

Effects of Experimental Sleep Restriction on Energy Intake, Energy Expenditure, and Visceral Obesity



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ABSTRACT

BACKGROUND Although the consequences of sleep deficiency for obesity risk are increasingly apparent, experimental evidence is limited and there are no studies on body fat distribution.

OBJECTIVES The purpose of this study was to investigate the effects of experimentally-induced sleep curtailment in the setting of free access to food on energy intake, energy expenditure, and regional body composition.

METHODS Twelve healthy, nonobese individuals (9 males, age range 19 to 39 years) completed a randomized, controlled, crossover, 21-day inpatient study comprising 4 days of acclimation, 14 days of experimental sleep restriction (4 hour sleep opportunity) or control sleep (9 hour sleep opportunity), and a 3-day recovery segment. Repeated measures of energy intake, energy expenditure, body weight, body composition, fat distribution and circulating biomarkers were acquired.

RESULTS With sleep restriction vs control, participants consumed more calories ($P = 0.015$), increasing protein ($P = 0.050$) and fat intake ($P = 0.046$). Energy expenditure was unchanged (all $P > 0.16$). Participants gained significantly more weight when exposed to experimental sleep restriction than during control sleep ($P = 0.008$). While changes in total body fat did not differ between conditions ($P = 0.710$), total abdominal fat increased only during sleep restriction ($P = 0.011$), with significant increases evident in both subcutaneous and visceral abdominal fat depots ($P = 0.047$ and $P = 0.042$, respectively).

CONCLUSIONS Sleep restriction combined with ad libitum food promotes excess energy intake without varying energy expenditure. Weight gain and particularly central accumulation of fat indicate that sleep loss predisposes to abdominal visceral obesity. (Sleep Restriction and Obesity; [NCT01580761](https://doi.org/10.1186/1745-7214-12-265)) (J Am Coll Cardiol 2022;79:1254-1265)
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Habitual sleep deficiency affects more than one-third of the U.S. adult population¹ and has been linked to obesity, morbidity, and premature mortality.^{2,3} Although null findings have been reported,^{4,5} observational population-based data implicating short sleep duration as a factor promoting obesity are strongly suggestive though

inferential.⁶⁻¹¹ Conversely, experimental studies on sleep curtailment and weight regulation are limited and conflicting, and few laboratory-based investigations have monitored concurrently both energy intake and energy expenditure.¹²⁻¹⁷ In addition, whether sleep loss actually induces fat gain is unclear, with major limitations of previous studies



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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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Σχόλιο:

Στο άρθρο αυτό , από την Mayo Clinic οι συγγραφείς πήραν μία ομάδα 12 υγιών μη παχύσαρκων ενηλίκων οι οποίοι συμπλήρωσαν μια τυχαιοποιημένη ελεγχόμενη μελέτη στην οποία στην πρώτη φάση κοιμόντουσαν 4 h το εικοσιτετράωρο και στην άλλη φάση είχαν χρόνο 9 h για να κοιμηθούν.

Η ομάδα με τον περιορισμό του ύπνου παρουσίασε μεγαλύτερη πρόσληψη θερμίδων και αύξηση του σωματικού βάρους, ενώ οι ενεργειακές ανάγκες ήταν σταθερές και στις δύο ομάδες.

Η ομάδα με τον περιορισμένο ύπνο εμφάνισε αύξηση του σπλαχνικού λίπους και αύξηση στην πρόσληψη θερμίδων.

Ο καλός ύπνος προστατεύει από την παχυσαρκία αλλά είναι και απαραίτητος για να έχουμε ένα επιτυχημένο πρόγραμμα αδυνατίσματος. Το αποτέλεσμα αυτής της μελέτης συμφωνεί με ανάλογα ευρήματα που έγιναν σε μελέτες του παρελθόντος.

Επιλογή άρθρου – Σχολιασμός: Μάνος Βαγιάκης

SCIENTIFIC INVESTIGATIONS

Obstructive sleep apnea and nocturnal attacks of paroxysmal atrial fibrillation

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Study Objectives: Obstructive sleep apnea (OSA) is commonly seen in patients with atrial fibrillation (AF), but it is unclear to what extent this relationship is one of causation or association. We examined a cohort of patients with paroxysmal AF to determine whether the presence of OSA (apnea-hypopnea index ≥ 15 events/h) affects the time of onset of symptomatic AF episodes.

Methods: Patients with a recent emergency department visit for a symptomatic episode of paroxysmal AF were recruited from an AF clinic. The time of onset of the AF attack was classified as occurring in "sleeping hours" or "waking hours" based on direct history from the patient and emergency department visit documentation.

Results: Of 152 patients with paroxysmal AF, 67 underwent polysomnography; 1 (1.5%) had central sleep apnea, 46 (68.7%) had mild or no OSA, and 20 (29.8%) had OSA. In the OSA group, 14/20 (70.0%) had their symptomatic AF attack during sleeping hours compared to 12/46 (26.1%) in the mild or no OSA group ($P = .001$). Compared with those who had a paroxysmal AF attack during waking hours, and adjusting for confounders, those who had a paroxysmal AF attack during sleeping hours had almost 6 times the odds of having OSA (odds ratio, 5.53; $P = .007$).

Conclusions: Compared to patients with paroxysmal AF with mild or no OSA, those with OSA were far more likely to have a symptomatic AF attack during sleeping hours, supporting a causal role for OSA in the pathogenesis of AF in this population. These findings strongly suggest that patients who have nocturnal AF attacks should be evaluated for OSA.

Keywords: obstructive sleep apnea, paroxysmal atrial fibrillation, nocturnal, left atrium

Citation: Lin C-H, Timofeeva M, O'Brien T, Lyons OD. Obstructive sleep apnea and nocturnal attacks of paroxysmal atrial fibrillation. *J Clin Sleep Med*. 2022;18(5):1279-1286.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea is known to be commonly associated with atrial fibrillation (AF). However, the clinical features in patients with AF suggestive of a causal role of obstructive sleep apnea that should prompt a sleep study have not yet been described.

Study Impact: Our study shows that patients with a paroxysmal AF attack during sleeping hours had a higher likelihood of having underlying obstructive sleep apnea than those with a paroxysmal AF attack during waking hours. This clinical feature can help physicians select or prioritize patients with AF for a sleep study.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is associated with significant morbidity and mortality and an increased use of health care resources, including an increased rate of emergency department (ED) visits and hospital admissions.^{1,2} Although rate control and/or rhythm control therapies remain key aspects of the management of AF,^{3,4} in recent years there has been an increasing emphasis on the importance of the recognition and modification of risk factors of AF in individual patients,⁵ including novel risk factors such as obstructive sleep apnea (OSA).^{5,6}

OSA is a sleep-related breathing disorder characterized by repetitive collapse of the upper airway during sleep, leading to sleep fragmentation, excessive daytime sleepiness, and an increased risk of motor vehicle accidents.⁷⁻⁹ OSA can also

interrupt the normal cardiovascular quiescence associated with sleep,^{10,11} and its presence has been associated with an increased risk of hypertension, congestive heart failure, stroke, and arrhythmias,^{12,13} along with a higher likelihood of nocturnal acute cardiac events such as myocardial infarction, ventricular arrhythmia, and sudden cardiac death.^{14,15}

Compared to the prevalence rate of moderate-severe OSA in the general population of 10%,^{9,16} in AF cohorts, studies have reported prevalence rates of OSA around 50%.¹⁷ Although some of this increased prevalence of OSA in AF populations is likely explained by shared risk factors, such as increasing adult age and obesity, there is mounting evidence suggesting that OSA could play a causal role in the development or recurrence of AF. A cross-sectional analysis from the Sleep Heart Health Study found that those with OSA had 4 times the odds of the presence of AF as compared to those without OSA, after

Σχόλιο:

Η συσχέτιση της αποφρακτικής υπνικής άπνοιας με την κολπική μαρμαρυγή έχει αναδειχθεί σε πολλές εργασίες τα τελευταία χρόνια. Στην εργασία αυτή η συγγραφείς μελέτησαν ασθενείς που ήρθαν στα επείγοντα του νοσοκομείου λόγω κολπικής μαρμαρυγής.

Τους διαίρεσαν ανάλογα με το χρόνο εμφάνισης της κολπικής μαρμαρυγής εντός του 24ώρου. Ο χρόνος εμφάνισης της κολπικής μαρμαρυγής κατηγοριοποιήθηκε ως συμβάν ανάλογα με τις ώρες ύπνου ή τις ώρες εγρήγορσης (όπως αναφέρθηκε στο ιστορικό του ασθενούς και του χρόνου επίσκεψης στο τμήμα επειγόντων). Από τους 152 ασθενείς με παροξυσμική κολπική μαρμαρυγή, 67 υπεβλήθησαν σε πολυπνογραφία και βρέθηκε ότι 46,68% δεν είχαν άπνοια ή είχαν ήπια άπνοια και το 29,8% είχαν αποφρακτική άπνοια. Στην ομάδα της αποφρακτικής άπνοιας, το 70% είχαν την έναρξη της κολπικής μαρμαρυγής κατά τη διάρκεια των ωρών ύπνου σε αντίθεση με το 26% που είχαν ήπια άπνοια ή καθόλου άπνοια και εμφάνισε την κολπική μαρμαρυγή τις ώρες ύπνου.

Τα συμπεράσματα των συγγραφέων ήταν ότι οι ασθενείς με υπνική άπνοια είναι πολύ περισσότερο πιθανό να έχουν έναρξη κολπικής μαρμαρυγής κατά τη διάρκεια του ύπνου, γεγονός που συνηγορεί για τον αιτιολογικό ρόλο της υπνικής άπνοιας στην παθογένεση της κολπικής μαρμαρυγής.

Τα ευρήματα αυτά συνηγορούν στο ότι οι ασθενείς οι οποίοι εμφανίζουν κολπική μαρμαρυγή κατά τη διάρκεια του ύπνου πρέπει να εξετάζονται για την ύπαρξη υπνικής άπνοιας.

Επιλογή άρθρου – Σχολιασμός: Μάνος Βαγιάκης

Incidence of VTE in Patients With OSA

A Cohort Study



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BACKGROUND: Previous studies suggesting that OSA may be an independent risk factor for VTE have been limited by reliance on administrative data and lack of adjustment for clinical variables, including obesity.

RESEARCH QUESTION: Does OSA confer an independent risk of incident VTE among a large clinical cohort referred for sleep-disordered breathing evaluation?

STUDY DESIGN AND METHODS: We analyzed the clinical outcomes of 31,309 patients undergoing overnight polysomnography within a large hospital system. We evaluated the association of OSA severity with incident VTE, using Cox proportional hazards modeling accounting for age, sex, BMI, and common comorbid conditions.

RESULTS: Patients were of mean age 50.4 years, and 50.1% were female. There were 1,791 VTE events identified over a mean follow-up of 5.3 years. In age- and sex-adjusted analyses, each 10-event/h increase in the apnea-hypopnea index was associated with a 4% increase in incident VTE risk (hazard ratio [HR], 1.04; 95% CI, 1.02-1.06). After adjusting for BMI, this association disappeared (HR, 1.01; 95% CI, 0.99-1.03). In contrast, nocturnal hypoxemia had an independent association with incident VTE. Patients with > 50% sleep time spent with oxyhemoglobin saturation < 90% are at 48% increased VTE risk compared with those without nocturnal hypoxemia (HR, 1.48; 95% CI, 1.16-1.69).

INTERPRETATION: In this large cohort, we found that patients with more severe OSA as measured by the apnea-hypopnea index are more likely to have incident VTE. Adjusted analyses suggest that this association is explained on the basis of confounding by obesity. However, severe nocturnal hypoxemia may be a mechanism by which OSA heightens VTE risk.

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KEY WORDS: epidemiology; incidence; obesity; OSA; VTE

ABBREVIATIONS: AHI = apnea-hypopnea index; CSA = central sleep apnea; EHR = electronic health record; HR = hazard ratio; PE = pulmonary embolus; T90 = percentage of sleep time with oxyhemoglobin saturation < 90%

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Σχόλιο:

Επίπτωση της θρομβοεμβολικής νόσου σε ασθενείς με Αποφρακτική Υπνική Άπνοια (μελέτη κοόρτης)

Η μελέτη αυτή προσπάθησε να απαντήσει στο ερώτημα εάν η αποφρακτική υπνική άπνοια αποτελεί ανεξάρτητο παράγοντα κινδύνου για θρομβοεμβολικά επεισόδια. Η αποφρακτική υπνική άπνοια προκαλεί υπερπηκτικότητα μέσω της φλεγμονής, της διαταραχής του ενδοθηλίου των αγγείων και της ενεργοποίησης των αιμοπεταλίων. Επιπλέον, η παχυσαρκία που συχνά συνυπάρχει με την υπνική άπνοια αυξάνει τον κίνδυνο για θρομβοεμβολικά επεισόδια.

Αναλύθηκαν 31.309 άτομα τα οποία υποβλήθηκαν σε πολυκαταγραφική μελέτη ύπνου και συσχετίστηκε η βαρύτητα της αποφρακτικής άπνοιας με βάση τον AHI και το ποσοστό του χρόνου ύπνου στον οποίο οι ασθενείς έχουν κορεσμό αιμοσφαιρίνης σε οξυγόνο <90% με τον κίνδυνο θρομβοεμβολικών επεισοδίων σε μια μέση περίοδο παρακολούθησης 5,3 ετών.

Η νυκτερινή υποξαιμία έδειξε να αποτελεί ανεξάρτητο παράγοντα κινδύνου για θρομβοεμβολικά επεισόδια. Ασθενείς οι οποίοι είχαν SatO₂<90% για >50% του χρόνου ύπνου, εμφάνιζαν 48% μεγαλύτερη πιθανότητα να εμφανίσουν κάποιο θρομβοεμβολικό επεισόδιο σε σχέση με τους υπόλοιπους ασθενείς. Η αύξηση του κινδύνου σε σχέση με την αύξηση του AHI φάνηκε να σχετίζεται κυρίως με την συνύπαρξη παχυσαρκίας.

Περιορισμούς της μελέτης αποτελούν η πιθανή συνύπαρξη και άλλων νοσημάτων ως αίτια της νυκτερινής υποξαιμίας, όπως η χρόνια αποφρακτική πνευμονοπάθεια δεδομένου ότι δεν έγινε λειτουργικός έλεγχος πνευμόνων σε όλους τους ασθενείς, ή το σύνδρομο υποαερισμού-παχυσαρκίας. Επίσης, αναφέρεται από τους συγγραφείς ότι δεν υπήρχαν στοιχεία για τη λήψη αντιπηκτικής αγωγής ή τη χρήση θεραπειών για την αποφρακτική υπνική άπνοια.”

Επιλογή άρθρου – Σχολιασμός: Αθηνά Βλάχου

SCIENTIFIC INVESTIGATIONS

Dose-response relationship between weight loss and improvements in obstructive sleep apnea severity after a diet/lifestyle interventions: secondary analyses of the “MIMOSA” randomized clinical trial

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Study Objectives: Lifestyle-induced weight loss is a complementary therapeutic approach for obstructive sleep apnea (OSA). We aimed at identifying the dose-response relationship between weight loss and OSA severity improvement.

