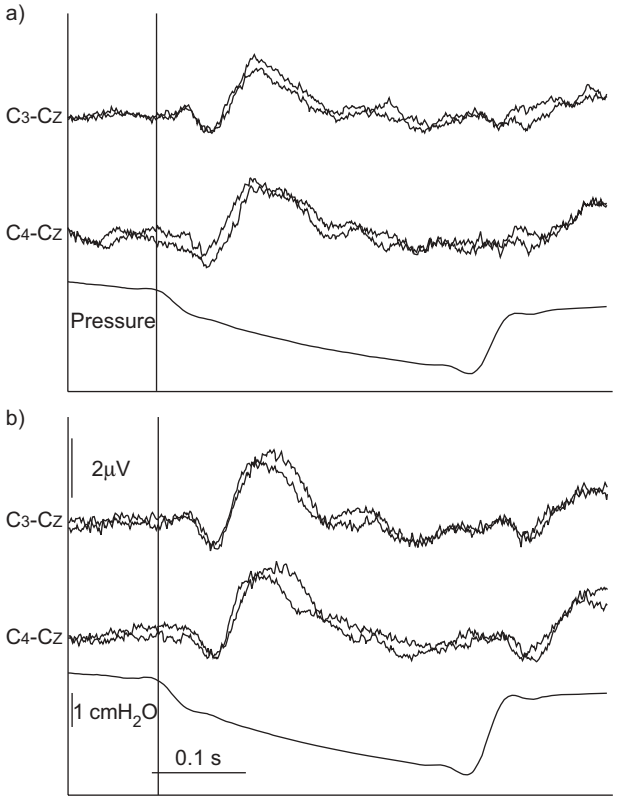

FIGURE 1. Respiratory-related evoked potentials elicited by mid-inspiratory occlusions applied during a) mouth breathing and b) nose breathing in 15 subjects in whom both breathing routes were compared. C3–Cz and C4–Cz corresponds to the ensemble averaging of the inspiratory occlusion-related electroencephalogram epochs obtained in all the subjects. In each of the C3–Cz and C4–Cz derivation in a) and b), one of the two traces corresponds to the potentials recorded at baseline and the other one to the potentials recorded after upper airway anaesthesia (no significant difference). The potentials recorded during nose breathing appear slightly sharper than those recorded during mouth breathing, but the latencies and amplitudes were not significantly different. The vertical line indicates the zero point (see Materials and methods).

Upper airway anaesthesia (21 subjects) did not decrease the number of occurrences of the respiratory-related evoked potentials and of their successive components. It did not affect the latencies of the components and did not influence their amplitudes (figs 1 and 2; tables 1 and 2). This was true on either side and during both mouth and nose breathing. In the six subjects so tested, the washout data were not different from the baseline and anaesthesia data (fig. 2).

Similarly, the inhalation of L-menthol (six subjects) did not decrease the number of occurrences of the respiratory-related evoked potentials and of their successive components. It did not affect the latencies of the components nor did it influence their amplitudes (fig. 3; tables 3 and 4). In the six subjects tested, the washout data were not different from the baseline and anaesthesia data (fig. 3).

Upper airway anaesthesia consistently abolished the cold-like sensation associated with the inhalation of L-menthol during both nose breathing and mouth breathing.

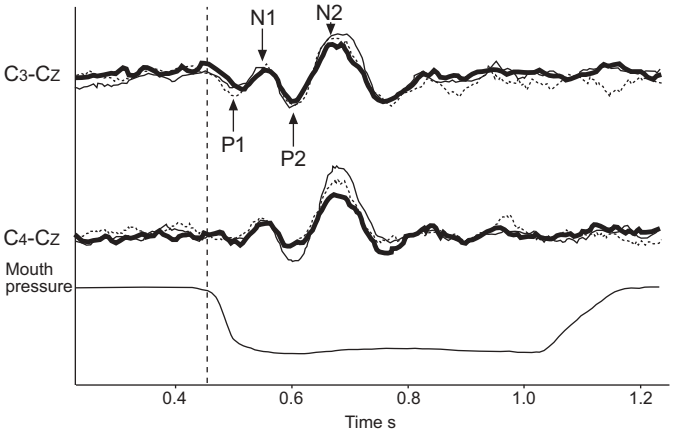

FIGURE 2. An example of the respiratory-related evoked potentials observed before (——), during (**—**) and after (·····) upper airway anaesthesia in one subject. Each trace in C3–Cz and C4–Cz corresponds to the ensemble averaging of two separate superimposable traces obtained from 80 mid-inspiratory occlusions. The vertical line indicates the zero point (see Materials and methods). Typically, the potentials begin with a first positive component (P1; 40–60 ms after the beginning of the load-related change in mouth pressure), considered to reflect the cortical arrival of the afferent message. Later components, typically negative, positive and negative again (N1, P2, and N2, respectively) may reflect the cognitive processing of the sensory information to various extents, as would further components occurring ~300 ms after the stimulus.

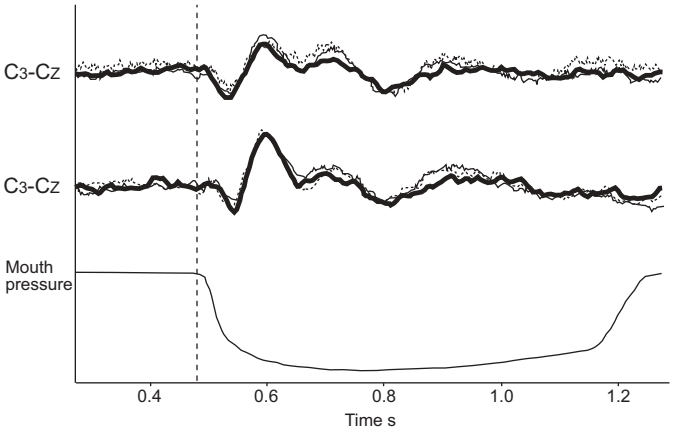

FIGURE 3. An example of the respiratory-related evoked potentials before (——), during (**—**) and after (·····) inhalation of L-menthol in one subject. Each trace in C3–Cz and C4–Cz corresponds to the ensemble averaging of two separate superimposable traces obtained from 80 mid-inspiratory occlusions. The vertical line indicates the zero point (see Materials and methods).

TABLE 1 Latencies of the components of the respiratory-related evoked potentials before and during upper airway anaesthesia in Cz–C3 and Cz–C4 during mouth breathing

	Cz–C3		Cz–C4	
	Before#	During#	Before#	During#
P1	50.56±14.19 (18)	55.82±17.58 (19)	51.42±16.02 (20)	55.04±14.27 (18)
N1	108.5±17.91 (20)	111.9±20.52 (19)	113.1±21.16 (20)	121.00±21.82 (19)
P2	175±22.49 (19)	172.7±32.23 (17)	188.5±37.27 (15)	193.7±37.75 (17)
N2	234.4±25.57 (17)	233.4±28.93 (15)	245.5±35.32 (12)	246.8±46.74 (14)

Data are presented as mean±SD of the measured latency in ms (number of occurrences of the component). P1, N1, P2, N2: peak latencies of the first positive, first negative, second positive and second negative components of the respiratory-related evoked potentials, respectively. #: n=21.

TABLE 2 Amplitudes of the components of the respiratory-related evoked potentials (measured from baseline to peak) before and during upper airway anaesthesia in Cz–C3 and Cz–C4 during mouth breathing

	Cz–C3		Cz–C4	
	Before#	During#	Before#	During#
P1	-1.32±0.77 (18)	-1.32±0.63 (19)	-1.39±1.03 (20)	-1.58±0.68 (18)
N1	2.35±0.89 (20)	2.47±1.5 (19)	2.82±1.22 (20)	2.72±1.14 (19)
P2	-0.80±0.97 (19)	-0.82±1.27 (17)	-0.59±1.11 (15)	-0.62±1.17 (17)
N2	1.16±1.40 (17)	1.75±1.53 (15)	2.28±1.97 (12)	1.70±1.50 (14)

Data are presented as mean±SD of the measured amplitudes in μV (number of occurrences of the component). P1, N1, P2, N2: peak latencies of the first positive, first negative, second positive and second negative components of the respiratory-related evoked potentials, respectively. #: n=21.

DISCUSSION

The present study shows that upper airway anaesthesia does not affect the cortical potentials evoked by mid-inspiratory occlusions in normal humans. This observation can be used to reason about the source of the respiratory-related evoked potentials, keeping in mind that the corresponding hypothesis may not extend to other categories of individuals.

