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EDITORIAL

# Sleep apnoea syndrome: how will physiologic knowledge position personalised medicine?

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The sleep apnoea field is no longer only a matter of nocturnal choking and noise-related partner sleep disturbances. There is now a body of literature demonstrating the huge impact of these nocturnal respiratory disturbances on tissular and systemic inflammatory processes, oxidative stress and endothelial dysfunction, as well as imbalance in sympathetic/parasympathetic activities. These factors interact to favour the development of systemic impairments that include alterations in vigilance/cognition, metabolic disturbances, vascular remodelling and atherosclerosis, making way for hypertension, ischaemic heart disease, heart failure, glucose intolerance/diabetes and non-alcoholic steatohepatitis. In the present issue of the *European Respiratory Review,* the article by LÉVY *et al.* [1] perfectly illustrates the need for a multi-dimensional approach in the management of this disease by piecing together the up-to-date parts of the puzzle represented by the knowledge on pathophysiology, investigations, mechanisms of comorbidity and treatment alternatives. The authors clearly demonstrate that investigating and treating sleep apnoea patients is not only a way to provide silent and quiet nights to patients and their environment, but that the investigation and treatment must be integrated into strategies aimed at preventing the development of comorbid conditions that, nowadays, are recognised as being independently associated with sleep apnoea phenotype. This article also highlights the fact that the mechanisms responsible for the occurrence of sleep apnoea, as well as for the metabolic consequences of the disease, may be individually modulated so that treatment strategies and expected benefits from a sleep apnoea cure may be heterogeneous.

From a mechanical point of view, WELLMAN *et al.* [2] recently reported that different physiological traits (pharyngeal anatomy/collapsibility, ventilatory loop gain, mechanical effectiveness of upper airway muscles recruitment and arousal threshold) may separately account for the occurrence of upper airway instability. Identifying the factor(s) responsible for upper airway closure in a given individual may open the door to different therapeutic approaches that have may not be effective when not taking into account the underlying mechanisms of upper airway collapse. In this context, strategies aimed at reducing loop gain (oxygen and acetazolamide), arousal threshold (sedatives) and/or improving upper airway gain (drug or nerve stimulation-induced upper airway muscles stimulation) could be selectively targeted depending on identified physiological defects. The same reasoning can be applied to new factors recently identified as being involved in the occurrence of sleep-disordered breathing (SDB) (*i.e.* leg fluid shift). Changes in neck circumference and in leg fluid volume were initially found to account for 67% of the variance of the apnoea/hypopnoea index (AHI) while factors considered as classical determinants of sleep apnoea risk (body mass index and neck circumference) were not found to influence this index [3]. Such dramatic impact of changes in leg fluid volume could represent a new therapeutic target (*i.e.* diuretics, elevation of the head and shoulders and prevention of daytime accumulation of fluid in the legs). This was recently tested in a non-randomised open study in non-obese sedentary males [4]. Wearing compression stockings during the daytime was found to be very effective in decreasing leg fluid shift but AHI improvement was half of that anticipated from the previous observation [3], despite the fact that the selected patients should have been particularly prone to improved breathing abnormalities when decreasing changes in leg fluid volume. This can be partially accounted for by the fact that important determinants of nocturnal breathing disturbances, such as body and neck position, have not been taken into account. Furthermore, the influence of leg volume shift on AHI was not found in a larger population including more obese subjects [5]. Such discrepancies demonstrate the need to refine the phenotypic characterisation of patients in whom modification in leg fluid shift could improve nocturnal breathing disturbances when taking into account that in the studies by REDOLFI and co-workers [3, 4], participants did not receive any medication similar to the majority of patients actually referred to sleep clinics (*i.e.* anti-hypertensive drugs).