Methods: This is a secondary analysis of a 6-month clinical trial in 180 adult, overweight/obese moderate-to-severe OSA patients. Participants were randomized to a standard care, a Mediterranean diet, or a Mediterranean lifestyle arm. All patients were prescribed with continuous positive airway pressure (CPAP), while intervention arms additionally participated in a weight-loss dietary/lifestyle intervention. Based on percent change in weight at 6 months, participants were categorized into a weight-stable/gain (WS/GG) group or 3 weight-loss groups (WLG): < 5%WLG, 5%–10%WLG, and ≥ 10%WLG. Polysomnographic data and OSA symptoms were evaluated preintervention and postintervention.

Results: Respiratory events and oximetry indices improved only in patients who lost weight and improvements were proportional to the degree of weight loss. Median percent change in apnea-hypopnea index (AHI) was –11.7%, –37.9%, and –49.3% in the < 5%WLG, 5%–10%WLG, and ≥ 10%WLG, respectively ($P < .001$). Compared to the WS/GG, the age-, sex-, baseline-, and CPAP use–adjusted relative risk (95% confidence interval) of severe OSA (AHI ≥ 30 events/h) was 0.45 (0.23–0.87) in the 5%–10%WLG and 0.32 (0.17–0.64) in the ≥ 10%WLG; the risk was also lower in the ≥ 10%WLG vs the < 5%WLG (0.42 [0.22–0.82]). Insomnia and daytime sleepiness also improved more in participants exhibiting ≥ 5% weight loss.

Conclusions: Even a < 5% weight loss can reduce respiratory events, but a ≥ 5% and ideally ≥ 10% weight loss is necessary for reducing the prevalence of severe OSA.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Mediterranean Diet/Lifestyle Intervention in Obstructive Sleep Apnea; URL: <https://clinicaltrials.gov/ct2/show/NCT02515357>; Identifier: NCT02515357.

Keywords: sleep apnea, apnea-hypopnea index, oximetry, weight loss, dose-response analysis

Citation: Georgoulis M, Yiannakouris N, Kechribari I, et al. Dose-response relationship between weight loss and improvements in obstructive sleep apnea severity after a diet/lifestyle intervention: secondary analyses of the “MIMOSA” randomized clinical trial. *J Clin Sleep Med*. 2022;18(X):XXX–XXX.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Weight loss is essential for obstructive sleep apnea (OSA) management. Although a positive association between the amount of weight loss and improvements in OSA severity has been reported, this dose-response relationship is not supported by all available data and optimal weight loss goals for OSA require further research.

Study Impact: Our results confirm a dose-response relationship between the degree of weight loss achieved through a dietary/lifestyle intervention and improvements in OSA severity. Even a < 5% weight loss was sufficient for improvements in respiratory events and oximetry indices, but the prevalence of severe OSA reduced only after a ≥ 5% weight loss, and patients achieving a ≥ 10% weight loss exhibited the greatest benefits compared to weight-stable/gain patients.

INTRODUCTION

Obstructive sleep apnea (OSA) represents one of the most common and serious sleep-related breathing disorders, with a high worldwide prevalence of almost 1 billion people¹ and well-established cardiometabolic consequences.² Excess body weight has emerged as the strongest modifiable predictor of the onset and severity of OSA.³ The prevalence of OSA in adults with obesity is almost twice compared to adults of normal weight, and approximately 40% of adult OSA cases are attributable to obesity.⁴ The involvement of obesity in the pathophysiology of OSA can be explained through several

mechanisms, including (1) central fat accumulation, mainly in abdominal viscera and around the neck, leading to increased mechanical load on upper airways; (2) increased leptin resistance, which can impair central respiratory control and lead to abnormal hypercapnic ventilatory response; (3) expression of proinflammatory cytokines, which negatively impact upper airway neuromuscular control; and (4) a state of increased oxidative stress, which reduces the force-generating capacity of upper airway muscles.⁵

On the basis of the well-established causal association between obesity and OSA, lifestyle-induced weight loss is currently advocated as an ancillary treatment for the disease. Available clinical

Georgoulis M, Yiannakouris N, Kechribari I, Lamprou K, Perraki E, Vagiakis E, Kontogianni MD. Dose-response relationship between weight loss and improvements in obstructive sleep apnea severity after a diet/lifestyle intervention: secondary analyses of the "MIMOSA" randomized clinical trial. *J Clin Sleep Med.* 2022 May 1;18(5):1251-1261. doi: 10.5664/jcsm.9834. PubMed PMID: 34915980. Πρωτότυπη εργασία.

Θεωρητικό υπόβαθρο: Η απώλεια βάρους έχει αναδειχθεί ως μια αποτελεσματική συμπληρωματική θεραπευτική προσέγγιση για τη διαχείριση της αποφρακτικής άπνοιας ύπνου (ΑΑΥ). Αν και στη βιβλιογραφία έχει αναφερθεί μια θετική συσχέτιση ανάμεσα στον βαθμό απώλειας βάρους και τη βελτίωση της βαρύτητας της ΑΑΥ, αυτή η δοσοεξαρτώμενη σχέση δεν υποστηρίζεται από όλα τα διαθέσιμα δεδομένα και δεν υπάρχουν καλά καθορισμένοι στόχοι απώλειας βάρους για τους ασθενείς με ΑΑΥ.

Σκοπός: Σκοπός της παρούσας μελέτης ήταν η διερεύνηση της επίδρασης διαφορετικών ποσοστών απώλειας βάρους στη διαχείριση της ΑΑΥ.

Μεθοδολογία: Πραγματοποιήθηκε δευτερεύουσα ανάλυση των δεδομένων μιας τυχαιοποιημένης ελεγχόμενης κλινικής δοκιμής διάρκειας 6 μηνών σε 180 ενήλικες, υπέρβαρους/παχύσαρκους ασθενείς με μέτρια/σοβαρή ΑΑΥ [δείκτης απνοιών-υποπνοιών (ΔΑΥ) ≥ 15 επεισόδια/ώρα]. Οι συμμετέχοντες τυχαιοποιήθηκαν στην ομάδα συνήθους φροντίδας, στην ομάδα Μεσογειακής δίαιτας ή στην ομάδα Μεσογειακού τρόπου ζωής. Και στις 3 ομάδες της μελέτης συνταγογραφήθηκε θεραπεία χορήγησης συνεχούς θετικής πίεσης στους αεραγωγούς (CPAP), ενώ οι ομάδες εντατικής παρέμβασης συμμετείχαν επιπλέον σε μια συμπεριφορική παρέμβαση απώλειας βάρους βασισμένη στο Μεσογειακό πρότυπο διατροφής/τρόπου ζωής διάρκειας 6 μηνών (7 συμβουλευτικές συνεδρίες με διαιτολόγο). Βάσει της ποσοστιαίας μεταβολής βάρους στον 6μηνο επανέλεγχο, οι συμμετέχοντες κατηγοριοποιήθηκαν σε μια ομάδα σταθερού βάρους ή αύξησης βάρους (ΟΣ/ΑΒ) (n=43) ή σε τρεις ομάδες απώλειας βάρους (OAB): OAB $<5\%$ (n=38), OAB $_{5-10\%}$ (n=52) και OAB $\geq 10\%$ (n=47). Οι συμμετέχοντες υποβλήθηκαν σε παρακολούθησιμη πολυυπνογραφία και αξιολογήθηκαν ως προς τα συμπτώματα της ΑΑΥ πριν και μετά την παρέμβαση. Η ανάλυση των δεδομένων πραγματοποιήθηκε με τη μέθοδο πρόθεση για θεραπεία (n=180).

Αποτελέσματα: Στο σύνολο του δείγματος παρατηρήθηκε μια ισχυρή θετική συσχέτιση ανάμεσα στην ποσοστιαία μεταβολή του σωματικού βάρους και την ποσοστιαία μεταβολή του ΔΑΥ (rho: 0,723, P<0,001). Τα αναπνευστικά επεισόδια (άπνοιες, υπόπνοιες, επεισόδια αποκορεσμού οξυγόνου) και οι δείκτες οξυμετρίας (ελάχιστος κορεσμός οξυγόνου και χρόνος με κορεσμό οξυγόνου <90%) βελτιώθηκαν μόνο στους ασθενείς που έχασαν βάρος και οι βελτιώσεις ήταν ανάλογες του βαθμού απώλειας βάρους. Η διάμεση (1^ο, 3^ο τεταρτημόριο) ποσοστιαία μεταβολή του ΔΑΥ ήταν -0,50% (-11,1, 16,7) στην ΟΣ/ΑΒ, -11,7% (-32,3, -2,78) στην OAB $<5\%$, -37,9% (-43,5, -14,7) στην OAB $_{5-10\%}$ και -49,3% (-72,3, -34,1) στην OAB $\geq 10\%$ (P_{μεταξύ_ομάδων}<0,001). Στον 6μηνο επανέλεγχο, ο προσαρμοσμένος για την ηλικία, το φύλο, την προ-παρέμβασης βαρύτητα της ΑΑΥ και την ημερήσια χρήση CPAP σχετικός κίνδυνος (95% διάστημα εμπιστοσύνης) σοβαρής ΑΑΥ (ΔΑΥ ≥ 30 επεισόδια/ώρα) ήταν 0,45 (0,23, 0,87) στην OAB $_{5-10\%}$ και 0,32 (0,17, 0,64) στην OAB $\geq 10\%$ συγκριτικά με την ΟΣ/ΑΒ, και 0,42 (0,22-0,82) στην OAB $\geq 10\%$ συγκριτικά με την OAB $<5\%$. Τα συμπτώματα αϋπνίας (σκορ στην κλίμακα αϋπνίας Αθηνών) και ημερήσιας υπνηλίας (σκορ στην κλίμακα υπνηλίας Erworth) βελτιώθηκαν, επίσης, περισσότερο στους συμμετέχοντες που εμφάνισαν απώλεια βάρους $\geq 5\%$.

Συμπεράσματα: Τα ευρήματα της παρούσας μελέτης επιβεβαιώνουν μια δοσοεξαρτώμενη σχέση ανάμεσα στον βαθμό απώλειας βάρους και τη βελτίωση της βαρύτητας της ΑΑΥ. Ακόμη και μια ήπια απώλεια βάρους (<5%) μπορεί να βελτιώσει τα αναπνευστικά επεισόδια και τα συμπτώματα της ΑΑΥ, αλλά μια μεγαλύτερη απώλεια βάρους, $\geq 5\%$ και ιδανικά $\geq 10\%$, φαίνεται να είναι απαραίτητη για τη μετάβαση από σοβαρής σε ηπιότερης βαρύτητας νόσο.

Σχολιασμός άρθρου : Μιχάλης Γεωργούλης

Evaluation and Management of Snoring



Yoke-Yeow Yap, MD, MMed (ORL-HNS)

KEYWORDS

- Snoring • Sleep-disordered breathing • Obstructive sleep apnea • Phenotypes
- Nasal airway complex • Mouth breathing

KEY POINTS

- Snoring can be harmless (primary) or a symptom of sleep-disordered breathing (SDB) (secondary) and should alert the physician to evaluate the patient for risks thereof.
- Phenotypes of snoring and SDB are anatomic and nonanatomic and identifying these phenotypes and their interrelationships are critical to effective therapy.
- Mouth breathing alerts the physician to nasal airway obstruction, signals orofacial growth changes in children, and heralds the progression of SDB.
- Systematic evaluation to establish phenotypes includes assessing sleep habits, comorbidities, upper airway examination, polysomnography, and drug-induced sleep endoscopy.
- Strategies for treatment should be personalized and precise to the phenotype(s) to achieve the most benefit.

INTRODUCTION

Snoring is biomechanically a vibratory noise produced in sleep from a cyclical obstruction and reopening of the upper airway at approximately $50x/s^1$, arising from the soft palate (100%), pharynx (53.8%), lateral pharyngeal wall (42.3%), epiglottis (42.3%), and tongue base (26.9%).² Solitary palatal fluttering is seen in simple snorers, palate & lateral pharyngeal wall vibration in mild-to-moderate obstructive sleep apnea (OSA), and combined palate-lateral pharyngeal wall-tongue base-epiglottis vibration in severe OSA.² Snoring in OSA occurs mostly in apnea-terminating hyperpneas when turbulence is maximum.³

SNORING AND SLEEP-DISORDERED BREATHING

Snoring indicates a 5x increased risk of OSA.⁴ In an online survey of 664 women and 575 men in the United Kingdom aged 18 to 100 years, snoring was reported in 38% of men and 30.4% of women, while pauses in breathing was reported in 8.7% of men and 5.6% of women.⁵ In women, regular

snoring is associated with increased risk of coronary heart disease (risk ratio (RR): 2.18) and stroke (RR 1.88)⁶. Primary snoring is not associated with sleepiness or medical hazards, whereas secondary snoring is symptomatic of sleep-disordered breathing (SDB)—a spectrum from upper airway resistance syndrome (UARS), to mild, moderate, and severe OSA. Population-based studies show 9% to 38% of adults more than 18 years old have OSA—13% to 33% in men and 6% to 19% in women and increases to 90% in men and 78% in women greater than 65 years of age.⁷ Multiple systemic chronic illnesses are associated with SDB.⁸ Polysomnographic classification, however, does not correlate well with the quality of life and comorbidities of SDB, nor does it guide treatment or predict outcome in a widely heterogeneous problem.

CAUSES AND PHENOTYPES OF SNORING AND SLEEP-DISORDERED BREATHING

Phenotyping and integrated analysis of multiple factors, augmented by machine learning, is needed to arrive at unique and meaningful categories to

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Σχόλιο:

Το ροχαλητό μπορεί να είναι καλοήθες (απλό ή πρωτοπαθές) ή να αποτελεί σύμπτωμα διαταραχής της αναπνοής στον ύπνο (δευτεροπαθές) η οποία πρέπει να αξιολογείται και να διερευνάται.

Η ταυτοποίηση των διαφόρων φαινοτύπων ροχαλητού και διαταραχών αναπνοής στον ύπνο, που διακρίνονται σε ανατομικούς και μη ανατομικούς, είναι σημαντική για την επιλογή της θεραπείας.

Η στοματική αναπνοή θέτει την υποψία ρινικής απόφραξης και γναθοπροσωπικών αναπτυξιακών παθήσεων στα παιδιά και αποτελεί προδρομικό σημείο μετάπτωσης σε σύνδρομο αποφρακτικής άπνοιας στον ύπνο. Επιπλέον, ανώμαλη έκφυση των οδόντων και αλλαγές στη συμπεριφορά ενός παιδιού θα πρέπει να εγείρουν την υπόνοια πιθανής ύπαρξης διαταραχής της αναπνοής στον ύπνο.

Η συστηματική αξιολόγηση για τον καθορισμό του συγκεκριμένου φαινοτύπου εμπεριέχει την εκτίμηση των συνηθειών και υγιεινής ύπνου, των ενδεχόμενων συννοσηροτήτων, την κλινική εξέταση του ανώτερου αεραγωγού (τόσο η ανατομία των μαλακών ιστών όσο και των δομών του σκελετού, αλλά και το εύρος κινητικότητας της γλώσσας θα πρέπει να εξετάζονται), την πολυύπνογραφία και την ενδοσκόπηση του αεραγωγού κατά τη διάρκεια του ύπνου (DISE).

