JOURNAL CLUB

Broken sleep: a new chronic intermittent hypoxia model for obstructive sleep apnoea

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Obstructive sleep apnoea (OSA) is a medical condition characterized by repeated episodes of apnoea and/or hypopnoea during sleep (Young *et al.* 2002; Foster *et al.* 2007). This condition has strong epidemiologic associations with cardiovascular disease and has been shown to be a risk factor for hypertension, myocardial infarction and stroke (Foster *et al.* 2007). A number of different research groups have attempted to address the mechanisms underlying the high risk for cardiovascular disease in patients with OSA. Given that obesity increases the risks of both OSA and cardiovascular disease, this has been proposed as one mechanism linking OSA and hypertension; certainly many OSA patients are obese or overweight. However, it may also be that the vasculature is directly influenced by intermittent hypoxia and/or hypercapnia secondary to periods of apnoea. Indeed, Peppard *et al.* (2000) state that the risk of cardiovascular disease is independent of obesity in OSA patients. Similarly, Foster *et al.* (2007) showed that intermittent hypoxia (IH) *per se* leads to vascular disease in OSA. Although the exact mechanism underlying vascular disease in OSA is still unknown, chemoreflex-mediated sympathetic nervous system overactivity with subsequent peripheral vasoconstriction is a proposed contributing factor. Another possible contributing factor is a decrease in nitric oxide production following IH, which would also promote vasoconstriction and hypertension.

Thus, while IH during spontaneous apnoeas in OSA patients is reported to increase their risk of cardiovascular disease, it would be advantageous to study the effects of IH as distinct from other cardiovascular risk factors that accompany OSA in experimental models. Therefore developing a healthy human model of IH that resembles OSA, and that would minimize potential confounding factors such as coexisting cardiovascular disease, is desired.

There have been many previous experimental models of OSA. They can be broadly divided into short-term, referring to tests approximately 1 h or less in duration, or chronic, referring to tests conducted over multiple days. Foster *et al.* (2007) provide an overview of some of these different models. Many short-term models cycle between 20 and 30 s of IH per minute, which is the approximate duration of an IH cycle in OSA. These studies typically employ a strong hypoxic stimulus, yielding arterial oxygen saturations in the range of 80–85%, considerably lower saturations than typically seen in patients with OSA. Furthermore, these tests last only 20–30 min, which may not provide an accurate model of the chronic effects of IH on the cardiovascular system. Chronic IH protocols that could address these problems have predominantly been performed in animals. Only one model evaluated chronic IH in humans, and it had some important shortcomings, such as 5 min cycles of hypoxia and normoxia and a short duration of exposure (1 h per day).

This Journal Club article focuses on a recent paper published in *The Journal of Physiology* by Foster *et al.* (2009) that describes a new and improved model of IH to simulate sleep apnoea. This model addresses many of the shortfalls that exist in current OSA models of IH. In the present study, Foster *et al.* (2009) used a much shorter hypoxia/normoxia cycle of 2 min and, importantly, exposed subjects to IH for 6 h per day, far more representative of an individual's sleep duration. Their study was also very well controlled. For example, subjects were exposed on two occasions (1 and 4 days before commencing the study) to 'sham IH' to enable familiarization to the test procedures and equipment during intermittent normoxia. This important aspect of this study minimizes any potential placebo effect. Tremendous efforts were also made to control for changes in physical activity and diet. All subjects were instructed to keep a record of their diet and exercise schedule in a daily diary to validate the findings. In addition, 80% of the subjects were monitored via an actigraphy system which provided a secondary index of physical activity and a measure of the sleep/wake schedules of each person. In all, this study, with its good experimental control and new experimental paradigm that addresses previous shortfalls in models of OSA, represents a significant advance in our understanding of the cardiorespiratory effects of chronic IH in humans, and sheds new insight on the pathophysiology of OSA.

However, although this new model from Foster *et al.* (2009) has many advantages over previous OSA models of IH, the paper does raise several questions.

In this model the IH component of OSA is being studied, but the carbon dioxide (CO_2) levels are not controlled. This leads to a decrease in end-tidal CO_2 caused by the ventilatory response to hypoxia. The decrease in end-tidal CO_2 in the model is in direct contrast to the hypercapnia seen during actual sleep apnoeas, as a consequence of airway obstruction. The authors acknowledge the potential importance of changes in CO_2 as a contributing factor for hypertension in OSA, but based on the absence of a strong vascular effect of CO_2 in animal models of OSA, they largely discount this role. In contrast, Cooper *et al.* (2005) have recently shown that in humans hypercapnia increases the set point of the vascular resistance limb of the baroreceptor reflex and consequently increases blood pressure, an effect that seems to be sustained even after removal of the hypercapnic stimulus. This raises the question as to whether the increase in blood pressure found by Foster *et al.* (2009) caused by intermittent hypoxia is an underestimation of the increase in blood pressure in OSA patients. This is supported by the finding that asphyxia (hypercapnia and hypoxia) promotes a greater increase in blood pressure than hypoxia alone (Cooper *et al.* 2004, 2005).

Nevertheless, the hypertension observed in the present study, with only 4 days of exposure to IH, was not inconsiderable and certainly sheds light on the pathological association between hypertension and chronic IH secondary to OSA. Further studies examining the relationship between

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IH and other cardiovascular parameters, such as muscle sympathetic nerve activity or catecholamine levels, would be of great mechanistic interest.