Preliminary considerations

First of all, it must be acknowledged that the absence of effects of upper airway anaesthesia on the respiratory-related evoked potentials could mean that the contribution of the upper airway to the respiratory-related evoked potentials is unimportant, or, alternatively, fully redundant. In patients with various types of inspiratory muscle pump dysfunction, DONZEL-RAYNAUD *et al.* [13] have shown that the upper airways are crucial for the early components of the respiratory-related evoked potentials to occur. However, comparable information is currently lacking in healthy subjects, and it is thus not completely possible to exclude that the observations made by DONZEL-RAYNAUD *et al.* [13], which were conditioned by the absence or abnormality of afferent traffic from the rib cage and ventilatory muscles in the patients studied. In healthy subjects or in other diseases, the mechanisms of regulation can be different. Notably, however, DAUBENSPECK *et al.* [12] observed an important fall in the global field power evoked by upper

TABLE 3 Latencies of the components of the respiratory-related evoked potentials before, during and after inhalation of L-menthol, in Cz–C3 and Cz–C4

	Cz–C3			Cz–C4		
	Before	During	After	Before	During	After
P1	38.00±8.00	39.60±3.21	39.00±4.47	40.20±8.14	38.20±10.71	41.80±13.44
N1	91.50±12.10	86.20±9.12	96.80±20.24	88.75±7.41	89.75±12.82	98.25±20.66
P2	148.00±9.57	163.80±22.92	163.60±20.11	148.25±15.90	146.50±35.24	170.75±21.93
N2	209.67±21.13	223.83±21.23	211.17±37.55	222.83±16.87	213.33±23.36	211.00±26.35

Data are presented as mean±SD of the measured latencies in ms (mouth breathing; n=6). P1, N1, P2, N2: peak latencies of the first positive, first negative, second positive and second negative components of the respiratory-related evoked potentials, respectively.

airway pressure changes when most of the upper airway (with the exception of the lower part of the larynx) was bypassed through the use of a laryngeal mask. All in all, the current authors feel that it is reasonable to base the following discussion on the fact that the upper airway contributes importantly to the respiratory-related evoked potentials, but are aware that other mechanisms may be involved.

Nose breathing and effects of L-menthol

It is worth nothing that the present authors did not observe significant differences between the mid-inspiratory occlusion potentials evoked during mouth breathing and during nose breathing, under baseline conditions as well as during anaesthesia. This suggests that this type of potential can be studied interchangeably during one or the other breathing route. This novel information is potentially important for future studies, as nose breathing is the normal breathing route in resting humans.

The inhalation of L-menthol did not affect the respiratory-related evoked potentials in the six subjects in which this was studied (tables 3 and 4). Insofar as ''cold-receptors'' are in fact flow receptors, this is not unexpected with an inspiratory occlusion paradigm. The strong activation of the receptors by L-menthol could also have led to a saturation of their sensory pathways. Finally, the size of this subgroup may have been insufficient to detect a difference.

TABLE 4 Amplitudes of the components of the respiratory-related evoked potentials (measured from baseline to peak) before, during and after the inhalation of L-menthol in Cz–C3 and Cz–C4

	Cz–C3			Cz–C4		
	Before	During	After	Before	During	After
P1	1.36±0.43	1.28±0.63	1.72±0.52	1.64±0.38	1.40±0.68	1.32±0.59
N1	2.93±1.25	2.84±0.55	3.00±0.58	3.30±1.83	3.10±1.83	3.60±1.34
P2	0.67±0.44	0.58±0.58	0.54±0.49	0.95±0.77	0.85±0.69	0.83±0.57
N2	2.97±1.65	2.47±1.67	2.50±1.31	3.03±1.87	3.30±2.29	3.33±1.94

Data are presented as mean±SD of the measured amplitudes in μV (mouth breathing; n=6). P1, N1, P2, N2: peak latencies of the first positive, first negative, second positive and second negative components of the respiratory-related evoked potentials, respectively.

Upper airway receptors and topical anaesthesia

The respiratory sensory innervation of the upper airway is most complex [14, 15, 19, 20] with major interspecies differences. Nasal afferent end-organs comprise many free nerve endings in the nasal epithelium and underneath it [15]. Their activity is markedly affected by topical anaesthesia [21]. Nasal pressure sensitive receptors exist in several species. Their activity is also easily attenuated by topical anaesthesia [19]. Pharyngeal respiratory receptors are scant, and the pharynx is not considered an important reflexogenic site for patency-maintaining reflexes [22]. However, the muscles of the pharyngeal wall contain receptors characteristic of skeletal muscles, as do the muscles of the palate and of the tongue [15]. The laryngeal region is densely innervated. It features flow receptors, abundant transmural pressure receptors and ''drive'' receptors stimulated by the contraction of intrinsic laryngeal muscle or of the passive motion of the larynx transmitted through the trachea or both [15, 23]. The first two categories are sensitive to topical anaesthesia [15, 24], whereas this is only partially the case for the ''drive receptors'' [23, 25] that require both muscle paralysis and tracheal immobilisation to be silenced. These receptors are likely to include ligament receptors, joint receptors and muscle receptors, very abundant in pharyngeal and laryngeal muscles. The afferent activity in response to the stretching of laryngeal muscular receptors is known to persist after topical anaesthesia [26].

Interpretation of results

In addition to the issues raised in the earlier ''preliminary considerations'' section, the failure of the anaesthetic to reach all the relevant receptors could be called on to explain the presented result. Indeed, although it is highly likely that nasal and pharyngeal receptors were correctly anesthetised, the current authors did not perform a visually controlled application of lidocaine on the lower part of the larynx. However, partial laryngeal anaesthesia is likely due to the swallowing difficulties noted by all the subjects and by the abolition of the L-menthol induced cold sensation that was consistently noted after anaesthesia during mouth breathing. Insofar as preventing part of the airway receptors from being exposed to a given

stimulus does significantly alter the corresponding potentials [12], even incomplete anaesthesia would be expected to have some effects on the respiratory-related evoked potentials. From this, the present authors submit that the complete absence of effect of topical lidocaine on the respiratory-related evoked potentials in the presented subjects indicates that the receptors activated by the inspiratory occlusions are not sensitive to topical anaesthesia (of note, it has been shown that upper airway receptors that are sensitive to topical anaesthesia are not essential for respiratory sensations related to volume changes [27]). Speculatively, this suggests that the upper airway receptors relevant to the respiratory-related evoked potentials could belong to the ''drive receptors'' described earlier (joint and muscular upper airway receptors). Although they would probably be very difficult to conduct in humans, studies specifically designed to test this hypothesis are warranted.

According to the earlier discussion, this makes a contribution of cold receptors and of pressure receptors unlikely (which is not surprising regarding cold receptors considering that the stimulus generated by mid-inspiratory occlusion occurs in the absence of flow; in this frame, modifying the baseline activity of the laryngeal flow receptors by the inhalation of L-menthol did not induce visible changes in the characteristics of the respiratory-related evoked potentials). In conclusion, the authors submit that the upper airway receptors involved in the respiratory-related evoked potentials following mid-inspiratory occlusions could mainly belong to the category of the ''drive receptors''. If this was correct, joint and muscular airway receptors would appear to be important determinants of the detection and processing of the mechanical changes induced by this type of stimulus by the cerebral cortex, phenomena that are paramount to the control of upper airway patency.

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étude 4

Etude des potentiels évoqués respiratoires, à l'éveil, au cours du syndrome d'apnées obstructives du sommeil sévère

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Abnormal respiratory-related evoked potentials in untreated awake patients with severe obstructive sleep apnea syndrome

Soumis (Sleep Medicine)

1. objectifs

Le syndrome d'apnées obstructives du sommeil (SAOS) est caractérisé par des occlusions pharyngées récurrentes survenant pendant le sommeil. L'obstruction des voies aériennes conduit généralement à un éveil bref ce qui permet la reprise de la ventilation.

L'éventualité d'altérations des perceptions respiratoires à la source du SAOS ou de sa gravité est sous-tendue par des données montrant une augmentation du seuil de détection et une sous-estimation de charges inspiratoires à l'éveil dans des groupes de patients apnéiques par rapport à des groupes contrôles (47). D'autre part, les afférences respiratoires naissant des voies aériennes supérieures semblent jouer un rôle particulièrement important dans les mécanismes d'éveil. L'anesthésie des voies aériennes supérieures augmente la durée des apnées et le niveau d'effort inspiratoire associé à l'éveil au cours du sommeil non paradoxal chez les patients présentant un SAOS (8, 5).