LÉVY *et al.* [1] clearly illustrate the important progression in the understanding of sleep apnoea cardio-metabolic consequences and the need for sleep apnoea treatment in a strategy aimed at decreasing such a risk, as well as the complexity of the interaction between potential important factors. This may contribute to the fact that sleep investigations still do not belong to the cardio-metabolic risk evaluation (*i.e.* in individuals with abdominal obesity, hypertension, type-2 diabetes and dyslipidaemia). It is now recognised that obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and short sleep duration have a significant impact on metabolic dysfunction. The prevalence of metabolic syndrome is significantly higher

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in OSAHS than in the overall population and obese apnoea-free subjects [6]. Results of large epidemiological studies suggest that recurrent oxygen desaturation is associated with metabolic disturbances independent of obesity [7]. Short sleep duration is associated with weight gain and obesity [8]. Both cross-sectional and prospective studies reported a higher degree of metabolic disturbances and hypertension in poor sleepers [9, 10]. These data have been confirmed by experimental models in humans aimed at modifying sleep duration or quality [11, 12]. Normalisation of SDB may improve several determinants of cardio-metabolic risk, such as improvement in lipid profile and glycaemic control, decrease in visceral adipose tissue and decrease in autonomic sympathetic activity [13, 14]. However, such improvements are not systematically reported [15, 16], even when taking into account the effects of treatment compliance and obesity, and the metabolic impact of OSAHS treatment is highly variable. The observations, therefore, suggest that SDB may differentially affect metabolic function depending on: 1) the nature/intensity of sleep apnoea-related stimuli; 2) their pathophysiological impact on metabolic pathways; and 3) genetically determined sensitivity to the various physiological consequences of SDB. The lack of precise identification of the sleep and respiratory variables and/or metabolic characteristics that predict which subjects will benefit from sleep apnoea treatment largely contributes to the absence of sleep investigation conducted as part of the cardio-metabolic risk evaluation in general medical practice.

Intermittent hypoxia and sleep fragmentation are thought to play a key role in the development of metabolic disturbances through the activation of the sympathetic nervous system and pro-inflammatory pathways (reactive oxygen species, inflammatory cytokines and hyperlipidaemia). Therefore, the target population that would benefit from SDB treatment could, theoretically, be identified by abbreviated recordings, such as nocturnal oximetry. However, the conventional threshold used to identify desaturation events (4% fall in arterial oxygen saturation) underestimates the association of SDB with glycaemic status abnormalities, with the latter being more strongly linked with lower grade desaturation events [17]. Furthermore, the increase in risk for developing diabetes overtime is increased in OSAHS independent of the decrease in arterial oxygen saturation [18]. However, sleep fragmentation due to cortical and autonomic arousals accounts for alterations in sympathetic/parasympathetic activity, and the simultaneous presence of metabolic syndrome and sleep apnoea further increases sympathetic activity and worsens glycaemic control, even after adjustment for body mass index [19]. Alteration in glucose metabolism and sympatho-vagal balance has been observed in normal subjects following two nights of experimental sleep fragmentation [20]. The effects of sleep restriction or alteration (loss of slow wave sleep) may further worsen the metabolic disturbances through their consequences on appetite regulation (leptin/ghrelin imbalance), increase in sympathetic activity, growth hormone release and activation of the hypothalamic–pituitary–adrenal axis. Finally, the susceptibility to nocturnal respiratory/autonomic stimuli may also relate to the individual metabolic status, but this issue is difficult to assess due to the paucity of published data evaluating the influence of SDB on the metabolic profile of subjects with metabolic syndrome. It must be acknowledged that no data are available in such a population concerning fat distribution (intra-abdominal *versus* subcutaneous), adipokines, chemokines and inflammatory cell profiles. However, genetic determinants of metabolic disturbances may play an important role in the development/worsening of metabolic syndrome/type-2 diabetes. Such genetic predisposition has been reported with angiotensin converting enzyme gene polymorphisms when linking SDB with the risk for hypertension [21]. Similar findings have been reported for β-adrenergic receptors [22], tumour necrosis factor-α and cytokines [23] but the link with the efficacy of SDB treatment has not yet been evaluated. Therefore, nocturnal phenotyping including assessment of sleep duration and fragmentation, quantification of nocturnal desaturation in addition to metabolic phenotype and gene polymorphisms, should represent the optimal targets to characterise the conditions favouring the development of sleep apnoea-related metabolic disturbances and identify subjects whose cardio-metabolic markers should *versus* should not improve following sleep apnoea treatment.

A better understanding of sleep apnoea mechanisms and of the tight and complex interaction between factors implicated in the cascade of systemic and metabolic disturbances puts into perspective the challenges the sleep apnoea field faces in the next decade. This highlights the need to conduct both mechanistic and basic science physiological studies aimed at developing personalised treatment approaches since randomised clinical trials cannot be tailored to reach these goals.

## STATEMENT OF INTEREST

None declared.