Accounting for CO_2 changes during IH could also influence the cerebral blood flow (CBF) responses. The normal cerebral response to hypoxia would be to increase CBF, but during the hypoxic phases of the IH protocol Foster *et al.* (2009) found that the CBF decreased (Fig. 4). We suggest that in this case the normal response to hypoxia is counteracted by hyperventilation-induced hypocapnia. Certainly, cerebral reactivity to CO_2 is typically much greater than to hypoxia. Indeed, previous studies have shown that the usual cerebral sensitivity to hypocapnia is approximately $1.75 \pm 0.6\%$ CBF $mmHg^{-1}$ (Norcliffe *et al.* 2005). In the current study the CO_2 levels fell by approximately 4 mmHg during the hypoxic cycle, and CBF decreased approximately 7–8%, which is compatible with the expected 7% decline according to Norcliffe *et al.* (2005). Although the authors acknowledge a possible role for CO_2 in the cerebral responses seen, this role is largely dismissed. However, we would argue that the reduction in CO_2 during the IH does influence the cerebrovascular resistance and therefore the CBF. For this reason it would be interesting to control CO_2 levels more rigorously, or even increase the CO_2 levels during IH (as would occur during actual sleep apnoea) to further elucidate the mechanisms involved.

Similarly, the fact that the decrease in CO_2 during each phase of IH was more profound the longer the subjects were exposed to IH is an interesting finding. Whilst this may shed insight into the mechanisms of IH, it is not applicable to OSA patients, since the CO_2 in these patients will not decrease, but increase.

Finally, Foster *et al.* (2009) report increases in cerebrovascular resistance responses to acute hypoxia with exposure to chronic IH. However, this would seem to be at odds with the data in Fig. 5, where the gradient describing the relationship between cerebrovascular resistance and oxygen saturation is shallower on day 4. It appears from these data that there is a blunted vasodilatation to hypoxia, and thus a decreased cerebrovascular resistance response with IH. Nevertheless, Foster *et al.* (2009) attribute this change in cerebral responsiveness to acute hypoxia to a decrease in nitric oxide production after IH. Nitric oxide is a potent vasodilator in the cerebral circulation and so this reduction would be expected to cause an increase in cerebrovascular resistance and a decrease in CBF. This is compatible with a blunted cerebral vasodilatory response to hypoxia.

We note that nitric oxide may also be involved in the cerebral reactivity to CO_2 (Lavi *et al.* 2003). Foster *et al.* (2009) found that resting CO_2 levels were lower following IH, and yet the resting CBF was not reduced as would be expected with hypocapnia. This suggests that the reduced nitric oxide production may also be blunting the CBF response to steady-state hypocapnia.

Therefore, the suggestion that IH reduces nitric oxide production, based on indirect measures from nitric oxide breakdown, is of great interest. However, further mechanistic studies examining this relationship using more direct assessments, including investigation of the effects of nitric oxide synthase inhibition, are warranted. Interestingly, Phillips *et al.* (2004) showed that, in rodents exposed to IH, responses to nitric oxide donors were intact, but vasodilatory responses to acetylcholine and an acute bout of hypoxia were blunted, supporting the suggestion that IH attenuates the release of no.

In summary, Foster *et al.* (2009) provide an improved model that addresses many of the shortcomings in previous models of chronic IH in OSA. This model provides new insights into the mechanistic link between OSA and cardiovascular disease. In agreement with the authors we feel that future models of IH should aim to provide 20 s cycles of hypoxia and normoxia to more accurately reflect the IH cycles in OSA. Furthermore, we feel future models of chronic IH should include an intermittent hypercapnic component in addition to the intermittent hypoxia to mirror the increased CO_2 levels found during sleep apnoea.

References

Cooper VL, Bowker CM, Pearson SB, Elliott MW & Hainsworth R (2004). Effects of simulated obstructive sleep apnoea on the human carotid baroreceptor-vascular resistance reflex. *J Physiol* **557**, 1055–1065.

Cooper VL, Pearson SB, Bowker CM, Elliott MW & Hainsworth R (2005). Interaction of chemoreceptor and baroreceptor reflexes by hypoxia and hypercapnia – a mechanism for promoting hypertension in obstructive sleep apnoea. *J Physiol* **568**, 677–687.

Foster GE, Poulin MJ & Hanly PJ (2007). Intermittent hypoxia and vascular function: implications for obstructive sleep apnoea. *Exp Physiol* **92**, 51–65.

Foster GE, Brugniaux JV, Pialoux V, Duggan CTC, Hanly PJ, Ahmed SB & Poulin MJ (2009). Cardiovascular and cerebrovascular responses to acute hypoxia following exposure to intermittent hypoxia in healthy humans. *J Physiol* **587**, 3287–3299.

Lavi S, Egbarya R, Lavi R & Jacob G (2003). Role of nitric oxide in the regulation of cerebral blood flow in humans: chemoregulation versus mechanoregulation. *Circulation* **107**, 1901–1905.

Norcliffe LJ, Rivera-Ch M, Claydon VE, Moore JP, Leon-Velarde F, Appenzeller O & Hainsworth R (2005). Cerebrovascular responses to hypoxia and hypocapnia in high-altitude dwellers. *J Physiol* **566**, 287–294.

Peppard PE, Young T, Palta M & Skatrud J (2000). Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* **342**, 1378–1384.

Phillips SA, Olsen EB, Morgan BJ, Lombard JH (2004). Chronic intermittent hypoxia impairs endothelium-dependent dilation in rat cerebral and skeletal muscle resistance arteries. *Am J Physiol* **586**, H388–H393.

Young T, Peppard PE & Gottlieb DJ (2002). Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* **165**, 1217–1239.

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