Plusieurs études ont recherché des anomalies des potentiels évoqués respiratoires à l'éveil ou pendant le sommeil chez les patients souffrant de SAOS. Les résultats de ces études ne sont pas univoques. Gora et coll. ont comparé les potentiels évoqués respiratoires de six patients porteurs de SAOS léger (index d'apnée-hypopnée < 15/heures) et de six témoins à l'éveil et pendant le sommeil lent léger (27). A l'éveil, la seule différence retrouvée était une diminution de l'amplitude de la composante N1 des potentiels évoqués respiratoires chez les patients. La diminution de l'amplitude de N1 n'a pas été retrouvée par Afifi et coll. qui ont étudiés les potentiels évoqués auditifs et respiratoires à l'éveil et pendant le sommeil chez dix patients souffrant de SAOS léger à modéré, avec un index d'apnée-hypopnée moyen de 21 ± 11 par heure (1). Pendant le sommeil, il existait une diminution d'amplitude et une augmentation de latence significatives d'une composante tardive (N550) des potentiels évoqués respiratoires chez les patients par rapport au groupe contrôle. Ces résultats étaient en faveur d'une altération spécifique du traitement cortical de l'occlusion inspiratoire au cours du sommeil chez les patients porteurs de SAOS. Ils ne concernaient cependant que des patients porteurs de SAOS légers à modérés. Akay et Daubenspeck ont étudié les afférences respiratoires à l'éveil, chez des patients porteurs de SAOS beaucoup plus sévères (index d'apnée-hypopnée moyen de 57,5 ± 11,2 par heure) mais avec une technique différente permettant de recueillir les réponses corticales

évoquées par l'application d'une pression négative à la bouche en début d'inspiration (2). L'utilisation d'un tel paradigme mettait en évidence une diminution d'amplitude de la réponse 55 à 70 ms après le stimulus chez les patients porteurs de SAOS par rapport à une population contrôle.

Le but de notre étude était de rechercher, chez des patients atteints de SAOS sévère, des modifications éventuelles des caractéristiques des potentiels évoqués respiratoires, à l'éveil, par comparaison à des sujets témoins.

2. méthodes

Les caractéristiques des potentiels évoqués respiratoires de 10 patients présentant un SAOS sévère (index d'apnée-hypopnée moyen de 55,8 ± 22,2 par heure) et de 8 sujets témoins ont été comparés, à l'éveil.

3. résultats

Les latences de la composante P1 étaient identiques dans les deux groupes étudiés.

Il n'y avait pas de différence significative entre les latences de la composante N1 des deux groupes dans la dérivation C3-Cz. Par contre, la latence de cette composante N1 dans la dérivation C4-Cz était allongée chez les malades souffrant de SAOS par rapport au groupe témoin (98 [16.00] ms vs. 79.5 [5.98] ms, $p<0.02$). Les latences des composantes P2 et N2 étaient allongées chez les patients dans les deux dérivations.

Il n'y avait pas de différences d'amplitudes des différentes composantes étudiées entre le groupe patient et le groupe témoin.

4. conclusions

Cette étude montre que, chez des patients atteints de SAOS sévère, à l'éveil, la composante initiale P1 des potentiels évoqués respiratoires n'est pas modifiée, tandis qu'il existe un allongement de la latence des composantes plus tardives.

L'absence de différence quant à la première composante P1 des potentiels évoqués respiratoires entre patients atteints de SAOS et sujets contrôles, suggère

que la transmission au cortex cérébral d'informations relatives à l'occlusion des voies aériennes supérieures pendant l'inspiration est normale au cours du SAOS, à l'éveil.

Par contre, l'allongement de la latence des composantes plus tardives de ces potentiels, est compatible avec l'existence d'anomalies du traitement cortical d'informations de source respiratoire, comme cela a été décrit au cours du SAOS pour le traitement d'informations visuelles (41) ou auditives (34, 54, 51). Ces anomalies consistent essentiellement en un allongement de latence de potentiels évoqués endogènes. Elles sont parfois corrélées au temps passé en hypoxie et semblent irréversibles. Elles ne sont pas spécifiques d'une fonction sensorielle particulière.

Les anomalies des composantes N1, P2 et N2 des potentiels évoqués respiratoires mises en évidence par notre travail confirment la très grande vraisemblance d'altérations des fonctions d'intégration cérébrale au cours du SAOS. Le fait que ces anomalies puissent porter sur des perceptions respiratoires pourrait conduire à une réponse corticale inadaptée aux informations de nature "mécaniques" envoyées au cortex cérébral pendant les épisodes de collapsus des voies aériennes survenant pendant le sommeil, ce qui pourrait constituer un facteur d'aggravation et d'auto entretien de la maladie.

Chez nos patients, l'allongement de la latence de la composante N1 des potentiels évoqués respiratoires au cours du SAOS n'a été retrouvée que dans la dérivation C4-Cz, qui correspond à la région rolandique droite (42). Une latéralisation à droite des projections corticales en rapport avec l'occlusion des voies aériennes a déjà été notée dans des études antérieures. En effet, l'amplitude pic à pic des composantes des potentiels évoqués respiratoires était significativement supérieure dans les dérivations hémisphériques droites par rapport aux dérivations hémisphériques gauches (56, 43). Par ailleurs, le raccourcissement des latences des composantes P1 et N1 observé lorsqu'on réalise des occlusions en milieu d'inspiration plutôt qu'en début d'inspiration n'était significatif que dans la dérivation~~s~~ C4-Cz (56). De plus, les études d'imagerie fonctionnelle cérébrale portant sur la dyspnée ont mis en évidence une activation préférentielle de structures cérébrales localisées à droite (4, 53). Il semblerait donc que l'hémisphère droit pourrait jouer un rôle prépondérant dans les sensations respiratoires. Dès lors, Il n'est pas illogique qu'une agression cérébrale globale ait

une expression latéralisée au regard des potentiels évoqués respiratoires, comme nos résultats le suggèrent.

Aucune modification de l'amplitude des potentiels évoqués respiratoires n'a été mise en évidence au cours de notre étude. D'une manière générale, en neurophysiologie, les amplitudes des potentiels évoqués cérébraux exogènes sont hautement variables d'un sujet à l'autre. (Lors de l'étude des potentiels évoqués visuels, seule une importante asymétrie des amplitudes est retenue comme pathologique. Les composantes des potentiels évoqués somesthésiques sont définies essentiellement par leur polarité et leur latence (30)) Il semble que l'amplitude soit une grandeur beaucoup plus « fragile » que la latence. Les différences de latence des composantes N1, P2 et N2 retrouvées dans notre étude paraissent ainsi beaucoup plus solides que les différences d'amplitude de N1 retrouvées par Gora et coll. (27). Cette dernière anomalie pourraient être attribuée à la somnolence excessive des patients, puisqu'il a été montré que l'amplitude de la composante N1 diminue pendant le sommeil lent léger (61).

Abnormal respiratory-related evoked potentials in untreated awake patients with severe obstructive sleep apnea syndrome

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Abstract

Background. Obstructive sleep apneas (OSA) generate an intense afferent traffic leading to arousal and apnea termination. Yet afferent denervation has been described in OSAS patients, and could be a determinant of disease severity. How mechanical changes within the respiratory system are processed in the brain can be studied through the analysis of airway occlusion related respiratory-related evoked potentials (RREPs). RREPs have been found altered during sleep in mild and moderate OSAS patients, with contradictory results during wake. We hypothesized that RREPs alterations during wake, if indeed a feature of the OSAS, should be clearly present in untreated severe patients.

Methods. 10 untreated severe OSAS patients and 8 matched controls were studied. Scalp RREPs were recorded in Cz-C3 and Cz-C4, and described in terms of the amplitudes and latencies of their successive components P1, N1, P2, N2.

Results. Components amplitudes were similar in both groups. There was no significant difference in P1 latencies, which fell in the normal range. This was also the case for N1 in Cz-C3. In contrast, N1 latencies in Cz-C4 were significantly longer in the OSAS patients (median 98 ms [interquartile range 16.00] vs. 79.5 ms [5.98], $P = 0.015$). P2 and N2 were also significantly delayed, on both sides.

Conclusion. The processing of airway occlusion related afferents is abnormal in untreated severe OSAS patients. This could be either a severity marker or an aggravating factor, or both.