Η θεραπευτική στρατηγική επιλέγεται μετά από ενδελεχή έλεγχο του φαινοτύπου του ασθενούς και προσωποποιείται για την επίτευξη του βέλτιστου αποτελέσματος.

Στο άρθρο αυτό περιγράφονται με αναλυτικό τρόπο οι ανατομικές παράμετροι και οι δυναμικοί αιτιοπαθογενετικοί μηχανισμοί του ροχαλητού ως παράγοντα διαταραχής της αναπνοής στον ύπνο, αλλά και οι επιλογές θεραπευτικής παρέμβασης, ενώ τονίζεται ακόμα μια φορά πως κάθε ασθενής που αναφέρει ροχαλητό πρέπει να διερευνάται για σημεία και συμπτώματα συμβατά με τέτοιες διαταραχές.

Επιλογή άρθρου - Σχολιασμός: Άγης Δέρβας



Sleep Difficulties among Mexican Adolescents: Subjective and Objective Assessments of Sleep

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ABSTRACT

Objective/Background: Self-reported sleep difficulties, such as insomnia symptoms, have been reported among adolescents. Yet, studies of their prevalence and correlates are scarce among Latin Americans. This study sought (1) to describe associations between sociodemographic and lifestyle factors with self-reported sleep difficulties and (2) to examine associations between self-reported sleep difficulties and actigraphy-based sleep.

Participants: Participants included 477 Mexican adolescents from the ELEMENT cohort.



Methods: Over 7 days, self-reported sleep measures (hard time falling asleep, overall sleep difficulties, and specific types of sleep difficulties) were obtained from daily sleep diaries. Actigraphy-based sleep measures (duration, i.e. sleep onset to morning wake, midpoint, and fragmentation) were concurrently assessed using a wrist actigraph.


Results: Mean (SD) age was 15.9 (2.2) years, and 53.5% were females. Mean (SD) sleep duration was 8.5 (1.2) h/night. Half reported a hard time falling asleep at least 3 days, and 25% had sleep difficulties at least 3 days over 7 days. The 3 types of sleep difficulties commonly reported among the entire cohort were insomnia/restlessness (29%), environmental (27%), and mental/emotional difficulties (19%). Female sex, smoking behavior, and socioeconomic indicators were among the most consistent factors associated with sleep difficulties. Subjective sleep difficulties were associated with shorter sleep duration ($\beta = -20.8 [-35.3, -6.2]$ min), while subjective hard time falling asleep was associated with longer sleep duration ($\beta = 11.3 [4.6, 27.2]$ min).

Conclusion: A high proportion of Mexican adolescents in the sample reported sleep difficulties. Findings demonstrate the importance of obtaining subjective and objective sleep measures for a more comprehensive assessment of adolescent sleep.

Introduction

Sleep deprivation among adolescents is a global public health issue (Do et al., 2013; Garaulet et al., 2011; Hysing et al., 2013; Meldrum & Restivo, 2014), although studies in Latin American populations

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 Supplemental data for this article can be accessed on the [publisher's website](#).

Σχόλιο:

Εισαγωγή: Οι αυτό-αναφερόμενες διαταραχές του ύπνου, όπως η αϋπνία αναφέρονται συχνά από εφήβους, όμως λίγες μελέτες υπάρχουν πάνω σε αυτό στο θέμα στην λατινική Αμερική. Αυτή η μελέτη περιγράφει συσχετίσεις μεταξύ κοινωνικοοικονομικών και περιβαλλοντικών παραγόντων με βάση την αυτό-αναφορά από ερωτηματολόγια. Επιπλέον, εξετάστηκαν συσχετίσεις μεταξύ αυτό-αναφοράς των παθήσεων του ύπνου και της ακτιγραφίας. Οι συμμετέχοντες ήταν 477 έφηβοι μεξικανοί από την μελέτη ELEMENT.

Μέθοδοι: Αυτό-αναφορά με βάση ερωτηματολόγια για 7 μέρες συμπτωμάτων. Εξετάστηκαν δυσκολία στην έναρξη του ύπνου, γενικά διαταραχές του ύπνου και ειδικές διαταραχές του ύπνου. Επίσης έγινε χρήση ακτιγραφίας στο χέρι (μέτρηση διάρκειας ύπνου, κατακερματισμός, μέτρηση πρωινών εγέρσεων του ύπνου).

Αποτελέσματα: Μέση ηλικία ήταν 15,9 έτη και το 53,5% ήταν έφηβες. Μέση διάρκεια του ύπνου ήταν 8,5 ώρες το βράδυ. Οι μισοί από τους συμμετέχοντες ανέφεραν ότι είχαν δυσκολία να κοιμηθούν για τουλάχιστον 3 μέρες την εβδομάδα και το 25% ανέφερε διαταραχές του ύπνου γενικά για το ίδιο χρονικό διάστημα. Οι 3 πιο κοινοί τύποι διαταραχών του ύπνου ήταν αϋπνία (29%), περιβαλλοντικοί (27%) και ψυχολογικοί παράγοντες (19%). Γυναικείο φύλο, κάπνισμα και δεινοί κοινωνικοοικονομικοί παράγοντες ήταν οι κύριες αιτίες που σχετίζονταν με διαταραχές του ύπνου γενικά. Υποκειμενικές διαταραχές του ύπνου (με βάση αυτό-αναφορά) σχετίζονταν με μειωμένη διάρκεια του ύπνου περίπου 20 λεπτών ενώ η δυσκολία στην επέλευση του ύπνου σχετιζόταν με μεγαλύτερη διάρκεια ύπνου συνολικά κατά περίπου 11,3 λεπτά.

Συμπέρασμα: ένα ικανό ποσοστό από εφήβους μεξικανικής καταγωγής ανέφεραν διαταραχές του ύπνου. Η χρήση αντικειμενικών μετρήσεων και ερωτηματολογίων είναι αρκετά χρήσιμη στην διερεύνηση αυτών των πληθυσμών

Σχόλιο: Το 1/3 των εφήβων μεξικανικής καταγωγής έχουν αναφερόμενες διαταραχές του ύπνου περίπου σε για σχεδόν την μισή βδομάδα. Κοινωνικοοικονομικοί παράγοντες και κάπνισμα παίζουν σημαντικό ρόλο στην δυσκολία επέλευσης του ύπνου σε αυτούς τους πληθυσμούς.

Επιλογή άρθρου – Σχολιασμός: Δημήτριος Κάντας



Insomnia Severity and Degree of Dysfunction: What Is to Be Learned When These Domains are Discordant?

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ABSTRACT

Objective/Background: Illness severity and resultant dysfunction are often linearly related and tightly coupled (concordant). Some percentage of individuals, however, exhibit discordant associations (high illness severity and low dysfunction [HL] or low illness severity and high dysfunction [LH]). In the present study, a sample of subjects with insomnia complaints were evaluated to determine what percentage of subjects exhibited discordant associations.

Participants: Archival data were drawn from a community-based sample ($n = 4,680$; 61.8% female; Ages 18–105).

Methods: Median splits were calculated for illness severity and daytime dysfunction and each individual was typed as High (H) or Low (L) for the concordant (HH and LL) and discordant domains (HL and LH).





Results: Given this typology, 61% were classified as concordant and 39% were classified as discordant. Of these, 38% were sub-typed as HH, 23% as LL, 26% as LH, and 13% as HL.

Conclusions: We propose that some of the discordance may be ascribable to a mismatch between sleep need and sleep ability. Those “who need a lot, may suffer a lot, in the face of only a little (LH)”, whereas those “who need a little, may suffer only a little, in the face of a lot (HL)”.

Introduction

In clinical practice and research, it is nearly axiomatic that illness positivity and/or severity and resultant dysfunction be linearly related and tightly coupled (concordant). This said, it is also commonly observed that some percentage of individuals exhibit discordant associations between pathophysiologic measures (and/or reported or observed symptoms) and patient-reported consequences. Such observations have been made for a variety of disorders such as chronic pain, cardiovascular disease, infectious disease, and insomnia disorder (Fichten et al., 1995; Greco et al., 2015; Mizumoto et al., 2020; Pan & Jones, 2018). Taking into account such discordances may provide clues regarding the factors that moderate or mediate disease expression and/or individual suffering.

In the context of sleep, there are instances where the sleep continuity disturbance (i.e., insomnia) and the related consequences do not align. The concept that individuals can experience poor sleep but not experience distress, dissatisfaction, or dysfunction was first described by Fichten and colleagues in 1995. In this study, 396 subjects between the ages of 55 and 88 completed a variety of sleep measures (sleep history, sleep behaviors, sleep distress, and daytime sleepiness), psychological adjustment (arousal, anxiety, worry, and life

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Σχόλιο:

Background: Η βαρύτητα της αϋπνίας και η συνεπακόλουθη κλινική δυσλειτουργία του ατόμου έχουν γραμμική συσχέτιση και σχεδόν πάντα υπάρχει σύζευξη μεταξύ τους. Παρόλα αυτά κάποιοι ασθενείς εμφανίζουν ασυμβίβαστη εικόνα βαρύτητας νόσου και κλινικής εικόνας (αυξημένη βαρύτητα και μικρή κλινική δυσλειτουργία ή χαμηλή βαρύτητα και δυσανάλογα αυξημένη κλινική δυσλειτουργία). Η παρούσα μελέτη εξετάζει αυτή την αποκλίνουσα συσχέτιση μεταξύ βαρύτητας και δυσλειτουργίας.

Συμμετέχοντες: Τα δεδομένα αναλύθηκαν από μία βάση δεδομένων $n = 4,680$; 61.8% γυναίκες ηλικίες 18–105.

Μέθοδοι: Η μέση απόκλιση μετρήθηκε στατιστικά στις δύο μεταβλητές (βαρύτητα νόσου και κλινική δυσλειτουργία).

Αποτελέσματα: Με βάση την ανάλυση 61% των συμμετεχόντων κατηγοριοποιήθηκε σαν συγκλίνουσα κλινική εικόνας και βαρύτητα και το 39% σαν αποκλίνουσα.

Αποτελέσματα: Η υπόθεση εργασίας είναι ότι υπάρχει απόκλιση μεταξύ ανάγκης για ύπνου και δυνατότητας να κοιμηθεί κάποιο άτομο. Αυτοί που “ χρειάζονται πολύ ύπνο μπορεί να έχουν σοβαρή κλινική δυσλειτουργία” από την άλλη αυτοί που “ χρειάζονται λίγο ύπνο μπορεί να έχουν μικρή δυσλειτουργία”.

Σχόλιο: “Όσον αφορά την αϋπνία μπορεί να υπάρχει απόκλιση μεταξύ κλινικής εικόνας και βαρύτητας της νόσου. Σε ποσοστό περίπου 39 % φαίνεται ότι υπάρχει απόκλιση ενώ η σύγκλιση είναι περίπου 61 %. Από τα ανωτέρω προκύπτει “ότι one size does not fit all”.

Επιλογή άρθρου – Σχολιασμός: Δημήτριος Κάντας



Sleep apnoea and heart failure

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Number 2 in the series “Challenges in sleep apnoea”
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Shareable abstract (@ERSpublications)

Obstructive sleep apnoea (OSA) may result in myocardial damage. Central sleep apnoea (CSA-CSR) occurs as a consequence of heart failure (HF). There is a worse prognosis than in HF without sleep apnoea. More evidence is needed regarding treatment impact. <https://bit.ly/2Xn1j3i>

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Abstract

Heart failure and sleep disordered breathing (SDB) are two common conditions that frequently overlap and have been studied extensively in the past three decades. Obstructive sleep apnoea (OSA) may result in myocardial damage due to intermittent hypoxia that leads to increased sympathetic activity and transmural pressures, low-grade vascular inflammation, and oxidative stress. On the other hand, central sleep apnoea and Cheyne–Stokes respiration (CSA-CSR) occurs in heart failure, irrespective of ejection fraction, either reduced (HF_rEF), preserved (HF_pEF) or mildly reduced (HF_{mr}EF). The pathophysiology of CSA-CSR relies on several mechanisms leading to hyperventilation, breathing cessation and periodic breathing. Pharyngeal collapse may result at least in part from fluid accumulation in the neck, owing to daytime fluid retention and overnight rostral fluid shift from the legs. Although both OSA and CSA-CSR occur in heart failure, the symptoms are less suggestive than in typical (non-heart failure-related) OSA. Overnight monitoring is mandatory for a proper diagnosis, with accurate measurement and scoring of central and obstructive events, since the management will be different depending on whether the sleep apnoea in heart failure is predominantly OSA or CSA-CSR. SDB in heart failure is associated with worse prognosis, including higher mortality, than in patients with heart failure but without SDB. However, there is currently no evidence that treating SDB improves clinically important outcomes in patients with heart failure, such as cardiovascular morbidity and mortality.

Introduction

Heart failure is a clinical syndrome with current or prior symptoms and/or signs caused by a structural and/or functional cardiac abnormality, corroborated by either elevated natriuretic peptide and/or objective evidence of cardiogenic pulmonary or systemic congestion [1]. A characteristic feature of heart failure is its association with neurohumoral activation and, in particular, increased sympathetic nervous system activity (SNA) [2]. The clinical manifestations of heart failure may vary from a largely asymptomatic state (with treatment) to a variable combination of symptoms of variable severity. The prevalence of heart failure ranges from ~1% in subjects aged 45–54 years to >10% in subjects aged >75 years. Heart failure represents an important healthcare problem, especially in the elderly, because of its association with low quality of life (QoL), high healthcare costs largely due to frequent hospital admission and poor prognosis.