## REFERENCES


1 Lévy P, Tamisier R, Minville C, *et al*. Sleep apnoea syndrome in 2011: current concepts and future directions. *Eur Respir Rev* 2011; 20: 134–146.
2 Wellman A, Eckert DJ, Jordan AS, *et al.* A method for measuring and modeling the physiological traits causing obstructive sleep apnoea. *J Appl Physiol* 2011; 110: 1627–1637.
3 Redolfi S, Yumino D, Ruttanaumpawan P, *et al.* Relationship between overnight rostral fluid shift and obstructive sleep apnoea in nonobese males. *Am J Respir Crit Care Med* 2009; 179: 241–246.
4 Redolfi S, Arnulf I, Pottier M, *et al.* Effects of venous compression of the legs on overnight rostral fluid shift and obstructive sleep apnoea. *Respir Physiol Neurobiol* 2011; 175: 390–393.
5 Jafari B, Mohsenin V. Overnight rostral fluid shift in obstructive sleep apnoea: does it affect the severity of sleep-disordered breathing? *Chest* 2011; [Epub ahead of print DOI: 10.1378/chest.11-0044].
6 Kahn R, Buse J, Ferrannini E, *et al*. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005; 28: 2289–2304.
7 Punjabi NM, Sorkin JD, Katzel LI, *et al.* Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med.* 2002; 165: 677–682.
8 Cappuccio FP, Taggart FM, Kandala NB, *et al.* Meta-analysis of short sleep duration and obesity in children and adults. *Sleep* 2008; 31: 619–626.

9 Knutson KL, Ryden AM, Mander BA, *et al.* Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. *Arch Intern Med* 2006; 166: 1768–1774.
10 Jennings JR, Muldoon MF, Hall M, *et al.* Self-reported sleep quality is associated with the metabolic syndrome. *Sleep* 2007; 30: 219–223.
11 Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; 354: 1435–1439.
12 Tasali E, Leproult R, Ehrmann DA, *et al.* Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci USA* 2008; 105: 1044–1049.
13 Steiropoulos P, Tsara V, Nena E, *et al.* Effect of continuous positive airway pressure treatment on serum cardiovascular risk factors in patients with obstructive sleep apnea-hypopnea syndrome. *Chest* 2007; 132: 843–851.
14 Harsch IA, Hahn EG, Pour Schahin S. Effect of CPAP on insulin resistance in patients with obstructive sleep apnoea and type 2 diabetes. *Thorax* 2008; 63: 384–385.
15 West SD, Nicoll DJ, Wallace TM, *et al.* Effect of CPAP on insulin resistance and HbA1c in males with obstructive sleep apnoea and type 2 diabetes. *Thorax* 2007; 62: 969–974.
16 Coughlin SR, Mawdsley L, Mugarza JA, *et al.* Cardiovascular and metabolic effects of CPAP in obese males with OSA. *Eur Respir J* 2007; 29: 720–727.
17 Stamatakis K, Sanders MH, Caffo B, *et al.* Fasting glycemia in sleep disordered breathing: lowering the threshold on oxyhemoglobin desaturation. *Sleep* 2008; 31: 1018–1024.
18 Botros N, Concato J, Mohsenin V, *et al.* Obstructive sleep apnoea as a risk factor for type 2 diabetes. *Am J Med* 2009; 122: 1122–1127.
19 Grassi G, Seravalle G, Quarti-Trevano F, *et al.* Reinforcement of the adrenergic overdrive in the metabolic syndrome complicated by obstructive sleep apnoea. *J Hypertens* 2010; 28: 1313–1320.
20 Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest* 2010; 137: 95–101.
21 Zhang J, Zhao B, Gesongluobu, *et al.* Angiotensin-converting enzyme gene insertion/deletion (I/D) polymorphism in hypertensive patients with different degrees of obstructive sleep apnoea. *Hypertens Res* 2000; 23: 407–411.
22 Bartels NK, Börgel J, Wieczorek S, *et al.* Risk factors and myocardial infarction in patients with obstructive sleep apnoea: impact of beta2-adrenergic receptor polymorphisms. *BMC Med* 2007; 5: 1.
23 Popko K, Gorska E, Potapinska O, *et al.* Frequency of distribution of inflammatory cytokines IL-1, IL-6 and TNF-alpha gene polymorphism in patients with obstructive sleep apnoea. *J Physiol Pharmacol* 2008; 59: Suppl. 6, 607–614.