Key words

obstructive sleep apnea, respiratory-related evoked potentials, respiratory sensations, cortical processing,

1. Introduction

The obstructive sleep apnea syndrome (OSAS) derives from recurrent sleep-related occlusions of the upper airway. Each obstructive episode is associated with alveolar hypoventilation, increasingly intense inspiratory efforts, and a neurovegetative burst. This generates an intense chemical and mechanical afferent traffic that leads to arousal. Arousal restores upper airway patency, allowing ventilation to resume and the afferent storm to subside. The perception of increasing inspiratory efforts plays an important role in apnea termination [1] and, per contra, impaired respiratory afferents are likely to be a factor of apnea prolongation. Thus, it has been shown that the involvement of pharyngeal nerves by Charcot-Marie-Tooth disease, an hereditary sensory neuropathy, promotes obstructive sleep apneas [2]. Afferent denervation has been described in OSAS patients [3], who have impaired oropharyngeal temperature thresholds [4], increased pharyngeal thresholds for the detection of mucosal airflow [5], and a decreased two-point pharyngeal sensory discrimination [6,7]. They also exhibit a decreased inspiratory load detection sensitivity [8,9].

How respiratory events are detected and processed by the brain can be studied through the analysis of the cortical potentials evoked, for example, by inspiratory airway occlusions (respiratory-related evoked potentials -RREPs-)[10] or by negative pressure pulses applied to the airway during inspiration [11] and expiration [12]. Typically, these potentials consist in a sequence of components reflecting the arrival of the information to the cortex (generally a positive wave P1, circa 50 ms post-stimulus), its early processing (negative N1, in the 80-120 ms post-stimulus window), and its late processing (P2 N2 complex, in the 120-250 ms post-stimulus window occurring), with a later P300 component interpreted as being of cognitive nature. Respiratory-related evoked potentials are markedly altered during NREM sleep in normal individuals [13]. This is also the case in OSAS patients, but in an exaggerated manner [14,15]. Whether or not the OSAS-related dampening of cortical respiratory perceptions during sleep is associated to similar abnormalities during wake is less clear. The potentials evoked by inspiratory efforts against the occluded airway were not found altered in a 10 treatment-free moderate OSAS patients studied during wake and compared to 10 control subjects [15]. In contrast, in 6 treatment-free patients with mild

OSAS a significant reduction in the amplitude of the N1 component of similar cortical potentials was observed, without latency changes [14]. Akay et al. [16] reported a decreased cortical activity within the 55-70 ms post-stimulus time window in 14 awake severe OSAS patients who were compared to 18 controls. However, in this study the stimulation paradigm consisted in negative pressure pulses superimposed on inspiration as opposed to inspiratory efforts against an occluded airway, and cortical activity was analyzed in terms of global field power. These features make the comparison with the other two studies difficult. In addition, in the study by Akay et al. [16], all the patients but one were efficiently treated by continuous positive airway pressure, which could conceivably have interfered with their cortical processes [17].

The present study was therefore conducted in untreated severe OSAS patients during wake. It relied on inspiratory occlusion-related cortical potentials in order to provide data as comparable as possible with those available in less severe forms of the syndrome [14,15]. We hypothesized that if alterations in the cortical processing of respiratory events during wake were indeed a feature of the OSAS, they should be more marked in severe treatment-free patients than previously described.

2. Methods

2.1. Study population

Ten severe OSAS patients (6 men, 4 women; age 46 ± 11; body mass index 30.9 ± 8.3 kg/m^2, apnea hypopnea index 55.8 ± 22.2 -see section 2.1-) and 8 control individuals (5 men, 3 women; age 41.1 ±12.0; body mass index 26.8 ± 4.5 kg/m^2, apnea index ≤ 5, apnea hypopnea index ≤ 15 -see section 2.1-) participated in the study. They were free of any respiratory or neurological disease. None had had previous upper airway surgery, except for childhood tonsillectomy in some cases. The study was conducted after legal and ethical clearance from the appropriate local authority (Comité de Protection des Personnes se prêtant à des Recherches Biomédicales Pitié-Salpêtrière, Paris, France). All the participants were informed in detail of its purpose and of the methods used, and gave written consent.

2.2. Sleep studies

The diagnosis and severity of the OSAS were established from all-night recordings of respiratory signals (airflow through nasal pressure and tracheal sounds, thoracic and

abdominal movements, transcutaneous oxygen saturation) and of neurophysiological signals (fronto-temporal and occipito-central bipolar electroencephalogram -EEG- according to the international 10-20 system, electro-oculogram, submental and tibialis anterior electromyograms)(Cidelec 104 et 108, Cidelec, Angers, France). In 4 patients, only the respiratory signals were recorded, whereas in the other 6 patients both the respiratory and the neurophysiological signals were recorded. In these cases, sleep stages were scored according to Rechstchaffen and Kales criteria [18] and arousals and micro-arousals were identified according to the criteria of the American Sleep Disorders Association [19]. Apneas were defined as complete cessations of airflow for more than 10 seconds and were classified as obstructive, mixed or central according to the criteria of the American Academy of Sleep Medicine (AASM) task force [20]. Hypopneas were defined as a 50% decrease in airflow signal for at least 10 seconds associated with a micro arousal or an oxygen desaturation of at least 3 %.

2.3. Respiratory-related evoked potentials

Experimental conditions. The participants were studied seated in a reclining lounge chair, with the back, neck, and head comfortably supported. During the experimental sequence, the patients wore earplugs and headphones through which they listened to a musical piece of their choice, in order to mask auditory cues. Care was taken to support the breathing circuit, to eliminate the need for the patients to bite the mouthpiece and therefore to avoid artifacts due to the activity of facial muscles. The participants were instructed to relax but to keep their eyes open in order to avoid any risk of falling asleep, and the investigator in charge of the recordings constantly verified that the patients did not fall asleep during the study and provided frequent stimulations to avoid that.

Breathing circuit (Figure 1). The study participants breathed through a mouthpiece while wearing a nose clip. The airway opening was connected to a heated pneumotachograph (3700 series, Hans Rudolf, Kansas City, MO, USA) combined with a ± 2 cmH2O linear differential pressure transducer (Validyne, Northridge, CA, USA) to measure the ventilatory flow. The pneumotachograph was connected to a nonrebreathing valve (2600 series; Hans Rudolph, Kansas City, MO, USA) of which the inspiratory port

could be silently occluded by an inflatable balloon (Hans-Rudolf 9340 series occlusion valve and 9330 series compressor, Hans Rudolph, Kansas City, MO, USA). Airway opening pressure (Pao) was measured from a side port of the valve proximal chamber, using a ± 50 cmH2O differential pressure transducer (DP 15-32, Validyne, Northridge, CA, USA).

Electroencephalographic activity. The electroencephalographic activity (EEG) was recorded using standard surface electrodes placed at the scalp positions C_Z, C_3, C_4 on the basis of the International 10-20 System. C_3 and C_4 were referenced to C_Z to record the left and right activity, respectively. A single reference surface electrode placed on the forehead was used. Electrode impedances were monitored and maintained below 5 k-ohms. The EEG electrodes were connected to a standard amplifier system (Neuropack , Nihon Kohden, Tokyo, Japan). The signal was sampled at a 1 kHz over a 0.5Hz-500 Hz bandwidth and stored on an Apple Macintosh computer for the subsequent averaging and analysis process (PowerLab®, AD instruments, Hastings, UK).

Data analysis. Data acquisition was triggered from the flow signal. The EEG signals, airway opening pressure and flow were digitized 100 milliseconds before and 2 seconds after the inspiratory onset defined as the point of zero flow (MacLab/16, AD Instruments, Castle Hill Australia). Respiratory-related potentials were evoked by mid-inspiratory occlusions [21] lasting 400-500 ms, randomly presented every two to four breaths. One hundred occlusions were presented for a given trial. Two trials were performed in each participant, separated by a period of rest. Subsequently, all the stimulus presentations for a given trial were recalled from computer memory and displayed. A given stimulus presentation was retained for averaging if an only if the EEG signal had a stable pre-occlusion baseline, was free of voltage changes in excess of 50 microvolt, and was free of high frequency noise. For each trial, a minimum of 60 presentations were averaged. In addition, "control" trials were obtained by averaging the same number of unoccluded breaths.

Four components of the respiratory related evoked potentials were defined according to the usual nomenclature (P1, N1, P2, N2, see ref). The latencies of these components were measured from the onset of inspiration determined according to

Davenport et al. [22] to their peaks. Baseline to peak amplitudes were determined separately for each component at each electrode site.