Σχόλιο:

Η καρδιακή ανεπάρκεια και το ΣΑΑΥ είναι δύο συχνές παθήσεις που αλληλοκαλύπτονται και έχουν αμφίδρομη σχέση. Το ΣΑΑΥ προκαλεί μυοκαρδιακή βλάβη λόγω της διαλείπουσας υποξίας, αύξησης τόνου συμπαθητικού, διατοχωματικών πιέσεων, χαμηλής έντασης αγγειακή φλεγμονή και οξειδωτικό stress. Αντίθετα οι κεντρικές άπνοιες και η αναπνοή Cheyne-Stokes παρατηρούνται στην καρδιακή ανεπάρκεια ανεξάρτητα από το κλάσμα εξώθησης με μηχανισμούς που προκαλούν υπεραερισμό, παύσεις αναπνοής και περιοδική αναπνοή. Αποφρακτικές άπνοιες λόγω σύγκλεισης του φάρυγγα γίνονται από κατακράτηση υγρών την ημέρα και μετακίνηση υγρών την νύκτα από τα πόδια. ΣΑΑΥ και περιοδική αναπνοή συνυπάρχουν στην καρδιακή ανεπάρκεια, τα συμπτώματα όμως δεν είναι εμφανή όπως στο ΣΑΑΥ. Η μελέτη ύπνου είναι απαραίτητη λόγω της διαφορετικής θεραπείας (επικρατεί το ΣΑΑΥ ή η περιοδική αναπνοή?). Ο επιπολασμός της καρδιακής ανεπάρκειας είναι >10% σε ηλικίες > 75 ετών, ενώ η περιοδική αναπνοή ανευρίσκεται σε 25-40% στην καρδιακή ανεπάρκεια με χαμηλό κλάσμα εξώθησης (<40%) με επιβαρυντικούς παράγοντες την κολπική μαρμαρυγή, την αύξηση διαστάσεων αριστ. κόλπου και την αύξηση συστολικής πίεσης πνευμονικής αρτηρίας. Σοβαρό ΣΑΑΥ (AHI > 30) δίδει πιθανότητα OR=2.88 για επιπολασμό και 1.58 για επίπτωση καρδιακής ανεπάρκειας. Στην εμφάνιση της περιοδικής αναπνοής συμμετέχουν δύο μηχανισμοί α) η αύξηση του loop gain και β) η ελάττωση του CO₂ reserve. Το loop gain αποτελείται από 3 συνιστώσες α) το controller gain οριζόμενο ως $\Delta VE / \Delta PaCO_2$, β) plant gain οριζόμενο ως $\Delta PaCO_2 / \Delta VE$, γ) Feed back gain οριζόμενο ως η ταχύτητα από το plant στο controller που εξαρτάται από το χρόνο κυκλοφορίας δηλ. καρδιακή παροχή. Το CO₂ reserve ορίζεται σαν η διαφορά μεταξύ του CO₂ set point και apneic threshold. Ανευρίσκεται μετατροπή από Cheyne-Stokes σε ΣΑΑΥ στο 18% ασθενών όταν ελαττωθεί ο χρόνος κυκλοφορίας και αυξηθεί το κλάσμα εξώθησης. Οι μικροαφυπνίσεις ενώ είναι προστατευτικές στο ΣΑΑΥ, αντίθετα φαίνεται να προκαλούν την περιοδική αναπνοή. Η θεραπεία με CPAP στην καρδιακή ανεπάρκεια βελτιώνει το κλάσμα εξώθησης, την ποιότητα ζωής και την υπνηλία όταν υπάρχει αποφρακτικό στοιχείο. Επι παρουσίας περιοδικής αναπνοής συνιστάται η ενδεδειγμένη θεραπεία της υποκειμένης νόσου, ενώ η χορήγηση ASV ή άλλων PAP θεραπειών σε ασθενείς με χαμηλό κλάσμα εξώθησης δεν συνιστάται. Επίσης δεν συνιστάται η χορήγηση οξυγονοθεραπείας για τους ασθενείς αυτούς λόγω του ότι η υπεροξία προκαλεί αύξηση του οξειδωτικού stress, αυξάνει τις αγγειακές αντιστάσεις, την αρτηριακή πίεση, τις πιέσεις πλήρωσης αριστ. κοιλίας, ελαττώνει την καρδιακή παροχή και σε βεβλαμένο μυοκάρδιο αυξάνει την θνητότητα.

Το άρθρο υπό την μορφή επίκαιρης ανασκόπησης στο ERJ (τεύχος Μαΐου), υπογράφεται και έχει σαν πρώτο όνομα τον διεθνούς φήμης Υπνολόγο καθηγητή Patrick Levy.

Όμως υπάρχουν αρκετές διαφωνίες από εμένα και αφορούν στα εξής:

Αναφέρεται ότι δεν υπάρχει evidence για χορήγηση οξυγονοθεραπείας σε ασθενείς με αμιγή περιοδική αναπνοή Cheyne-Stokes. Οι ίδιοι οι συγγραφείς αναφέρουν στο άρθρο ότι η υποξία μέσω της ελάττωσης του CO₂ reserve αλλά και του inhibition και δυσλειτουργίας των κεντρικών και περιφερικών χημειουποδοχέων συμβάλλει στην αποσταθεροποίηση της αναπνοής. Είναι γνωστό ότι η χορήγηση οξυγόνου σε ασθενείς που δεν παρουσιάζουν υποξυγοναιμία ελαττώνει το loop gain και συμβάλλει στην ύφεση της νόσου.

Επί πλέον αναφέρεται ότι η χορήγηση PAP therapy στους ασθενείς αυτούς δεν συνιστάται. Όμως είναι γνωστό ότι χαμηλά επίπεδα CPAP ελαττώνουν σημαντικά το loop gain και συνεπώς συμβάλλουν στη σταθεροποίηση της αναπνοής.

Προσωπική μου άποψη, μέχρις να υπάρξουν επί πλέον μελέτες που να διευκρινίζουν το θέμα, είναι ότι ο συνδυασμός οξυγονοθεραπείας και χαμηλών επιπέδων CPAP (όχι ASV), δύνανται να χορηγηθούν με προσοχή και έλεγχο του ασθενούς (trial and error).

Επιλογή άρθρου – Σχολιασμός: Παναγιώτης Πανάγου

Το άρθρο, είναι μια πολύ ωραία ανασκόπηση από εξαιρετικούς συγγραφείς. Παραθέτω αυτούσιο το κομμάτι για το οξυγόνο το οποίο αναφέρει ο κύριος Πανάγου Για να το δείτε ακριβώς στο πρωτότυπο. Βοηθάει να καταλάβουμε ότι το οξυγόνο είναι φάρμακο που εάν δεν χορηγείται με τις ενδείξεις αντί να ωφελεί μπορεί να βλάψει.

Μάνος Βαγιάκης



Adherence to CPAP therapy for sleep apnea in patients aged over 70 years old

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Abstract

Purpose Adherence to continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA) syndrome has not been established in patients over 70 years of age, whereas several studies have reported adherence below that age. This trial was designed to address this evidence gap.

Methods Consecutive senior (> 70 years) patients with OSA, mean respiratory event index (REI) 34/h, body mass index (BMI) 31 kg/m², and junior (< 50 years) patients (REI 37/h, BMI 31 kg/m²) were included.

Results At year follow-up among 72 senior patients (35 women) and 71 junior patients (17 women), there was no difference in the percentage of patients abandoning CPAP (senior 47% vs. junior 43%) or in CPAP daily use (4:53 ± 2:44 hh:min vs. 4:23 ± 3:00 hh:min).

Conclusions CPAP adherence in senior patients with OSA was not poorer than that of a younger group of OSA patients. Advanced age should not be an obstacle to CPAP initiation.

Keywords Adherence · Daily use · Elderly · Nine-hole test · Pinch-test

Introduction

Obstructive sleep apnea (OSA) is highly prevalent after the age of 65 years [1]. Sleep apnea leads to sleep disruption, resulting in excessive daytime sleepiness. In this manuscript, we use the term senior patient for those > 70 years old and junior patient for those < 50 years old. In senior patients, sleep apnea symptoms may be conflated with the functional impairments of aging [2]. Continuous positive airway pressure (CPAP) is an effective treatment for sleep apnea in all patients [3]. McMillan et al. also recommended CPAP therapy in senior patients suffering from OSA. They reported that CPAP reduces sleepiness and is marginally more cost-effective over 12 months than best supportive care alone.

With aging, memory may become impaired and physical dexterity decreases [4]. Memory loss may lead to reduced therapy adherence if not compensated with external aid [5]. CPAP therapy requires sufficient upper extremity mobilization and strength. We therefore believe that CPAP therapy adherence may be poorer in seniors compared to junior patients due to memory loss, weakness in upper extremities, and reduced dexterity.

The proportion of senior individuals among the general population is increasing in developed countries [<https://www.statista.com/statistics/521152/population-of-finland-by-age/>]. CPAP adherence in the community is generally poor, with rates ranging from 65 to 88% [6–8]. CPAP daily use in senior patients was reported by McMillan [2] to be very low at 1 year, with a median usage of 2 h and 22 min per night. The effect of age on CPAP adherence has not fully been studied; May et al. have reported recently that increasing age is associated with improved adherence in a study population < 65 years [9].

The purpose of this study is to evaluate CPAP adherence in patients > 70 years compared with younger patients < 50 years.

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Σχόλιο:

Τήρηση της θεραπείας CPAP για την υπνική άπνοια σε ηλικιωμένους ασθενείς άνω των 70 ετών.

Θα υπέθετε κανείς ότι η συμμόρφωση στη θεραπεία με CPAP μπορεί να είναι φτωχότερη στους ηλικιωμένους (>70 έτη) σε σύγκριση με τους νεότερους (<50 έτη) λόγω απώλειας μνήμης, αδυναμίας στα άνω άκρα και μειωμένης επιδεξιότητας.

Στη μελέτη συμπεριλήφθηκαν 72 ηλικιωμένοι (35 γυναίκες) με μέσο όρο αναπνευστικών συμβαμάτων 34/h, με δείκτη μάζας σώματος 31kg/m² και 71 νεότεροι ασθενείς (17 γυναίκες) με μέσο όρο αναπνευστικών συμβαμάτων 37/h και με δείκτη μάζας σώματος 31kg/m².

Έγινε ετήσια παρακολούθηση, η οποία δεν ανέδειξε στατιστικά σημαντική διαφορά στο ποσοστό των ασθενών που εγκατέλειψαν τη CPAP (47% των ηλικιωμένων CPAP έναντι 43% των νεότερων) ή στην καθημερινή χρήση της συσκευής (4:53±2:44 hh:min έναντι 4:23±3:00 hh:min).

Συνεπώς η προχωρημένη ηλικία δεν αποτελεί εμπόδιο για την έναρξη της θεραπείας με CPAP.

Επιλογή άρθρου – Σχολιασμός: Ελένη Περράκη

RESEARCH ARTICLE



Scoring heart rate increases as a surrogate arousal marker on portable monitor studies for obstructive sleep apnea: Impact on diagnostic accuracy and clinical decision-making

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Summary

Cortical arousal-related hypopneas are not scored on type 3 home devices, which therefore limits their diagnostic accuracy for obstructive sleep apnea. The objective of this study was to evaluate whether scoring heart rate accelerations as surrogate markers of arousal improves type 3 portable monitor diagnostic agreement compared with polysomnography and improves therapeutic decision-making. We prospectively recruited patients evaluated for obstructive sleep apnea to undergo in-laboratory simultaneous full polysomnography + type 3 portable monitoring. Hypopnea events were scored on portable monitor studies with and without autonomic scoring, which was defined as an associated increase in pulse oximetry-derived heart rate ≥ 6 beats per min (autonomic hypopnea). Portable monitor diagnostic agreement compared with polysomnography with and without autonomic hypopnea scoring was assessed. We also evaluated whether reporting autonomic hypopnea scoring improves portable monitor clinical treatment decision agreement after four physicians reviewed clinical data and sleep study results (polysomnography, portable monitor with autonomic hypopnea, portable monitor without autonomic hypopnea). Eighty-two participants completed simultaneous polysomnography and in-laboratory portable monitor studies. Scoring autonomic hypopnea resulted in a decreased mean difference between in-laboratory portable monitor respiratory event index and polysomnography apnea-hypopnea index in Bland-Altman analysis (mean difference 14.6 per hr without versus 6.1 per hr with autonomic hypopnea scoring [$p < 0.01$]), and increased intraclass correlation from 0.769 to 0.844. Inclusion of autonomic hypopnea scoring resulted in better accuracy between portable monitor and polysomnography expert's treatment decisions, and ultimately resulted in 24% fewer additional polysomnographies requested. The addition of pulse oximetry heart rate increases for autonomic hypopnea scoring during portable monitor resulted in better diagnostic agreement, improved clinical decision-making and reduced additional polysomnography testing.

Abbreviations: AHI, apnea-hypopnea index; AnH, autonomic hypopnea; AUC, area under the receiver operating characteristic curve; EEG, electroencephalogram; EMG, electromyography; HAI, hypopnea with arousal index; ICC, intraclass correlation; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; O₂, oxygen; PM, type 3 Portable monitor; PSG, polysomnography; PTT, pulse transit time; REI, respiratory event index; ROC, receiver operating characteristic; TRT, total recording time; TST, total sleep time; SpO₂, blood oxygen saturation.

Σχόλιο:

Οι μελέτες τύπου III αποτελούν μια εξέταση ρουτίνας για την διάγνωση του ΣΑΥΥ σε ασθενείς με λίγες συννοσηρότητες. Όμως είναι γνωστό ότι οι υπόπνοιες οι οποίες είναι συνδεδεμένες με τις φλοιικές αφυπνίσεις δεν γίνεται να σκοραριστούν με τις μελέτες ύπνου τύπου 3 με αποτέλεσμα ένα σημαντικό τμήμα ασθενών που έχουν ήπιο ή μέτριο ΣΑΥΥ να λαμβάνουν ψευδώς αρνητικό αποτέλεσμα σε ότι αφορά στην ύπαρξη ή μη του συνδρόμου. Έτσι έχουν προταθεί μία σειρά από δείκτες για το σκοράρισμα των υποπνοιών όπως είναι το pulse transit time/ η περιφερική αρτηριακή τονομετρία αλλά και το εύρος κύματος παλμού.

Σε αυτήν της μελέτη εξετάστηκε η δυνατότητα του σκοραρίσματος των υποπνοιών που είναι συνδεδεμένες με τη φλοιική αφύπνιση μέσω της ανόδου των καρδιακών παλμών κατά έξι σφύξεις το λεπτό (figure 1). Έγινε ταυτόχρονη πολυσωματοκαταγραφική μελέτη ύπνου αλλά και μελέτη ύπνου τύπου III με και χωρίς την προσθήκη του δείκτη αύξησης των καρδιακών παλμών σε 82 ασθενείς.

Βρέθηκε ότι η προσθήκη του δείκτη αύξησης καρδιακών σφίξεων ελάττωσε την διαφορά στον καταγραφόμενο AHI μεταξύ πολυυπνογραφίας και μελέτης τύπου III στην ανάλυση Bland–Altman (μέση διαφορά 14,6 ανά ώρα χωρίς τον δείκτη καρδιακού ρυθμού έναντι 6,1 ανά ώρα με τον δείκτη [$p < 0,01$]) και αυξημένη ενδοταξική συσχέτιση από 0,769 έως 0,844.) Η ενσωμάτωση αυτού του δείκτη βελτίωσε τις αποφάσεις για θεραπεία με CPAP από του υπνολόγους και τελικά οδήγησε σε 24% λιγότερες επιπλέον πολυυπνογραφίες

Να σημειώσουμε σε αυτό το σημείο ότι από την μελέτη αποκλείστηκαν άτομα με καρδιολογικές και νευρολογικές παθήσεις.

Ενδιαφέρον είναι να παρατηρήσει κανείς στο πρωτότυπο κείμενο και το figure 2/figure 4.