2.3. Statistical analysis

The statistical analysis was performed using the Prism 4.0 software and associated online calculators (Graphpad, San Diego, CA, USA) and the StatEl set of macrocommands for Microsoft Excel™ (AdScience, Paris, France). Each data set was first tested for normality using the Shapiro-Wilk test. Normal data are described in terms of their mean ± standard deviation, non-normal ones are described with their median and interquartile range (IQR). Grubb's test was used to identify outliers, which led to the exclusion of one aberrant latency value. Comparisons between groups were conducted with a Student unpaired t-test for normal data sets, and with the Wilcoxon non-parametric test for non-normal data sets. Correlations between the characteristics of the respiratory-related evoked potentials and severity of sleep-related respiratory disturbances were looked for using Spearman's correlation coefficient. A *P* value below 0.05 was considered indicative of statistical significance, namely of a less than 5% probability of erroneously rejecting the null hypothesis (type I error).

3. Results

3.1. Sleep

The OSAS patients and the control subjects did not significantly differ in age and body mass index. The 10 OSAS patients all exhibited daytime sleepiness (Epworth scale 10 [IQR 8]) or other symptoms compatible with the diagnosis of OSAS according to the AASM [20]. Their all-night recordings all showed more than 30 obstructive events per hour in all cases (from 31 to 94 in the 4 patients with respiratory polygraphic recordings, from 35 to 83 in the 6 patients with polysomnographic recordings). The 8 control individuals were non-snorers with no daytime sleepiness (Epworth scale 4.5[IQR 1.2]) and no nocturnal desaturations.

3.2. Respiratory-related evoked potentials.

The number of EEG epochs averaged to obtain the potentials in the OSAS patients was 84 ± 6 and 76 ± 12 in the control subjects (P = 0.17). The mid-inspiratory occlusion related fall in airway pressure was not significantly different between the patients and the controls (3.6 ± 1.1 cmH2O and 3.3 ± 0.7 cmH2O, respectively, P = 0.26). Respiratory-related evoked potentials could be identified neither from the raw data before averaging nor from the averaged unoccluded breaths. Conversely, respiratory-related evoked potentials could consistently be identified after averaging occluded breaths in both the OSAS patients and the control subjects (Figure 2).

The amplitudes of the corresponding sequential components did not differ between the patients and the control subjects (Table 1).

The latencies of the P1 component were also similar in the patients (43.75 ms [IQR 1.91] in Cz-C3, 40 ms [IQR 2.5] in Cz-C4) and in the control subjects (42.5 ms [IQR 3.75] in Cz-C3, ms [IQR 0.5] in Cz-C4), in both cases within the expected range (Figure 3).

The latencies of N1 were significantly longer in C4-Cz in the OSAS patients than in the controls (98 ms [IQR 16.00] vs. 79.5 ms [IQR 5.98], P = 0.015). This was not the case in Cz-C3 (102.75 ms [IQR 28.12] ms vs. 94.5 ms [IQR 6.00], P = 0.43) (Figure 3).

The latencies of P2 were significantly delayed in Cz-C4 in the patients (170.75 ms [IQR 24.10] vs. 143 ms [IQR 11.93], P = 0.029) and in Cz-C3 (172 ms [IQR 28.98] vs. 151.5 ms [IQR 43.1], P = 0.045) (Figure 3). The same pattern was found regarding N2 (in Cz-C4: 251.5 ms [IQR 11.59] vs. 214.75 ms [IQR 8.5], P <0.01; in Cz-C3: 258 ms [IQR 17.05] vs. 225 ms [IQR 23.5], P =0.03) (Figure 3).

Within the OSAS patients group, there was no correlation between the latencies of the evoked potentials component and the apnea-hypopnea index or the percentage of recording time spent with an SpO2 below 90%.

4. Discussion

This study shows that in awake patients with severe forms of the OSAS as compared to age- and BMI-matched subjects, there is no abnormality in the P1 component of the respiratory-related evoked potentials. In contrast, and except for N1 in Cz-C3, the subsequent components of the potentials are significantly delayed. According to the current interpretation of respiratory-related potentials, these findings suggest a normal transmission to the cortex of the sensory information related to inspiratory occlusions, but an impaired processing of this information. Of note, the EEG montage used in the present study and in other studies by our group [23-25] is best suited to study the P1-N1-P2-N2 sequence of the respiratory-related evoked potentials, but it does not give access to the frontal Nf described by Davenport et coll. [26], neither to the late components (such as P300) that have the most markedly cognitive dimension.

4.1. P1 component

In our study as in other studies of the cortical processing of respiratory occlusions during wake in OSAS patients [14,15], the first positive component of the respiratory-realted evoked potentials was of normal latency and amplitude. The corresponding primary sensory cortical region therefore seems normally activated by inspiratory occlusions in patients with severe forms of the OSAS, as it is in patients with a milder disease [14] [15]. Yet OSAS patients are known to exhibit impaired upper airway afferences. They have a reduced ability to detect sensory stimuli in the upper airway [27] [5], that further decreases with topical anaesthesia [5] and could be due to a pharyngeal neuropathy [3]. In this frame, the lack of P1 alterations in the OSAS patients that we studied can mean that these particular individuals were free of the above abnormalities. We did not look for signs of upper airway denervation in our patients, and do acknowledge that this is somehow a limitation to our study. However, even in the presence of a sensory neuropathy, normal P1 latencies are not unexpeted. Indeed, such a finding is in line with the lack of effect of upper airway anesthesia on the respiratory-related evoked potentials [23]. It is also in line with the likely redundant nature of these potentials that are considered by some to have multiple sources in the respiratory system [28].

4.2. N1 and subsequent components

The late components of somatosensory evoked potentials, also known as endogenous components, are associated with the cognitive processing of the corresponding sensory information. Their amplitude increases and their latency decreases when the stimulus is delivered in an “attend” condition as compared with an “ignore” condition [29]. This may also be the case for respiratory-related evoked potentials. While their P2 and N2 components seem to belong unambiguously to the "endogenous" category, N1 falls in an intermediate zone between early (<100ms) and late (>100ms) components. How N1 is affected by attention is uncompletely clear. Webster el al. [30] reported significant attention-related N1 changes, whereas Harver et al. [31] and Zhao et al. [32] failed to do so. N1 may thus have mixed features, and could in fact correspond to a "precognitive indicator" of the cortical processing of respiratory occlusions. The lengthening of the N1 latency in Cz-C4 in our patients could thus point to an impairement of the early phase of the inspiratory occlusion cortical processing in severe forms of the OSAS. Of note, this observation is at variance with the reports of Gora et al [14] and of Afifi et al. [15] , who showed that the cortical response to respiratory occlusions was normal in awake OSAS patients, and blunted only during sleep. Both these studies were however conducted in patients with a mild or moderate disease. Put together, our findings ant those of Gora et al [14] and Afifi et al [15] are compatible with the N1 latency lengthening being more consequential with the OSAS-related repeated hypoxic episodes than causative of the disorder. In that, the N1 latency lengthening may be comparable with other sensory abnormalities described in OSAS patients (e.g. auditory and visual evoked potentials [33-37]. These abnormalities may be in line with hypoxic brain damage. This is supported by the correlation that exist between some evoked potentials alterations (e.g. P300 lengthening [35]) and the severity of OSAS. Of note, abnormal endogenous evoked potentials in OSAS patients could stem from other factors than repeated hypoxic episodes: sleep fragmentation, or, more generally, disruptions in the architecture of sleep, could also be involved. Within this frame, the N1 latency lengthening in our patients could be hypothesized to be of a nature similar to the lengthening of P2 and N2 latencies that we observed. Of note, one way to assess the respective role of irreversible hypoxic damages and of sleep fragmentation in the abnormalities observed would be to study the effects of treatment with continuous

positive airway pressure or mandibular advancement. With other types of cortical potentials, various effects of treatment have been described [34,35]. It has been suggested that the persistence of electrophysiological abnormalities in spite of an efficient treatment illustrated by improved cognitive performance is in favor of irreversible hypoxic lesions [34]. The effects of OSAS-treatment of respiratory-related evoked potentials should thus be the object of future investigations.