Επιλογή άρθρου – Σχολιασμός : Χαράλαμπος Πρωτοπαπαδάκης

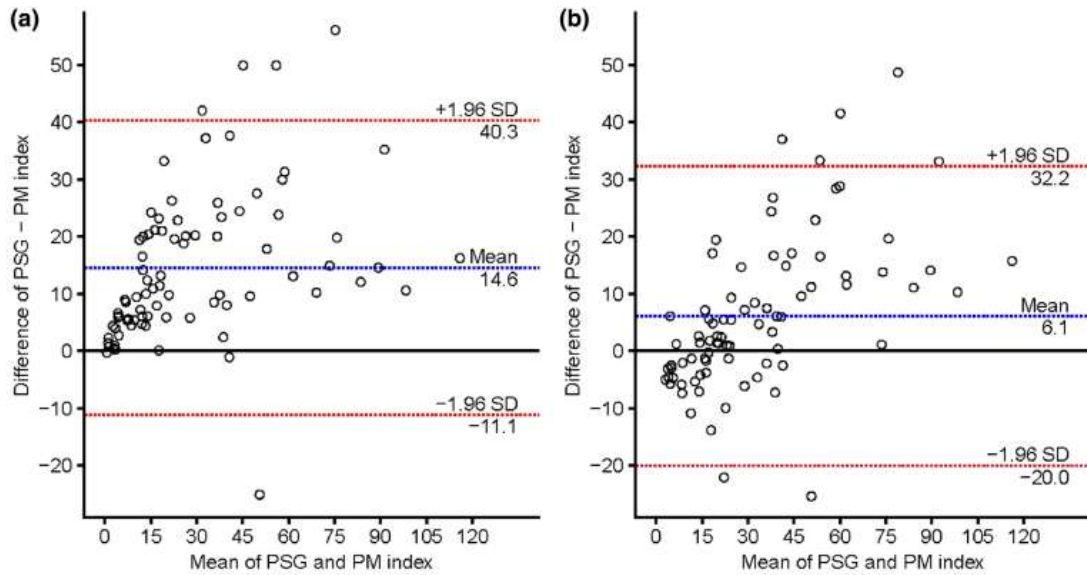


FIGURE 2 Bland-Altman plot display mean index $((\text{PSG AHI} + \text{Lab PM REI})/2)$ versus the difference between index $(\text{PSG AHI} - \text{Lab PM REI})$. (a) Without AnH scoring; (b) with AnH scoring. Blue line represents mean values, and red lines upper and lower limits of agreement. Abbreviations: AHI, apnea-hypopnea index; AnH, autonomic hypopnea index; Lab PM, portable monitoring performed in-laboratory; PSG, polysomnography; REI, respiratory event index; SD, standard deviation

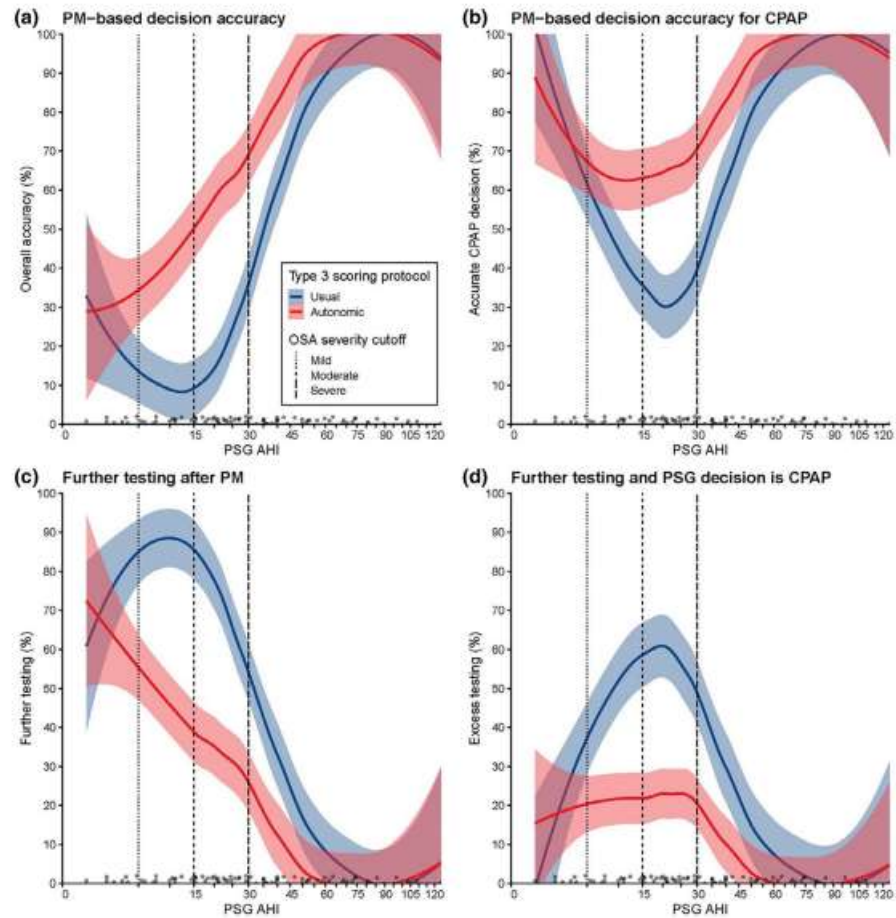


FIGURE 4 Comparison of agreement when using Lab PM conventional scoring (blue line) versus AnH scoring (red line) compared with PSG-based decisions. (a) Percent agreement for treatment decision. (b) Percent agreement for prescribing CPAP. (c) Percent agreement for recommending further testing. (d) Percent agreement for recommending further testing in patient recommended CPAP therapy based on PSG. Dots at the bottom represent PSG AHI of each unique subject. Abbreviations: AHI, apnea-hypopnea index; AnH, autonomic hypopnea index; CPAP, continuous positive airway pressure; Lab PM, portable monitoring performed in-laboratory; PM, portable monitoring; PSG, polysomnography

REVIEW ARTICLE



Rapid eye movement sleep behaviour disorder: Past, present, and future

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Summary

This manuscript presents an overview of REM sleep behaviour disorder (RBD) with a special focus on European contributions. After an introduction examining the history of the disorder, we address the pathophysiological and clinical aspects, as well as the diagnostic issues. Further, implications of RBD diagnosis and biomarkers are discussed. Contributions of European researchers to this field are highlighted.

KEYWORDS

alpha-synuclein, dream enactment, RBD, REM sleep without atonia, REM-parasomnia, RWA

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1 | INTRODUCTION: HISTORY OF RAPID EYE MOVEMENT SLEEP BEHAVIOUR DISORDER (RBD)

The first description of dream-enacting behaviours dates back to the early Roman empire where reports on animals were provided as proof that non-human animals also dream (Pliny the Elder, 1961). In the 17th century, Miguel de Cervantes described an episode of dream-enacting behaviour (Iranzo et al., 2004), in which Don Quixote shouts and vigorously attacks some wineskins while dreaming that he is fighting a giant. In 1881, Lasègue observed that patients with delirium tremens presented with dream-like behaviours, vocalisations, and rampaging in bed (Lasègue, 1881), features possibly resembling rapid eye movement (REM) sleep behaviour disorder (RBD). A major advance was made in 1965 when Jouvet and Delorme (1965) created an RBD model in cats 20 years before it was identified as a disorder in humans. Sastre and Jouvet sought to determine the origin of REM sleep muscle atonia and injected ibotenic acid in various nuclei to suppress atonia. They observed that lesions of the perilocus coeruleus alpha (an equivalent to the human locus subcoeruleus) resulted in dream-like behaviours (“oneiric behaviours”), including predatory attack, rage, flight, and grooming in cats (Sastre & Jouvet, 1979).

Europeans were also among the first to observe REM sleep without atonia (RWA) in individuals with parkinsonism. In 1969, Traczynska-Kubin et al. (1969) observed patients with Parkinson's disease (PD) having persistent mental electromyography (EMG) activity despite REMs resembling REM sleep. In 1975, Mouret (1975) described a persistence of mental EMG activity during paradoxical sleep in patients with PD compared with healthy individuals. Similar findings were named “stage 1-REM” by Japanese researchers (for a review see Tachibana, 2009) and “stage 7” sleep by Guilleminault et al. (1976) in patients with narcolepsy treated with clomipramine. The Europeans were also the first to document video-polysomnographic (v-PSG) recording of an RBD episode in a patient with Shy-Drager syndrome (Cocagna et al., 1985). Shortly after, Salva and Guilleminault (1986) described the disappearance of REM sleep atonia and the appearance of complex dream-enacting behaviours in patients with olivopontocerebellar degeneration. Following on from this there were several reports by Japanese researchers of stage 1-REM, possibly resembling RWA in otherwise healthy-seeming elderly individuals experiencing their first manifestations of somnambulism-like behaviours (Tachibana et al., 1991), as well as in patients with brainstem degeneration (Shimizu et al., 1990), and under clomipramine treatment (Niiyama et al., 1993). A more detailed history of the detection of RWA and RBD has been provided in a review (Frauscher & Högl, 2012).

The landmark discovery of RBD as a disorder is attributed to Carlos Schenck and Mark Mahowald who described the first case series of people showing dream-enacting behaviours linked to a polysomnographic confirmation of RWA and gave RBD its name. Schenck and Mahowald identified the sleep-related violence and risk of injury, linked it with Jouvet's cat model, and discovered the benefit of clonazepam (Schenck et al., 1986). In the first brain neuropathological

examination of a case with isolated RBD (iRBD), abnormal α -synuclein deposits were found in the locus coeruleus/subcoeruleus (Uchiyama et al., 1995). Schenck and Mahowald followed up their first 30 idiopathic RBD patients finding that one-third of their cohort later converted to parkinsonism (Schenck et al., 1996). This major finding occurred before Braak et al. suggested that abnormal α -synuclein propagates in a bottom-up pattern in prodromal and defined PD, starting in the gut and medulla oblongata (stage 1), then in the locus coeruleus/subcoeruleus (stage 2) and later in the substantia nigra (stages 3 and 4) and cortex (stages 5 and 6) (Del Tredici et al., 2002). In 2007, Boeve, Silber, et al. (2007b) postulated that dysfunction in the sublaterodorsal nucleus (corresponding to stage 2 in the Braak staging system) could lead to RWA and RBD. This phenocconversion from RBD to parkinsonism and dementia was later confirmed in several countries, and other synucleinopathies were associated with RBD (Fantini et al., 2005; Iranzo et al., 2006).

1.1 | RBD pathophysiology

Glutamatergic neurons located in a small pontine nucleus localised ventral to the laterodorsal tegmental nucleus (LDT) – named sublaterodorsal tegmental nucleus (SLD) in rats and locus subcoeruleus in humans – are responsible for inducing muscle atonia during REM sleep. These neurons express the vesicular transporter 2 of glutamate (vGLUT2), the specific marker of glutamatergic neurons, and cFos, a marker of activation in rats displaying a REM sleep hypersomnia (Clement et al., 2011). Unit recordings of these neurons confirmed that they are selectively active during REM sleep (Boucetta et al., 2014). It has also been shown that genetic inactivation of glutamatergic SLD neurons in rats and mice induces RBD and a 30% decrease in REM sleep quantities (Uchida et al., 2021; Valencia Garcia et al., 2017).

It has also been shown that combined microdialysis of bicuculline (a GABA-A antagonist), strychnine (glycine antagonist), and phaclophen (a GABA-B antagonist) in the trigeminal nucleus are necessary to restore jaw muscle tone during REM sleep (Brooks & Peever, 2012). Furthermore, SLD neurons directly excite GABA/glycinergic neurons located in the ventral medullary reticular nuclei (Boissard et al., 2002; Valencia Garcia et al., 2017; Valencia Garcia et al., 2018). Nearly all c-Fos-labelled neurons localised in these nuclei express GAD67 and glycine transporter 2mRNA after 3 h of paradoxical sleep recovery following 72 h of paradoxical sleep deprivation (Sapin et al., 2009; Valencia Garcia et al., 2018). These neurons directly project to spinal motoneurons (Valencia Garcia et al., 2018). Inactivation of the GABA and glycinergic neurons of these nuclei in rats and mice induces RBD (Uchida et al., 2021; Valencia Garcia et al., 2018). All these experiments indicate that GABA/glycine neurons located in the ventral medulla project to and hyperpolarise motoneurons during REM sleep leading to muscle atonia.

Interestingly, functional neuroimaging and postmortem brain studies report the presence of Lewy bodies and neuronal loss in SLD and ventral medulla (Arnulf, 2012; Boeve, Dickson, et al., 2007a;

Iranzo et al., 2013). It is, therefore, probable that RBD is due to specific neurodegeneration of the glutamate SLD and/or GABA/glycine medullary neurons.

It is well accepted that motoneurons are also phasically excited by glutamate during REM sleep (Burgess et al., 2008). It is, therefore, likely that RBD behaviours are due to phasic excitation of motoneurons by glutamate in the absence of tonic GABA/glycine inhibition. Glutamate pre-motoneurons are interneurons located in close vicinity of motoneurons and neurons located in ponto-medullary reticular nuclei and the red nucleus (Rekling et al., 2000). These neurons are directly excited by glutamatergic pyramidal neurons of the motor cortex to induce voluntary movements (Rekling et al., 2000). The reticular formation and the red nucleus could play a major role in exciting motoneurons during REM sleep without the need for cortical activation (Blumberg & Plumeau, 2016; Del Rio-Bermudez et al., 2015). However, patients often show long and complex behaviours, such as singing and giving long speeches, which strongly suggests that the motor cortex drives such behaviours (De Cock et al., 2007). In line with this, activation of the human motor cortex, similar to that observed during a voluntary movement during wakefulness, has been observed during REM sleep (De Carli et al., 2016).

Due to the characteristic emotional component of RBD dream-enacting behaviours and vocalisations, involvement of the limbic system has been postulated. This hypothesis is supported by animal studies on cats and by reports of RBD in humans affected by limbic encephalitis (Iranzo, 2018).

Everything considered, RBD is likely induced by neurodegeneration of the ponto-medullary GABA/glycinergic and/or glutamatergic neuronal system physiologically inducing muscle atonia during REM sleep, although other circuits are also involved in the generation of RWA and dream-enacting behaviours.

1.2 | Clinical features of isolated RBD (iRBD)

The prevalence of iRBD in the general population over 60 years old is 0.5–1% (Haba-Rubio et al., 2018; Pujol et al., 2017), and the mean age at clinical consultation is usually in the seventh decade. iRBD is rare in those under 50 years (Fernandez-Arcos et al., 2016). For unknown reasons, people seeking medical consultation for iRBD at sleep centres are more frequently men than women, although this finding may be due to a selection bias as RBD in men is more violent than in women. Ageing, head injury, farming, pesticide exposure, antidepressant therapy, and GBA mutations are all risk factors for developing iRBD (Postuma et al., 2012). Hyposmia, depression, and constipation are more common in iRBD than in controls (Aguirre-Mardones et al., 2015).

The main clinical features of iRBD are dream-enacting behaviours and nightmares, but this symptomatology also occurs in posttraumatic sleep disorder, sleep terrors, as well as in some patients with severe obstructive sleep apnoea and periodic limb movement disorder. Recalled dreams are short, vivid, intense, frightening, and negatively toned (e.g., being attacked or chased by an unknown person for an unknown

reason). Clinical manifestations consist in vocalisations (e.g., yelling, swearing, crying, or laughing) and vigorous behaviours (punching, kicking, jumping out of bed) where patients appear to be enacting their dreams. These behaviours occur in REM sleep, with eyes closed, are usually confined to the bed, and may result in injuries to the patient and the bed partner (Fernandez-Arcos et al., 2016). However, the most common abnormal behaviours seen in REM sleep during video-polysomnography (v-PSG) are prominent jerks. Interestingly, an important proportion of iRBD patients report good sleep quality and are unaware of their nocturnal episodes, indicating that bed partners are essential for informing about and describing these behaviours. To reduce the intensity and frequency of the nightmares and motor behaviours (therefore, also reducing the risk of injury) clonazepam and melatonin can be used. Both these treatments are suggested as Level B treatment for RBD by the Standards of Practice Committee of the American Academy of Sleep Medicine (Aurora et al., 2010). Clonazepam is usually effective at a dose <2 mg, melatonin at a dose 3–12 mg. Long-term treatment is usually required. Melatonin has a favourable side effect profile (dose-related side effects include morning headache, morning sleepiness, and delusions/hallucinations), whereas clonazepam should be used with caution in patients with dementia, gait disorders, or concomitant obstructive sleep apnea. The most common side effects of clonazepam are sedation, impotence, early morning motor incoordination, confusion, and memory dysfunction (Aurora et al., 2010). Besides symptomatic treatment, improving safety within the bedroom environment is also often necessary (Fernandez-Arcos et al., 2016).