We did not study our patients during sleep, because this was not the aim of the study, and because marked alterations of respiratory-related evoked potentials have already consistently been described during NREM sleep both in nomal individuals [13] and in other types of OSAS patients [14-16]. This effect of NREM sleep on respiratory-related evoked potentials leads to raise an important issue. In our patients suffering from severe OSAS and consistently complaining of daytime sleepiness, a tendency to fall asleep during the experiments could have explained the latency lengthenings that we observed. There are several arguments against this hypothesis. Firstly, care was taken to keep the subjects awake during the experiments: they were asked to keep their eyes opened, and were often verbally stimulated by the investigator. Secondly, this mechanism should have resulted in a combination of longer latencies and smaller amplitudes, which we did not observe. Thirdly, and perhaps more importantly, we observed that the N1 latency lengthening was lateralized. It was present in Cz-C4 but lacked in Cz-C3. This could be in line with the right lateralization of certain respiratory afferents that has been previously described [38,39]. It would then be an argument for the respiratory specificity of the N1 anomaly described here.

4.3. Relationships between OSAS severity and respiratory-related evoked potentials abnormalities.

We did not find significant relationships between the EEG abnormalities described in our patients and the severity of the sleep-related respiratory disturbancies (e.g. apnea-hypopnea index, or time spent under hypoxemic conditions). This in contrast with observations made with other type of cortical potentials [34,35], and may be due to a lack of power due to the small size of the population.

4.4 Perspectives

Athough there are few longitudinal studies of the natural history of the OSAS, some data suggest that the severity of OSA can worsen over time [40]. One factor for such an evolution could be the progressive impairment over time of the ability of the cerebral cortex process the sensory information generated by inspiratory occlusions. In this hypothesis, the respiratory-related evoked potentials abnormalities described here in severe OSAS patients would not only be the consequences of hypoxic damages to the brain or of sleep fragmentation, as discussed above, but also a worsening factor, fueling a vicious circle by contributing to the prolongation of apneic episodes. In line with this hypothesis is the fact that the short-term withdrawal of nasal continuous positive airway pressure in severe OSAS patients increases the level of inspiratory effort associated with arousal, suggesting that apnea impairs the arousal response to upper airway occlusion [41]. Again, studying the effects of treatment on respiratory-related evoked potentials in severe OSAS patients will possibly bring an answer. This will have to be the object of further studies.

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Legends to the figures

Figure 1.

Schematic representation of experimental apparatus. C3, C4, Cz, scalps positions of the EEG electrodes (international 10-20 system).

Figure 2.

Example of the respiratory-related evoked potentials elicited by mid-inspiratory occlusions in one control subject (top) and one patient suffering from a severe form of the obstructive apnea syndrome (bottom). The recordings correspond to the Cz-C4 derivation. In each case, two consecutive recordings in the same patient are superimposed. The vertical arrows correspond to the stimulus, determined from the mouth pressure trace after the inspiratory occlusion. The four components (P1, N1, P2, N2) of the potentials are identified by vertical dotted lines.

Figure 3.

Latencies (in ms) of the P1, N1, P2 and N2 components of the respiratory-related evoked potentials in the Cz-C3 recording site (left column of panels) and in the Cz-C4 site (right column). In each panel, the values in the control subjects are depicted by the leftmost box and whiskers representation, whereas the values in the obstructive sleep apnea patients are depicted by the rightmost one. The boxes depict the 25^{th} to 75^{th} percentile of the data with indication of the median value. The horizontal lines outside the boxes depict the 10^{th} to 90^{th} percentile. Outliers are shown as circles. The "*" symbol indicates a significant difference.

Figure 1

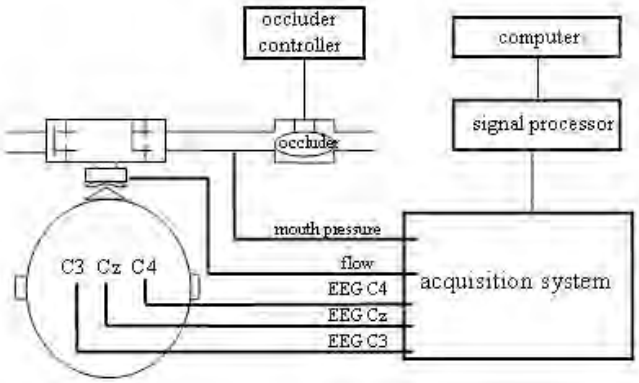
occluder
controller
computer
signal processor
occluder
mouth pressure
flow
EEG C4
EEG Cz
EEG C3
C3 Cz C4
acquisition system

Figure 2

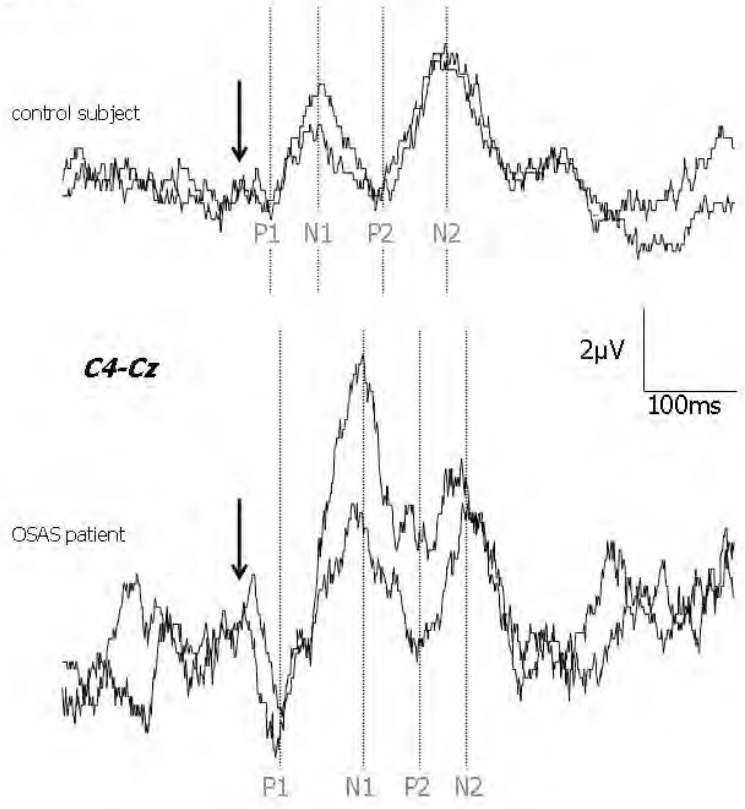
control subject
P1
N1
P2
N2
C4-Cz
2µV
100ms
OSAS patient
P1
N1
P2
N2

Figure 3

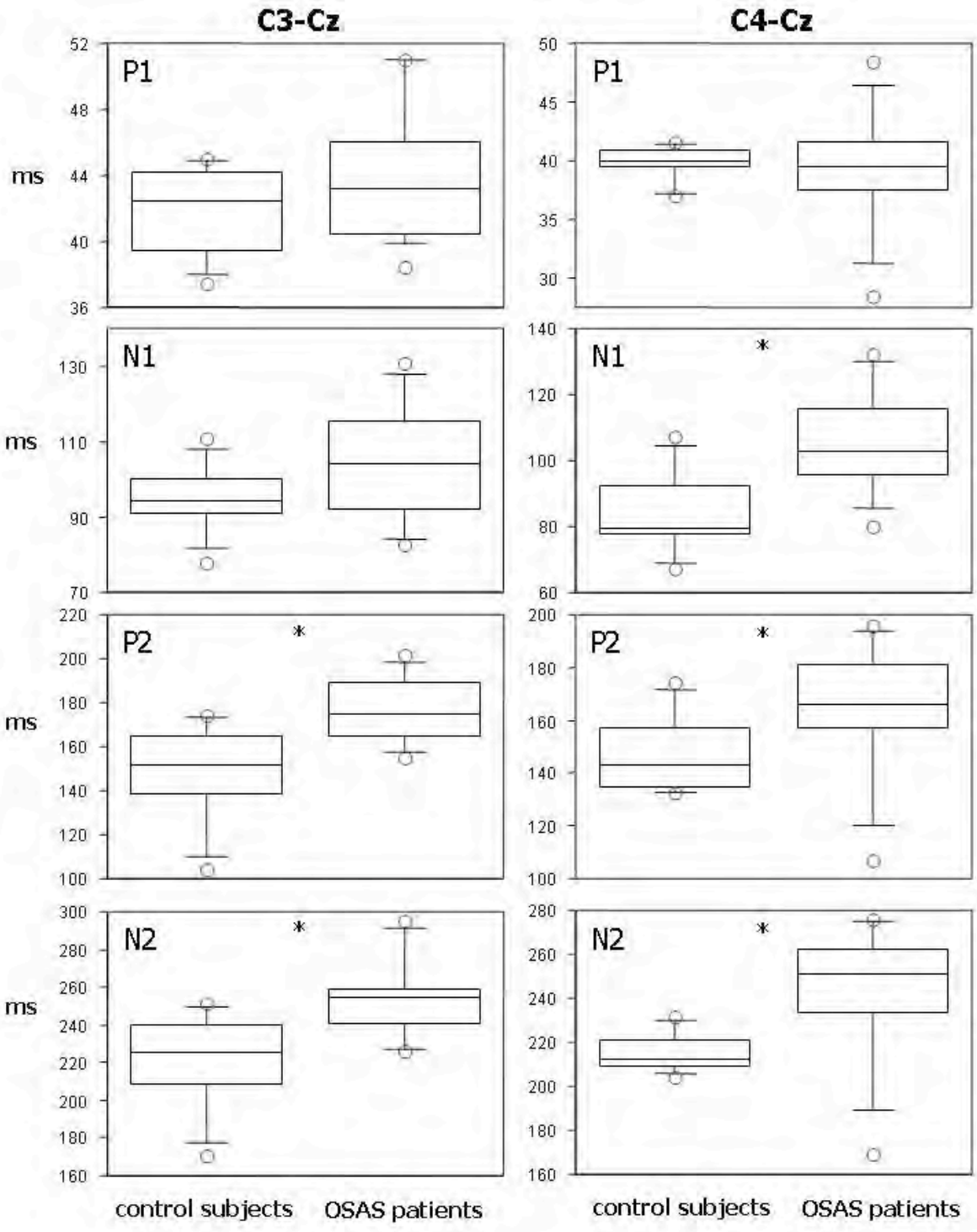

Table 1. Amplitudes of the components of the respiratory-related evoked potentials in the control subjects and the patients, in the Cz-C3 and Cz-C4 scalp positions.

	Cz-C3			**Cz-C4**		
amplitude	**controls**	**patients**		**controls**	**patients**	
P1	2.25 [0.68]	1.6 [0.73]	ns	2 [0.66]	1.85 [0.55]	ns
N1	-1.2 [0.83]	-1.55 [1.01]	ns	-1.5 [0.52]	-1.6 [0.48]	ns
P2	1.6 [1.06]	1.6 [0.42]	ns	0.9 [0.48]	1.6 [0.61]	ns
N2	-2.4 [0.34]	-2.7 [0.29]	ns	-2.6 [1.18]	-2.5 [0.23]	ns

data in μV, median [IQR]

conclusions

La synthèse des travaux de cette thèse permet de dégager des conclusions et d'ouvrir de nouvelles perspectives.

1. déterminants physiologiques des potentiels évoqués respiratoires

Au démarrage des travaux de cette thèse, l'origine et les afférences mises en jeu dans les potentiels évoqués respiratoires étaient totalement inconnues, même si quelques hypothèses semblaient plus probables que d'autres. L'étude de patients trachéotomisés a permis de montrer que les voies aériennes supérieures en étaient vraisemblablement l'une des sources principales (étude 2). Les récepteurs qui, en leur sein, sont sensibles à l'anesthésie locale, ne semblent cependant pas jouer de rôle important (étude 3). Il est ainsi probable que l'origine principale des potentiels évoqués respiratoires réside dans des récepteurs profonds, jonctionnels ou musculaires situés au niveau des voies aériennes supérieures.

Par ailleurs, notre première étude suggère que les mécanorécepteurs du diaphragme ne contribuent pas pour une part importante à la constitution des potentiels évoqués respiratoires.

Les potentiels évoqués respiratoires se distinguent des autres potentiels évoqués exogènes par la nature du stimulus qui leur donne naissance. Les caractéristiques des composantes des potentiels évoqués somesthésiques, visuel et auditifs, sont ainsi directement liées aux caractéristiques de la stimulation (type, intensité, durée, fréquence). Le stimulus à l'origine des potentiels évoqués respiratoires n'est, en revanche, pas clairement défini. L'occlusion des voies aériennes, qu'elle ait lieu en milieu d'inspiration ou à un autre moment du cycle ventilatoire, ne constitue pas directement le point de départ de l'information comme c'est typiquement le cas pour une stimulation électrique. Au contraire, elle n'est que le promoteur du stimulus, qui va être "construit" par l'action des muscles respiratoires contre les voies aériennes occluses. Le stimulus source des potentiels évoqués respiratoires dépend donc en partie du moment auquel survient l'occlusion et des caractéristiques de l'inspiration concernée, par exemple de l'intensité la commande ventilatoire. Ceci est illustré par les différences de latences et d'amplitudes des potentiels évoqués respiratoires lorsque les occlusions sont

réalisées en début ou en milieu d'inspiration (56). Lors de l'enregistrement des potentiels évoqués respiratoires, l'intensité, la durée et la fréquence du stimulus ne sont donc pas définis à priori mais dépendent des caractéristiques de l'activité inspiratoire du sujet. Par conséquent, les potentiels évoqués respiratoires ne se présentent pas comme d'authentiques potentiels évoqués exogènes, ce qui rend délicate l'interprétation d'éventuelles anomalies des composantes précoces.

2. étude des potentiels évoqués respiratoires au cours du SAOS

2.1. absence d'anomalie de la composante P1

Des altérations des récepteurs sensoriels de la muqueuse des voies aériennes supérieures, qui pourraient participer à la prolongation des apnées, ont été mises en évidence chez les apnéiques et les ronfleurs (38). Il existe également des arguments histologiques en faveur de l'existence d'une neuropathie pharyngée sensitive ou motrice pouvant être à l'origine d'une altération du réflexe dilatateur du pharynx qui protège les voies aériennes supérieures du collapsus survenant pendant le sommeil (24). A cet égard, Dematteis et coll. ont récemment démontré que des patients apnéiques avaient un seuil de détection psychophysique d'un jet d'air appliqué sur le voile du palais plus élevé que des sujets témoins, et une sensibilité exagérée de ce seuil à l'anesthésie locale (20).

L'existence d'un lien entre neuropathie pharyngée et apnées du sommeil est également fortement soutenue par la fréquence du SAOS au cours de certaines formes de la neuropathie dégénérative congénitale de Charcot-Marie-Tooth (21) et par la corrélation retrouvée entre sévérité de la neuropathie et sévérité des troubles respiratoires pendant le sommeil.

L'absence de différence quant à la première composante P1 des potentiels évoqués respiratoires entre patients atteints de syndrome d'apnées obstructives du sommeil et sujets contrôles, suggère que l'étude des potentiels évoqués respiratoires ne constitue pas un outil adéquat pour objectiver l'impact d'une éventuelle neuropathie pharyngée au cours du SAOS. Ceci pourrait être lié au caractère relativement focal des anomalies pharyngées liées au SAOS, alors que

l'occlusion des voies aériennes pendant l'inspiration stimule très probablement cette région de façon diffuse.

Par ailleurs, il a été montré que l'anesthésie des voies aériennes supérieures par la xylocaïne majore les troubles de la sensibilité pharyngée au cours du SAOS (8, 5) et nous avons montrés que la xylocaïne ne modifie pas les potentiels évoqués respiratoires (55). Il est donc probable que les afférences mises en jeu lors des occlusions inspiratoires soient distinctes des afférences mises en jeu lorsqu'on étudie la sensibilité pharyngée et qui semblent altérées au cours du SAOS.

2.2. allongement des latences de composantes N1, P2, N2

L'allongement des latences des composantes plus tardives, est compatible avec l'existence d'anomalies du traitement cortical d'informations de nature respiratoire, comme cela a été décrit au cours du SAOS pour le traitement d'informations visuelles ou auditives (41, 51, 34).

Bien que la plupart de ces études rapportent une corrélation entre hypoxie nocturne et altérations des potentiels évoqués endogènes (34, 41), il n'est pas impossible que la fragmentation du sommeil et/ou les modifications de l'architecture du sommeil participent aux troubles cognitifs rencontrés chez les patients présentant un SAOS. Pour certains ces troubles cognitifs sont ainsi à mettre sur le compte du déficit attentionnel lié à la privation de sommeil, observé au cours de cette pathologie (28).

Quoiqu'il en soit, nos résultats, ainsi que les données fournies par les études de Gora et coll. et Affifi et coll., sont en faveur d'une altération spécifique du traitement cortical de l'occlusion inspiratoire des voies aériennes chez les patients porteurs de SAOS(27, 1) . Ces anomalies pourraient être à l'origine d'une réponse inadaptée aux informations de nature "mécaniques" envoyées au cortex cérébral pendant les épisodes de collapsus des voies aériennes survenant pendant le sommeil, ce qui pourrait constituer un facteur d'aggravation et d'auto entretien du SAOS.