After 15 years of follow-up, about 95% of iRBD patients will be clinically diagnosed with the synucleinopathies dementia with Lewy bodies (DLB, 45%), PD (45%), or multiple system atrophy (MSA, 5%) (Iranzo et al., 2016). Indeed, the presence of abnormal synuclein in the cerebral spinal fluid (CSF), olfactory mucosa, and peripheral organs (colon, skin, and salivary glands) is detected in most iRBD patients. Markers of short-term conversion to a clinically overt synucleinopathy are hyposmia, abnormal DAT-SPECT, mild cognitive impairment, and minor parkinsonian signs. Patients with long-standing iRBD of more than 15 years may show synuclein in the CSF and organs, hyposmia and DAT deficit, indicating a slow but ongoing neurodegenerative process (Högl et al., 2018; Iranzo et al., 2017; Teigen et al., 2021).

2 | VIDEO-POLYSOMNOGRAPHY (V-PSG) AS A DIAGNOSTIC REQUIREMENT AND PROGRESSION MARKER IN RBD

The current criteria for the diagnosis of RBD (American Academy of Sleep Medicine, 2014) require the demonstration of RWA on v-PSG. Several manual/visual methods have been proposed to quantify RWA, but the most validated method that is also recommended by recent international guidelines (Cesari et al., 2021) is the one proposed by the Sleep Innsbruck Barcelona (SINBAR) group (Frauscher et al., 2012). This method measures “any” (i.e. phasic or tonic) muscular activity in the chin and phasic muscular activity in both flexor

digitorum superficialis muscles in the upper limbs, either in 30 s epochs or in 3 s epochs, and the respective cut-offs of 27% and 32% have shown to be sensitive and specific to distinguish RBD from controls (Frauscher et al., 2012). Quantification of RWA in the lower extremities has lower specificity than in the upper extremities (Cesari et al., 2021). Because manual/visual RWA quantification is extremely laborious, several (semi-)automatic methods have been proposed. Of these, the REM atonia index (Ferri et al., 2010) is the most validated one, but it quantifies RWA only in the chin. Only one semi-automatic method measures muscular activity both in the chin and the upper extremities (Frauscher et al., 2014).

RWA is not only the electrophysiological hallmark of RBD but is also a biomarker of neurodegeneration in iRBD (McCarter et al., 2019; Nepozitek et al., 2019) and could potentially be used as a biomarker for impending progression to an overt α -synucleinopathy in iRBD patients, although more studies are needed to confirm this.

v-PSG documentation of behaviours during REM sleep is not strictly required in the current American Academy of Sleep Medicine (AASM) criteria (American Academy of Sleep Medicine, 2014), but new diagnostic guidelines by the International RBD study group (Cesari et al., 2021) require the demonstration of at least one RBD episode. An RBD episode is defined as one or more motor events and/or vocalisation in REM sleep suggestive of dream enactment, thus including jerky, discontinuous simple and complex movements with or without vocalisations. Studies have shown that large, vigorous movements during REM sleep represent only the tip of the iceberg in RBD patients, who mostly have simple, minor jerks, requiring a careful video analysis (Frauscher et al., 2007). Research to develop automatic tools that can identify such movements and, therefore, help to diagnose RBD (Waser et al., 2020), is essential.

2.1 | Sex issues in RBD

Since the seminal first description of five patients with RBD, a male predominance has been reported (Schenck et al., 1986). This was supported by subsequent studies that reported up to 80% of RBD patients being male (Schenck et al., 2019).

A more recent epidemiological study, however, suggested that the prevalence of RWA does not differ between the sexes (Haba-Rubio et al., 2018). As women with RBD often present less violent dreams and behaviours, it has been suggested that RBD might be underestimated in women due to milder symptoms or lack of perception by bed partners (Fernandez-Arcos et al., 2016).

Differences in dream content between men and women, investigated in people with PD-RBD, showed that women dream more about activities of daily living, family and friends, while men have more performance-related dreams, including about sports, employment and can also be more aggressive (Borek et al., 2007), although data on this in iRBD are lacking. Nonetheless, differences in dream content could explain why men more often show harmful behaviours during RBD episodes (Mahale et al., 2016) and have a higher risk of injuries compared with women (Comella et al., 1998).

In line with this, a polysomnographic study investigating motor features of sleep behaviours reported that men have higher EMG phasic activity, more myoclonic movements, and more movements involving the trunk, whereas segmental movements were more frequent in women (Bugalho & Salavisa, 2019). Another polysomnographic study investigating RWA in both legs and arms, reported a higher RWA index in the legs in men compared with women, and a higher RWA index in the arms in women. The authors postulated that this finding might reflect a different character of RWA among the sexes (Borek et al., 2007; Tatman & Sind, 1996).

Despite frequent reports of sex differences in RBD phenotypes, this aspect has yet to be studied extensively. Future studies are needed to better elucidate the reasons for sex differences in the prevalence of RBD, as well as to characterise potential differences in muscle activity and motor events during REM sleep between women and men (Bodkin & Schenck, 2009; Borek et al., 2007; Bugalho & Salavisa, 2019; Comella et al., 1998; Fernandez-Arcos et al., 2016; Haba-Rubio et al., 2018; Mahale et al., 2016; Schenck et al., 1986; Tatman & Sind, 1996; Zhou et al., 2015).

2.2 | The genetics of RBD

Great strides forward have been made in iRBD genetic research over the past several years. iRBD likely has a distinct genetic risk profile compared with overt α -synucleinopathies, with evidence of both overlapping and contrasting risk loci across the conditions. RBD heritability, explained by common variants, is estimated at 12.3%, which is similar to the current estimation for DLB, and five RBD genetic loci have been identified by a genome-wide association study (GWAS) (Krohn et al., 2021). These genes are concentrated in the autophagy-lysosomal pathway (ALP) and are more specific to this pathway than any similarly powered GWAS of PD or DLB. Each of these RBD genes, *SNCA*, *GBA*, *TMEM175*, *INPP5F*, and *SCARB2*, are nominated PD risk loci (Nalls et al., 2019). However, the driving risk variants in *SNCA* and *SCARB2* are independent, meaning different genetic mechanisms are driving the risk for RBD and PD at these loci. The top *SNCA* variant associated with an increased risk for PD may have an opposite effect in RBD, decreasing the risk (Krohn et al., 2020). There is evidence that these RBD and PD variants may be affecting gene expression differently, and in different brain regions, with RBD variants localised in cortical regions (Krohn et al., 2021). Additionally, prominent PD genes such as *LRRK2* (Fernandez-Santiago et al., 2016), *MAPT*, and autosomal recessive genes (Mufti, Rudakou, et al., 2021a) are not associated with isolated RBD. A similar pattern is found between RBD and DLB, where ALP genes *SNCA*, *GBA*, and *TMEM175* are shared risk factors in both conditions, however, DLB genes *APOE* and *BIN1* (Chia et al., 2021) are not associated with RBD (Gan-Or et al., 2017; Krohn et al., 2021). Mutations in *PSAP*, encoding for saposin C, a lysosomal activator of *GBA*, have also been implicated in iRBD (Sosero et al., 2022), as well as rare variants in *LAMP3* (encoding the lysosomal associated membrane protein 3) and other genes (Mufti, Yu, et al., 2021b). Overall, the shared loci across RBD and overt

α -synucleinopathies are localised in the ALP, and genes associated with other neurodegenerative mechanisms (e.g., tau aggregation, mitochondrial dysfunction) do not appear to play a major role in RBD susceptibility. Genetics may also contribute to the phenoconversion rate from RBD to overt neurodegeneration; studies in *SNCA* (Krohn et al., 2020) and *GBA* (Honeycutt et al., 2019) show evidence that risk variants are associated with rapid phenoconversion, however, with limited confidence at these sample sizes.

2.3 | Biomarkers – classical and recent

Clinical trials with putative neuropreventive strategies in PD have been largely unsuccessful in the past, in part because the target populations were early/de novo PD patients with characteristic motor symptoms already present. At this stage, the degeneration of dopaminergic neurons is advanced with over 50% of nigrostriatal dopaminergic neurons already being affected by neurodegeneration. Therefore, strategies to prevent future disease conversion need to focus on risk cohorts. To achieve this important step, studies should be conducted in iRBD patients to assess progression biomarkers in the early disease stage in parallel to larger cohorts of at-risk individuals. With an average of only 6.3% of iRBD patients converting to disease per year (Postuma et al., 2019), conversion alone cannot serve as an outcome measure for future clinical trials and further objective trait markers are needed. Also, individuals with iRBD convert into different α -synuclein aggregation diseases (i.e., PD, MSA, DLB). It may, therefore, be important to stratify these groups in the prodromal state. For prodromal individuals and population-based screens, which are becoming more popular for identifying individuals at risk, we need biomarkers that are less invasive than CSF, as well as widely applicable screening instruments. Several strategies are currently being investigated, including imaging studies (e.g., dopamine transporter imaging, ^{18}F FDG-PET), objective quantitative assessment of emerging mild motor disease, cognitive testing and tissue analyses with aggregation chemistry for α -synuclein (Miglis et al., 2021).

The total α -synuclein in CSF is 15% lower in PD and MSA, while in iRBD levels are slightly higher for, as yet, unknown reasons (Mollenhauer et al., 2019). More promising is the detection of α -synuclein aggregation by seeding aggregation assays (SAA; RT-QuIC or PMCA) with sensitivities and specificities above 90–95% for PD in CSF (Shahnawaz et al., 2017). One study in iRBD showed a sensitivity of 90.4% and a specificity of 90.0%. In one individual, positivity of SAA was detected 10 years before the conversion to disease (Iranzo et al., 2021). Major hurdles faced by SAA are the lack of quantification and the fact that the best performance is shown in CSF compared with colon, salivary glands, olfactory mucosa, and skin (Antelmi et al., 2017; Doppler et al., 2017; Fernandez-Arcos et al., 2016; Iranzo et al., 2018; Sprenger et al., 2015; Stefani & Höggl, 2021; Vilas et al., 2016). The current mechanism of the molecular processes leading to α -synuclein aggregation and disease are still unknown and cannot yet be explained in relation to the assay parameters. While for CSF the results are promising, the first studies also report SAA

positivity in skin samples in PD as well as in olfactory mucosa (De Luca et al., 2019; Wang et al., 2020). Some groups also show different seeding dynamics in patients with MSA and PD, which could indicate different α -synuclein strains (Shahnawaz et al., 2020).

A more peripherally acting biomarker is the neurofilament light chain (NfL), which can now reliably be quantified in peripheral blood. Although nonspecific and elevated in several other neurological diseases, slightly higher values of plasma NfL are shown for PD and RBD and markedly higher for MSA patients (Mollenhauer et al., 2020).

In the future, we will know if other biomarkers such as inflammatory panels, faecal microbiome, and miRNA hold their promise of being adequate screening tools for those at risk of converting to disease. Unfortunately, none of the previous biomarkers, including SAA, can be currently used for individual quantification to differentiate between individuals at risk for conversion and those remaining free of a neurodegenerative disease. Larger cohorts are needed.

2.4 | Implications of the RBD diagnosis

The implications of establishing the diagnosis of RBD are multifaceted. These encompass (i) clinical implications centred on the management strategies and risk mitigation of potential injurious RBD behaviours, (ii) implications related to very strong associations between RBD and evolving synuclein-specific neurodegeneration, (iii) the need to increase awareness about this disorder among physicians, allied health professionals, and the general public, and (iv) the opportunity to engage numerous stakeholders around RBD as a unique disorder that is positioned on the intersection of neurology, sleep medicine, and neuroscience.

The clinical implications of RBD as a parasomnia are centred on symptomatic management and safety precautions in sleeping environments aimed at preventing injuries from RBD-related motor behaviours (St Louis & Boeve, 2017). The relative paucity of well-designed randomised symptomatic clinical trials should be a call for action for a more robust clinical trial RBD pipeline (Gilat et al., 2020; Shin et al., 2019). The success of such trials will largely depend on the adequate selection of outcome measures and trial duration, which will allow for proper ascertainment of the intervention's effectiveness.

Implications of RBD as a prodromal stage of an evolving α -synucleinopathy are complex. RBD patients are increasingly becoming aware of their risk of developing one of these disorders in the future. This necessitates proper counselling on the risk of phenoconversion so that appropriate planning for the future can be considered. Currently, there is a substantial gap in prognostic counselling offered to the patient as reports indicate that only 50% of patients with RBD receive counselling (Feinstein et al., 2019). There is, therefore, a need to develop best practices for prognostic counselling in iRBD.

One of the most important implications of RBD as a prodromal synucleinopathy is an opportunity to position the iRBD population as an ideal study cohort for testing disease-modifying treatments aimed at delaying or preventing phenoconversion to a synucleinopathy (Höggl

et al., 2018). Selecting the ideal patient candidates for disease-modifying trials, having effective and reliable screening and recruitment methods, employing robust clinical trial designs, and choosing appropriate outcome measures capable of demonstrating disease modification within the reasonable trial duration are the critical aspects of trial planning for iRBD. Some of these elements are more straightforward than others. The International RBD study group published two consensus statements on clinical trials in the RBD population that detail these aspects relevant to organisations and implementation of RBD clinical trials (Schenck et al., 2013; Videnovic et al., 2020).

Finally, raising awareness and promoting education about RBD is a very important implication of RBD, which is overall underdiagnosed, or the diagnosis is quite delayed. Bringing together various stakeholders such as clinicians, scientists, patients, disease-specific foundations, government agencies, industry, and the general public will enable us to advance various aspects of RBD clinic care, research, and therapeutic development.

3 | FUTURE DIRECTIONS

Since the first description of RBD, the disease has been better characterised through pathophysiological, clinical and v-PSG studies, as well as through extensive research on biomarkers and genetics.

Despite these advances, the phase of phenoconversion from iRBD to overt α -synucleinopathy still needs to be further investigated. A combination of biomarkers will likely allow better identification of those with iRBD at high risk of short-term phenoconversion, whereas it is still unclear how iRBD individuals that go on to develop PD will be differentiated from those phenoconverting into DLB or MSA. Although a combination of biomarkers might be useful, it is also likely that a better phenotypic characterisation will be achieved through the identification of biomarkers or α -synuclein aggregates in biofluids or tissues, which are specific for one α -synucleinopathy (i.e., DLB, PD or MSA).

Another aspect that will become more relevant in the future and deserves further investigation is prodromal RBD. It has been defined as a stage in which symptoms and signs of evolving RBD are present, but do not yet meet established diagnostic criteria (Cesari et al., 2021; Hogl et al., 2018). International guidelines for the identification of prodromal RBD have been published recently by the International RBD study group, providing a framework that will ensure harmonised studies and, therefore, a better understanding of the clinical relevance of this condition and its evolution into iRBD.