En effet, la rupture d'une apnée dépend pour partie de la perception par le système nerveux central d'informations afférentes liées aux modifications respiratoires induites d'une part par l'interruption des échanges gazeux et d'autre part par l'existence d'efforts ventilatoires inefficaces. Il est donc logique de faire

l'hypothèse qu'en présence d'altérations de la perception de ces informations par le système nerveux central, les apnées puissent être plus longues et leur retentissement plus important. Il a ainsi été montré que l'interruption du traitement par pression positive continue nocturne pendant trois nuits entraîne une augmentation du niveau d'effort inspiratoire induisant le réveil chez des patients porteurs d'un SAOS sévère traité (6). Par ailleurs, la perception des signaux afférents pourrait être variable au cours de la nuit. Montserrat et coll. ont ainsi montré que la prolongation des apnées au cours de la nuit pourrait être due à un émoussement progressif de la réponse aux stimulus neurologiques produits pendant les efforts inspiratoires exercés contre l'obstruction(48) .

perspectives

1. potentiels évoqués et sensations respiratoires

Puisque les sensations respiratoires sont le fruit d'interactions multiples entre facteurs physiologiques, psychologiques, et environnementaux, il parait logique de développer des paradigmes expérimentaux permettant d'explorer des signaux de nature plus spécifiquement cognitive.

La « mismatch negativity » fournit, par exemple, une mesure objective de la discrimination auditive à partir de potentiels évoqués cognitifs (50). Il s'agit d'une composante négative qui apparaît lorsqu'on étudie la réponse corticale à un stimulus auditif « discordant », c'est à dire « rare » ou « déviant ». Par exemple un son grave est présenté avec une probabilité d'apparition de 80% et un son aigu est présenté avec une probabilité d'apparition de 20%. On peut ainsi étudier l'acuité de la discrimination entre deux stimulus plus ou moins discordants. Par exemple, il a été montré qu'il n'y avait pas de différence de « mismatch negativity » entre des sujets contrôles et des sujets dyslexiques lorsque des différences importantes de tonalités sonores étaient étudiées (90Hz). En revanche quand les différences de tonalités étaient moindres, la « mismatch negativity » avait une amplitude nettement diminuée chez les patients dyslexiques (49). Un des intérêts de cette technique est qu'elle ne nécessite pas la coopération du sujet.

On pourrait envisager d'appliquer ce type de paradigme aux sensations respiratoires en présentant aux sujets des charges inspiratoires de différents niveaux afin de mettre en évidence des troubles de la discrimination entre deux charges au cours de certaines pathologies. Dans cette optique, il pourrait être intéressant d'étudier d'éventuels parallélisme entre sévérité d'une pathologie et altération d' « une mismatch negativity » d'origine respiratoire.

En cas de confirmation de la faisabilité de ce type d'étude, il serait fondamental de comparer les résultats obtenus avec un stimulus de nature respiratoire et avec un stimulus « témoin » de nature auditive ou visuelle, afin de s'assurer du caractère spécifique « respiratoire » des anomalies cognitives ainsi mises en évidence.

Il serait également pertinent de mettre en parallèle les résultats obtenus avec ces techniques de neurophysiologie et les résultats obtenus avec des méthodes psychophysiologiques.

2. potentiels évoqués et syndrome d'apnées obstructives du sommeil

Afin de préciser la valeur des anomalies des latences des composantes tardives des potentiels évoqués respiratoires chez les patients souffrant de SAOS, il serait intéressant de poursuivre cette étude avec un plus grand nombre de patients. Ceci permettrait de rechercher d'éventuelles corrélations entre troubles du sommeil et altération des potentiels évoqués respiratoires. Par soucis de rigueur, l'utilisation de paradigme de type « cognitif » devrait être privilégiée, en y associant un enregistrement de potentiels évoqués cognitifs auditifs ou visuels permettant d'établir le caractère spécifique ou non des altérations des potentiels évoqués respiratoires. L'étude de l'effet du traitement par pression positive continue nocturne sur les allongements de latence des composantes tardives des potentiels évoqués respiratoires pourrait constituer également un moyen de progresser dans la compréhension de la signification des anomalies observées.

Par ailleurs, en vue de préciser les mécanismes à l'origine de la rupture de l'apnée au cours du SAOS, il serait intéressant de rechercher s'il existe un lien entre la terminaison de l'apnée et un éventuel potentiel cortical évoqué par l'occlusion des voies aériennes supérieures, qui survient pendant le sommeil au cours de cette pathologie. Dans cette hypothèse, le moyennage des époques d'EEG faisant suite aux efforts inspiratoires survenant lors des collapsus répétés des voies aériennes, pourrait révéler un potentiel évoqué.

Enfin, pour obtenir une traduction objective, « primaire » des anomalies des voies aériennes supérieures qui sous-tendent l'atténuation de la sensibilité pharyngée au cours du SAOS, il conviendrait de développer d'autres techniques. A cet égard, l'enregistrement de potentiels somesthésiques du voile du palais évoqués par la projection focale d'un jet d'air paraît intéressant (65).

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Déterminants physiologiques des potentiels évoqués respiratoires Application au syndrome d'apnées obstructives du sommeil

Travail réalisé au sein de l'UPRES EA2397, Université Pierre et Marie Curie, Paris 6

Les potentiels évoqués respiratoires (PER) correspondent aux projections corticales d'afférences mises en jeu lors d'occlusions inspiratoires brèves. Ils pourraient constituer un outil d'étude des voies afférentes et des systèmes d'intégrations cérébraux impliqués dans le contrôle supra-pontique de la ventilation et dans certaines sensations respiratoires. Les travaux présentés dans cette thèse visent à caractériser les déterminants des PER et à étudier leurs éventuelles modifications au cours du syndrome d'apnées obstructives du sommeil sévère.
La première étude montre que la fatigue diaphragmatique ne modifie pas les caractéristiques des PER. La deuxième étude suggère un rôle déterminant des afférences provenant des voies aériennes supérieures dans la constitution des PER. La troisième étude montre que l'anesthésie locale des voies aériennes supérieures n'affecte pas les PER. La quatrième étude révèle que la transmission au cortex cérébral d'informations relatives à l'occlusion inspiratoire des voies aériennes supérieures, est normale au cours du syndrome d'apnées obstructives du sommeil, à l'éveil. Elle met cependant en évidence l'existence d'anomalies du traitement cortical d'informations de source respiratoire. Le rôle de ces anomalies dans une éventuelle prolongation des troubles respiratoires nocturnes, reste à déterminer.
Au terme de ce travail, et aux vues des différentes données de la littérature, il apparaît que les déterminants des PER sont probablement multiples et complexes. La place de cette technique en tant qu'outil d'investigation des sensations respiratoire reste à préciser.

Mots-clefs : potentiels évoqués respiratoires, afférences respiratoires, sensations respiratoires, voies aériennes supérieures, syndrome d'apnées obstructives du sommeil, potentiels évoqués cognitifs

Physiological determinants of respiratory-related evoked potentials Application to the obstructive sleep apnea syndrome

Work carried out in the UPRES EA 2397, University Pierre et Marie Curie, paris6

Respiratory-related evoked potentials (RREP) reflect the activity of cortical neurons in response to occlusions of the airway at the mouth during inspiration. They may provide insights into afferents pathways and cortical processes underlying supra-pontine control of breathing and perception of respiratory sensations. This thesis aimed at clarifying the origin of the RREP and at assessing whether severe obstructive sleep apnea syndrome (OSAS) would be associated to changes in their characteristics, during wakefulness. The first study of this thesis showed that predominant diaphragm fatigue did not affect the RREP. The second study showed that upper airway afferents were a paramount source for the early components of the RREP. The third study showed that upper airway anesthesia did not modify the RREP. The results of the fourth study were consistent with a normal projection to the cortex of sensory inputs related to upper airway occlusion, in severe OSAS patients during wakefulness. However, these results were also consistent with an impairment of the cortical processing of these inputs. The role of this impairment in the pathogenesis of OSAS remains to be assessed.
Together with other published data, the results of this thesis suggest that the sources and the determinants of the RREP may be multiple and complex. Further investigations are therefore needed before clinical applications.

Keywords: respiratory-related evoked potentials, respiratory afferents, upper airway, respiratory sensations, obstructive sleep apnea syndrome, event-related potentials