All the previously mentioned aspects, as well as the identification of RBD in the general population, will likely take advantage of the implementation of artificial intelligence. Machine-learning approaches may provide new ways of identifying RBD patients (e.g., considering both muscle activity and movements), as well as new ways of phenotypic characterisation (e.g., based on a combination of biomarkers), dramatically improving detection and classification of RBD.

Some open issues in the RBD research field concern treatment. New insights into pathophysiology deriving from basic

science may lead to the development of novel treatments acting on specific pathways involved in the generation of RBD. Double-blind, randomised, controlled trials are still needed to assess the efficacy of symptomatic RBD treatment. Moreover, clinical trials testing neuroprotective drugs may represent a turning point in the development of disease-modulating treatments for alpha-synucleinopathies.

AUTHORS' CONTRIBUTIONS

BH and AS planned, coordinated, and edited the manuscript. All authors drafted a section of the work and revised the entire work critically for important intellectual content and gave final approval of the version to be published.

CONFLICT OF INTEREST

Author conflicts of interest in relation to the content of this manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Σχόλιο:

Ανασκόπηση σε διαταραχή ύπνου κατά το στάδιο REM

Άξια επισήμανσης η γνωστή κατάληξη του 95% των ασθενών με διαταραχές σταδίου REM μετά από 15 χρόνια σε σουνουκλείνοπάθειες(45% Parkinson/45% άνοια με σωμάτια Lewy και 5% σε πλάγια μυατροφική σκλήρυνση.) Έχω υπογραμμίσει σε κείμενο κυριότερα σημεία έχοντας κάνει και ένα μικρό σχόλιο

- **Σημείωση 1 παθοφυσιολογία**
- **Σημείωση 2 καταληξη**
- **Σημείωση 3 αναγκη για νεες κατευθυντηριες οδηγιες**
- **Σημείωση 4 κληρονομικοτητα**
- **Σημείωση 5 α σουνουκλεινη σε ENY**

Επιλογή άρθρου – Σχολιασμός: Χαράλαμπος Πρωτοπαπαδάκης



ORIGINAL ARTICLE

Continuous positive airway pressure and adverse cardiovascular events in obstructive sleep apnea: are participants of randomized trials representative of sleep clinic patients?

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Abstract

Study Objectives: Randomized controlled trials (RCTs) have shown no reduction in adverse cardiovascular (CV) events in patients randomized to continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea (OSA). This study examined whether randomized study populations were representative of OSA patients attending a sleep clinic.

Methods: Sleep clinic patients were 3,965 consecutive adults diagnosed with OSA by in-laboratory polysomnography from 2006 to 2010 at a tertiary hospital sleep clinic. Characteristics of these patients were compared with participants of five recent RCTs examining the effect of CPAP on adverse CV events in OSA. The percentage of patients with severe (apnea-hypopnea index, [AHI] ≥ 30 events/h) or any OSA (AHI ≥ 5 events/h) who met the eligibility criteria of each RCT was determined, and those criteria that excluded the most patients identified.

Results: Compared to RCT participants, sleep clinic OSA patients were younger, sleepier, more likely to be female and less likely to have established CV disease. The percentage of patients with severe or any OSA who met the RCT eligibility criteria ranged from 1.2% to 20.9% and 0.8% to 21.9%, respectively. The eligibility criteria that excluded most patients were preexisting CV disease, symptoms of excessive sleepiness, nocturnal hypoxemia and co-morbidities.

Conclusions: A minority of sleep clinic patients diagnosed with OSA meet the eligibility criteria of RCTs of CPAP on adverse CV events in OSA. OSA populations in these RCTs differ considerably from typical sleep clinic OSA patients. This suggests that the findings of such OSA treatment-related RCTs are not generalizable to sleep clinic OSA patients.

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Σχόλιο:

Η αποφρακτική υπνική άπνοια είναι ένας σημαντικός τροποποιήσιμος παράγοντας κινδύνου για αρνητική έκβαση καρδιαγγειακών συμβαμάτων. Οι τυχαιοποιημένες ελεγχόμενες μελέτες (RCTs) δεν δείχνουν μείωση στην αρνητική έκβαση των καρδιαγγειακών γεγονότων σε ασθενείς υπό θεραπεία με CPAP.

Αυτή είναι η πρώτη μελέτη που εξετάζει το αν οι ασθενείς που συμμετείχαν στις RCTs ήταν αντιπροσωπευτικοί του πληθυσμού των ασθενών με αποφρακτική υπνική άπνοια που παρακολουθούνται σε κέντρα μελέτης ύπνου.

Τα χαρακτηριστικά 3965 ασθενών που διαγνώστηκαν με αποφρακτική υπνική άπνοια μετά από πολυπνογραφία (το χρονικό διάστημα από 2006-2010) συγκρίθηκαν με αυτά συμμετεχόντων σε 5 πρόσφατες RCTs που εξέταζαν την επίδραση της CPAP σε αρνητική έκβαση καρδιαγγειακών γεγονότων ασθενών με αποφρακτική υπνική άπνοια. Βρέθηκε η αναλογία των ασθενών με σοβαρή (AHI>30) ή οποιασδήποτε βαρύτητας υπνική άπνοια (AHI>5) που πληρούσαν τα κριτήρια συμμετοχής στις RCTs και ανιχνευτήκαν τα κριτήρια που απέκλεισαν ασθενείς από τις RCTs.

Συγκριτικά με τους συμμετέχοντες στις RCTs, οι ασθενείς των κλινικών μελέτης ύπνου ήταν νεότεροι, πιο υπνηλικοί, συχνότερα γυναίκες και λιγότερο συχνό να έχουν διαγνωσμένα καρδιαγγειακά νοσήματα. Τα ποσοστά των ασθενών με σοβαρή ή οποιασδήποτε βαρύτητας υπνική άπνοια που ικανοποιούσαν τα κριτήρια εισαγωγής στις RCTs ποικίλουν από 1,2%-20,9% και 0,8%-21,9% αντιστοίχως. Τα κριτήρια που απέκλεισαν τους περισσότερους ασθενείς ήταν : προυπάρχουσα καρδιαγγειακή νόσος , αίσθημα ημερήσιας υπνηλίας , νυχτερινή υποξαιμία και συννοσηρότητες.

Συμπερασματικά μια μειοψηφία των ασθενών των κέντρων μελέτης ύπνου ικανοποιούσε τα κριτήρια των RCTs που εξέταζαν την επίδραση της CPAP σε αρνητική έκβαση καρδιαγγειακών γεγονότων. Συνεπώς τα ευρήματα των προαναφερθέντων RCTs δεν μπορούν να γενικευτούν στον πληθυσμό που παρακολουθούνται στα κέντρα μελέτης ύπνου.

Επιλογή άρθρου – Σχολιασμός : Ευαγγελία Φλώρου



Obstruction level associated with outcome in hypoglossal nerve stimulation

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Abstract

Purpose Selective hypoglossal nerve stimulation (sHNS) constitutes an effective surgical alternative for patients with obstructive sleep apnea (OSA). sHNS results in tongue protrusion and consecutive alleviation of obstructions at the tongue base level (lower obstructions). Furthermore, obstructions at the soft palate level (upper obstructions) may be prevented through palatoglossal coupling as seen on sleep endoscopy. However, it has not been studied if the distribution of obstruction level during a whole night measurement is a relevant factor for the treatment outcome.

Methods Obstruction levels were measured with a manometry system during a whole night of sleep in 26 patients with OSA ($f=1$, $m=25$; age 59.4 ± 11.3 ; BMI $=29.6 \pm 3.6$) either before ($n=9$) or after sHNS implantation ($n=12$). Five patients received a measurement before and after implantation. Obstructions were categorized into velar (soft palate and above), infravelar (below soft palate), and multilevel obstructions. An association between obstruction level and treatment outcome was calculated.

Results The mean distribution of preoperative obstruction level could be divided into the following: 38% velar, 46% multilevel, and 16% infravelar obstructions. Patients with a good treatment response (defined as AHI $<15/h$ and AHI reduction of 50%) had fewer preoperative velar obstructions compared to non-responder (17% vs. 54%, p -value = 0.006). In patients measured after sHNS implantation, a significantly higher rate of multilevel obstructions per hour was measured in non-responders (p -value = 0.012).

Conclusions Selective hypoglossal nerve stimulation was more effective in patients with fewer obstructions at the soft palate level. Manometry may be a complementary diagnostic procedure for the selection of patients for HNS.

Keywords Manometry · OSA · Selective hypoglossal nerve stimulation · Obstruction level

Introduction

About 20% of women and 50% of men suffer from moderate to severe sleep disordered breathing (SDB) according to a recent population-based study [1]. Most patients with SDB suffer from obstructive sleep apnea (OSA) [2]. Patients complain of excessive daytime sleepiness and cognitive deficits [3]. OSA also has a high societal relevance since approximately 20% of car accidents are related to sleep deprivation of which OSA is a main cause [4]. In addition,

OSA is associated with secondary diseases especially of the cardiovascular system such as hypertension, coronary artery disease, and cardiac arrhythmias [5]. Several treatment options exist for patients with OSA ranging from conservative methods such as positive airway pressure (PAP) therapy and mandibular advancement devices to surgical interventions [6, 7]. For patients with poor compliance to conservative therapies and moderate to severe OSA, selective hypoglossal nerve stimulation (sHNS) may constitute an effective surgical alternative [8].

In sHNS, the main pharyngeal airway dilatory muscle and tongue protruder is activated to prevent airway collapse during sleep [9]. Different stimulation techniques have been developed ranging from the activation of proximal sectors to distal fibers of the nerve [10]. One system frequently implanted stimulates the branches of the hypoglossal nerve which are required for tongue protrusion and is

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Σχόλιο:

Η επιλεκτική διέγερση του υπογλωσσίου νεύρου (sHNS) αποτελεί μια εναλλακτική αποτελεσματική χειρουργική μέθοδο για ασθενείς με αποφρακτική

υπνική άπνοια (OSA). Η sHNS έχει ως αποτέλεσμα την πρόταση προς τα μπροστά της γλώσσας και τη διαδοχική εξάλειψη των αποφρακτικών επεισοδίων στο επίπεδο της βάσης της γλώσσας

(χαμηλή απόφραξη). Επιπλέον, η απόφραξη στο επίπεδο της μαλακής υπερώας (υψηλή απόφραξη) μπορεί να προληφθεί μέσω

υπερωογλωσσικής σύζευξης όπως φαίνεται στην ενδοσκόπηση κατά τη διάρκεια του ύπνου.

Ωστόσο, δεν έχει μελετηθεί εάν η κατανομή του επιπέδου απόφραξης

κατά τη διάρκεια μιας ολόκληρης νυχτερινής μέτρησης είναι ένας σημαντικός παράγοντας για το αποτέλεσμα της θεραπείας.

Τα επίπεδα απόφραξης μετρήθηκαν με σύστημα μανομετρίας κατά τη διάρκεια μιας ολόκληρης νύχτας ύπνου σε 26 ασθενείς με

OSA (f = 1, m = 25, ηλικία $59,4 \pm 11,3$, BMI = $29,6 \pm 3,6$) είτε πριν (n = 9) είτε μετά την εμφύτευση sHNS (n = 12). Πέντε ασθενείς

έλαβε μέτρηση πριν και μετά την εμφύτευση.

Η απόφραξη κατηγοριοποιήθηκε σε 3 επίπεδα. Το πρώτο στο επίπεδο του ουρανίσκου (μαλακή υπερώα και άνω), το δεύτερο κάτω από το επίπεδο του ουρανίσκου (κάτω από την μαλακή υπερώα) και το τρίτο σε απόφραξη πολλαπλών επιπέδων. Έγινε συσχέτιση μεταξύ του επιπέδου απόφραξης και του αποτελέσματος της θεραπείας. Η μέση κατανομή του προεγχειρητικού επιπέδου απόφραξης θα μπορούσε να χωριστεί στα εξής: 38% πρώτο επίπεδο, 46% πολλαπλά επίπεδα,

και 16% δεύτερο επίπεδο.

Ασθενείς με καλή ανταπόκριση στη θεραπεία (ορίζεται ως AHI < 15/h και μείωση AHI

του 50%) είχαν λιγότερες προεγχειρητικές αποφράξεις στο πρώτο επίπεδο σε σύγκριση με τους μη ανταποκρινόμενους (17% έναντι 54%, p-value = 0,006). Σε ασθενείς που

μετρήθηκαν μετά την εμφύτευση sHNS, παρατηρήθηκε σημαντικά υψηλότερο ποσοστό σε απόφραξη πολλαπλών επιπέδων ανά ώρα στα άτομα που δεν ανταποκρίθηκαν

(p-value = 0,012).

Συμπερασματικά, η εκλεκτική διέγερση του υπογλωσσίου νεύρου ήταν πιο αποτελεσματική σε ασθενείς με λιγότερες αποφράξεις στο επίπεδο της μαλακής υπερώας. Η μανομετρία μπορεί να είναι μια συμπληρωματική διαγνωστική διαδικασία για την επιλογή ασθενών για HNS.

Επιλογή άρθρου – Σχολιασμός: Κυριακή Χολίδου



Efficacy of atomoxetine plus oxybutynin in the treatment of obstructive sleep apnea with moderate pharyngeal collapsibility

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Abstract

Purpose Preliminary studies have shown a significant decrease in severity of obstructive sleep apnea (OSA) with the use of a combination of atomoxetine and oxybutynin, with patients having moderate pharyngeal collapsibility during sleep more likely to respond. This study evaluated the efficacy and safety of AD036 (atomoxetine 80 mg and oxybutynin 5 mg) in the treatment of OSA.

Methods This trial was a phase 2, randomized, placebo-controlled crossover study comparing AD036, atomoxetine 80 mg alone, and placebo during three home sleep studies, each separated by about 1 week. The trial included patients with OSA and moderate pharyngeal collapsibility as defined by a higher proportion of hypopneas to apneas and mild oxygen desaturation.

Results Of 62 patients who were randomized, 60 were included in efficacy analyses. The apnea–hypopnea index (AHI) from a median (interquartile range) of 14.2 (5.4 to 22.3) events/h on placebo to 6.2 (2.8 to 13.6) with AD036 and 4.8 (1.4 to 11.6) with atomoxetine alone ($p < .0001$). Both drugs also decreased the oxygen desaturation index (ODI) and the hypoxic burden ($p < .0001$). AD036, but not atomoxetine alone, reduced the respiratory arousal index and improved ventilation at the respiratory arousal threshold (greater V_{active}). There was a trend for total sleep time to be decreased more with atomoxetine alone than with AD036. The most common adverse event was insomnia (12% with AD036, 18% with atomoxetine).

Conclusion AD036 significantly improved OSA severity in patients with moderate pharyngeal collapsibility. Atomoxetine may account for the majority of improvement in OSA severity, while the addition of oxybutynin may mitigate the disruptive effect of atomoxetine on sleep and further improve ventilation.

Trial registration Clinical trial registered with www.clinicaltrials.gov (NCT04445688).

Keywords Obstructive sleep apnea · AD036 · Atomoxetine · Oxybutynin · OSA pharmacotherapy

Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder, affecting over 930 million adults globally, and approximately 17% of women and 34% of men in the USA [1, 2]. Untreated OSA is associated with increased incidence of hypertension, coronary heart disease, arrhythmias, heart failure, and stroke [3]. Continuous positive airway pressure (CPAP), the primary therapy for OSA, is very effective, but its use is limited by poor tolerance and adherence in a substantial number of patients [4–6]. The principal alternative treatment options, which include mandibular advancement devices and upper airway surgery, are not effective in all patients, and prediction of efficacy is challenging [2]. There are currently no approved pharmacotherapies for OSA, and efforts to develop such therapies have been generally unsuccessful

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Σχόλιο:

Προκαταρκτικές μελέτες έχουν δείξει σημαντική μείωση στη σοβαρότητα της αποφρακτικής άπνοιας ύπνου (OSA) με τη χρήση συνδυασμού ατομοξετίνης και οξυβουτινίνης, με ασθενείς με μέτρια φαρυγγική απόφραξη κατά τη διάρκεια του ύπνου πιο πιθανό να ανταποκριθούν. Αυτή η μελέτη αξιολόγησε την αποτελεσματικότητα και την ασφάλεια του AD036 (ατομοξετίνη 80 mg και οξυβουτινίνη 5 mg) στη θεραπεία της OSA και του εικονικού φάρμακ

κατά τη διάρκεια τριών μελετών ύπνου στο σπίτι, η καθεμία ανά 1 εβδομάδα. Η δοκιμή περιελάμβανε ασθενείς με OSA και μέτρια φαρυγγική απόφραξη όπως ορίζεται από την υψηλότερη αναλογία υποπνοιών/απνοιών και ήπιο αποκορεσμό οξυγόνου. Από 62 ασθενείς που τυχαιοποιήθηκαν, 60 τελικά συμπεριλήφθηκαν σε αναλύσεις αποτελεσματικότητας. Ο δείκτης άπνοιας-υπόπνοιας (AHI) ήταν 14,2 (5,4 έως 22,3) συμβάντων/ώρα στο εικονικό φάρμακο και 6,2 (2,8 έως 13,6) με AD036 και 4,8 (1,4 έως 11,6) με ατομοξετίνη. Και τα δύο φάρμακα μείωσαν επίσης τον δείκτη αποκορεσμού οξυγόνου (ODI) και το υποξικό φορτίο ($p < 0,0001$). Το AD036, αλλά όχι μόνη της η ατομοξετίνη, μείωσε τον δείκτη των αφυπνίσεων και βελτίωσε τον αερισμό στο κατώφλι αναπνευστικής διέγερσης (μεγαλύτερο Vactive). Υπήρχε μια τάση ο συνολικός χρόνος ύπνου να μειώνεται περισσότερο με την ατομοξετίνη μόνο παρά με το AD036. Η πιο συχνή ανεπιθύμητη ενέργεια ήταν η αϋπνία (12% με AD036, 18% με ατομοξετίνη). Η AD036 βελτίωσε σημαντικά τη σοβαρότητα της OSA σε ασθενείς με μέτρια φαρυγγική απόφραξη. Η ατομοξετίνη μπορεί να ευθύνεται για την πλειονότητα της βελτίωσης της σοβαρότητας της OSA, ενώ η προσθήκη οξυβουτινίνης μπορεί να μετριάσει τη διασπαστική επίδραση της ατομοξετίνης στον ύπνο και να βελτιώσει περαιτέρω τον αερισμό.

Επιλογή άρθρου – Σχολιασμός: Κυριακή Χολίδου

Child Neurology: A Case Series of Heterogeneous Neuropsychiatric Symptoms and Outcome in Very Early-Onset Narcolepsy Type 1

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Abstract

Narcolepsy type 1 is a central disorder of hypersomnolence characterized by excessive daytime sleepiness, cataplexy (i.e., sudden loss of muscle tone during wakefulness triggered by emotions), and REM sleep-related manifestations that can present with a peculiar phenotype when arising at a pediatric age. Several features of childhood-onset narcolepsy type 1 are also common in neuropsychiatric conditions; discrete neuropsychiatric comorbidity has also been demonstrated. Here, we report on 3 children with very early narcolepsy type 1. All 3 patients had psychiatric features at the time of symptom onset coupled with peculiar motor disturbances. The course of narcolepsy symptoms also paralleled neuropsychiatric symptoms, suggesting a possible intrinsic link between sleep and psychological features. Multidisciplinary management is mandatory for pediatric narcolepsy type 1 since prompt disease management addressing neuropsychiatric symptoms could lead to better clinical outcomes and quality of life.

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Child Neurology: A Case Series of Heterogeneous Neuropsychiatric Symptoms and Outcome in Very Early-Onset Narcolepsy Type 1

Neurology, 2022

Η Ναρκοληψία Τύπου 1 (NT1) είναι Κεντρική Διαταραχή Υπερυπνικού Τύπου, που χαρακτηρίζεται από υπερβολική υπνηλία κατά τη διάρκεια της ημέρας, καταπληξία και διαταραχές που συνδέονται με τον ύπνο REM.

Η NT1 συνδέεται με ανεπάρκεια της υποκρετίνης 1 στο ENY, γεγονός που αντικατοπτρίζει την απώλεια υποθαλαμικών νευρώνων, οι οποίοι παράγουν υποκρετίνη, πιθανόν λόγω μιας αυτοάνοσης διαταραχής.

Η NT1 τυπικά ξεκινά κατά την εφηβεία και τη νεαρή ενήλικη ζωή με χαρακτηριστικά τα οποία είναι τυπικά της ηλικίας.

Η παιδική NT1 έχει μια ασυνήθιστη εμφάνιση πολλές φορές με την υπερβολική υπνηλία κατά την ημέρα να εκδηλώνεται ως αυξημένη ανάγκη για ύπνο ή υπερκινητικότητα με διαταραχές συμπεριφοράς και την καταπληξία να εμφανίζεται ως μια σύνθετη κινητική διαταραχή, η οποία συμπεριλαμβάνει διαταραχή της βάδισης ή επιμένουσα υποτονία, η οποία τυπικά εμφανίζεται στο πρόσωπο (προσωπείο καταπληξίας), αναμειγμένα αυτά τα φαινόμενα με υπερκινητικά χαρακτηριστικά. Επιπρόσθετα εμφανίζονται νευροψυχιατρικές και ενδοκρινολογικές διαταραχές. Ως αποτέλεσμα των ανωτέρω, η διάγνωση της Ναρκοληψίας στην παιδική ηλικία μπορεί να καθυστερήσει και πολύ συχνά να γίνει λανθασμένη διάγνωση και θεραπεία. Η εργασία αυτή ανακοινώνει 3 ενδιαφέροντα περιστατικά NT1 σε παιδιά κάτω των 5 ετών με το μικρότερο από αυτά να έχει έναρξη των συμπτωμάτων σε ηλικία 2 ετών και 9 μηνών. Το ενδιαφέρον του άρθρου αυτού είναι ότι και οι 3 ασθενείς με πολύ πρώιμης έναρξης NT1 είχαν νευροψυχιατρικές εκδηλώσεις καθώς επίσης και έντονες κινητικές διαταραχές, όπως ανωτέρω, δηλαδή προσωπείο καταπληξίας μαζί με διαταραχές βάδισης και υπερκινητικότητα. Παράλληλα, τα μικρά αυτά παιδιά είχαν διαταραχές ύπνου, που φαίνονταν να επιτείνονται από τις νευροψυχιατρικές εκδηλώσεις. Από τα περιστατικά αυτά φαίνεται ότι η NT1 σε πρώιμη παιδική ηλικία έχει κλινικές εκδηλώσεις που συμπίπτουν με κοινές νευροψυχιατρικές διαταραχές, με κοινά νευροψυχιατρικά συμπτώματα, όπως για παράδειγμα ευερεθιστότητα, υπερκινητικότητα, συναισθηματική αποσταθεροποίηση, επιθετική συμπεριφορά, παρορμητικότητα και κακή προσοχή. Η νευροψυχιατρική συννοσηρότητα που αναδεικνύεται στα παιδιά με NT1, συμπεριλαμβάνει ΔΕΠ-Υ σε ποσοστό 29%, Διαταραχές της Διάθεσης σε ποσοστό 20%, Αγχώδη Διαταραχή σε ποσοστό 10%, Εναντιωματική Προκλητική Διαταραχή σε ποσοστό 7%, ΔΑΦ που δεν καθορίζεται περαιτέρω 3% και Διαταραχές Σίτισης στο 3%. Επίσης, δεν είναι γνωστό πόσο συχνός είναι ο αυτισμός σε παιδιά που έχουν NT1, αλλά είναι σαφές ότι υπάρχει μια αλληλεπίδραση των συμπτωμάτων που συνδέονται με την NT1 και αυτιστικών χαρακτηριστικών και δεν είναι γνωστό αν η ανεπάρκεια της υποκρετίνης και τα συμπτώματα της NT1 στις πολύ νεαρές ηλικίες μπορεί να οδηγήσουν νευροψυχιατρική διαταραχή ή αν οι 2 κατηγορίες συμπτωμάτων οφείλονται σε μια υποκείμενη νευροαναπτυξιακή διαταραχή.

Επιλογή άρθρου-Σχολιασμός: Αντιγόνη Παπαβασιλείου

Metabolomics Signature of Patients With Narcolepsy

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Abstract

Background and Objectives

Narcolepsy type 1 (NT1) is an orphan brain disorder caused by the irreversible destruction of orexin neurons. Metabolic disturbances are common in patients with NT1 who have a body mass index (BMI) 10% to 20% higher than the general population, with one-third being obese (BMI >30 kg/m²). Besides the destruction of orexin neurons in NT1, the metabolic alterations in obese and nonobese patients with NT1 remain unknown. The aim of this study was to identify possible differences in plasma metabolic profiles between patients with NT1 and controls as a function of their BMI status.

Methods

We used a targeted liquid chromatography–mass spectrometry metabolomics approach to measure 141 circulating, low-molecular-weight metabolites in drug-free fasted plasma samples from 117 patients with NT1 (including 41 obese individuals) compared with 116 BMI-matched controls (including 57 obese individuals).

Results

Common metabolites driving the difference between patients with NT1 and controls, regardless of BMI, were identified, namely sarcosine, glutamate, nonylcarnitine (C9), 5 long-chain lysophosphatidylcholine acyls, 1 sphingolipid, 12 phosphatidylcholine diacyls, and 11 phosphatidylcholine acyl-alkyls, all showing increased concentrations in NT1. Metabolite concentrations significantly affected by NT1 (n = 42) and BMI category (n = 40) showed little overlap (n = 5). Quantitative enrichment analysis revealed common metabolic pathways that were implicated in the NT1/control differences in both normal BMI and obese comparisons, namely glycine and serine, arachidonic acid, and tryptophan metabolism. The metabolites driving these differences were glutamate, sarcosine, and ornithine (glycine and serine metabolism); glutamate and PC aa C34:4 (arachidonic acid metabolism); and glutamate, serotonin, and tryptophan (tryptophan metabolism). Linear metabolite-endophenotype regression analyses highlight that as part of the NT1 metabolic phenotype, most of the relationships between the sleep parameters (i.e., slow-wave sleep duration, sleep latency, and periodic leg movement) and metabolite concentrations seen in the controls were lost.

Discussion

These results represent the most comprehensive metabolic profiling of patients with NT1 as a function of BMI and propose some metabolic diagnostic biomarkers for NT1, namely glutamate, sarcosine, serotonin, tryptophan, nonylcarnitine, and some phosphatidylcholines. The metabolic pathways identified offer, if confirmed, possible targets for treatment of obesity in NT1.

Classification of Evidence

This study provides Class II evidence that a distinct metabolic profile can differentiate patients with NT1 from patients without the disorder.

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Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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METABOLOMICS SIGNATURE OF PATIENTS WITH NARCOLEPSY

Neurology, FEB 2022

Η Ναρκοληψία Τύπου I (NT1) είναι εγκεφαλική διαταραχή, η οποία προκαλείται από μη αναστρέψιμη καταστροφή των νευρώνων της ορεξίνης. Η ορεξίνη ή υποκρετίνη είναι ένα νευροπεπτίδιο το οποίο ρυθμίζει την εγρήγορση και την όρεξη.

Μεταβολικές διαταραχές είναι συχνές στους ασθενείς με NT1 που έχουν Δείκτη Μάζας Σώματος (BMI) 10% έως 20% υψηλότερο από ό,τι ο γενικός πληθυσμός. Το 1/3 από αυτούς τους ασθενείς είναι παχύσαρκοι με BMI πάνω από 30.

Η παρούσα μελέτη στόχευσε να προσδιορίσει πιθανές μεταβολές στο μεταβολικό προφίλ του πλάσματος των ασθενών που πάσχουν από NT1 σε σχέση με υγιείς μάρτυρες, σε συσχέτισμό με το BMI.

Ελέγχθηκαν 117 ασθενείς με NT1, μεταξύ των οποίων οι 41 ήταν παχύσαρκοι και συγκρίθηκαν με 116 μάρτυρες με αντίστοιχο (matched) BMI. Μετρήθηκαν 141 μεταβολίτες χαμηλού μοριακού βάρους στο πλάσμα και εξετάστηκαν οι διαφορές μεταξύ των ατόμων με NT1 έναντι των μαρτύρων ανεξαρτήτως από τον BMI, καθώς και μεταβολίτες οι οποίοι μεταβάλλονταν σε σχέση με τη διάγνωση NT1 και την κατηγορία του BMI.

Η διεξοδική αυτή καταγραφή του μεταβολικού προφίλ των ατόμων με NT1 σε σχέση με το BMI κατέληξε στο ότι υπάρχουν κάποιοι μεταβολικοί βιοδείκτες, που είναι διαγνωστικοί για την NT1 και πιο συγκεκριμένα, οι συγκεντρώσεις γλουταμικού, σαρκοσίνης, σεροτονίνης, τρυπτοφάνης, nonylcarnitine καθώς και μερικών φωσφατιδυλοχολινών.

Η μελέτη αυτή παρέχει Class II Evidence σχετικά με την ύπαρξη ενός ξεχωριστού μεταβολικού προφίλ σε άτομα με NT1 το οποίο μπορεί να διαφοροποιήσει τους πάσχοντες από Ναρκοληψία Τύπου 1 από άτομα χωρίς αυτή τη διαταραχή. Επιπλέον, τα μεταβολικά μονοπάτια που βρέθηκαν να ενοχοποιούνται για τις διαφορές μεταξύ ατόμων με NT1 και μαρτύρων, τόσο σε αυτούς με φυσιολογικό δείκτη μάζας σώματος όσο και σε εκείνους με παχυσαρκία, είναι συνήθη και εφόσον επιβεβαιωθούν, μπορεί να αποτελέσουν πιθανούς στόχους για τη θεραπεία της παχυσαρκίας στην NT1.

Οι περιορισμοί της μελέτης ήταν ο σχετικά μικρός αριθμός των υγιών μαρτύρων καθώς και η ποσοτική ανάλυση ενός περιορισμένου αριθμού τάξεων μεταβολιτών.

Επιλογή άρθρου-Σχολιασμός: Αντιγόνη Παπαβασιλείου

