EDITORIAL
SLEEP

Stressful sleep

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Obstructive sleep apnoea increases the stress hormone cortisol, and CPAP can correct this problem
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Few would challenge the assertion that the inability to breathe is stressful. In fact, inhaling carbon dioxide to simulate asphyxia is a time-honoured research protocol to unmask panic disorder [1]. Sleep loss is also stressful, as evidenced by increased cortisol and sympathetic tone in insomnia [2] or sleep deprivation [3, 4]. In the case of obstructive sleep apnoea (OSA), impaired breathing efforts may jolt the sleeper awake with surges in heart rate, blood pressure, sympathetic nerve activity and catecholamines. The treatment of OSA normalises many of these parameters [5]. Hence, OSA clearly engages the "fight or flight" response; a term coined in 1915 by Walter Cannon to describe activation of the sympathetic nervous system to defend homeostasis [6]. In 1936, Hans Selye defined stress as "the non-specific response of the body to any demand upon it" and postulated the General Adaptation Syndrome [7] describing how repeated physical or psychological demands elicit initially adaptive, then maladaptive responses. When stress induces negative consequences, it shifts from potentially productive stress (eustress) to damaging distress. Unrelenting distress may lead to a variety of disorders through hypercortisolism [8]. The ideas of Cannon and Selye have helped formulate the still widespread view that all threats, whether real or imagined, are countered by a global and stereotyped activation of the neuroendocrine system.

The neuroendocrine response to stress is now appreciated to be far more complex [9, 10]. Central nervous system (CNS) responses elicit at least three discrete, sometimes overlapping pathways: the sympathoneural axis (CNS output to efferent nerves with signalling *via* noradrenaline); the adrenomedullary axis (CNS output to the adrenal medulla leading to adrenaline secretion); and the hypothalamic–pituitary–adrenocortical (HPA) axis (CNS output to the adrenal cortex leading to cortisol secretion). Activation of the sympathoneural, adrenomedullary and HPA systems often occur in a stressor-specific manner. For example, hypoglycaemia typically induces adrenaline and adrenocorticotropic hormone release, whereas cold exposure predominantly and selectively increases noradrenaline [11, 12]. Certain stimuli also exhibit a predilection for triggering the HPA axis. For example, cortisol secretion is most likely to accompany psychological stress that involves a perceived lack of control or social-evaluative threat [13]. However, there is considerable inter-individual variability in HPA activation during physical or mental stimulation [14, 15]. Some factors that might account for this variability include acclimation/habituation [16], early life experiences [17], sex [18] and genetics [14].

Whether OSA stimulates the HPA axis in addition to its recognised impact on the sympathoneural and adrenomedullary axes is uncertain [19] and worthy of investigation. In this issue of the *European Respiratory Journal*, Kritikou *et al.* [20] examined the effects of OSA and its treatment with continuous positive airway pressure (CPAP) on 24-h cortisol secretion profiles. Investigators recruited subjects with OSA (apnoea–hypopnoea index (AHI) >10 in women and >15 in men) and controls of similar weight. They were careful to exclude medical or psychological comorbidities known to affect the HPA axis,

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including circadian rhythm disorders and obesity. In total, 72 patients (35 OSA and 37 controls), were acclimated to a sleep laboratory for four nights. Hourly blood samples were drawn over the last 24-h period. OSA patients were then assigned to CPAP or sham CPAP for 2 months, with a 1 week washout period between crossover treatments, in random order. Following each CPAP or sham-CPAP period, another 4-day study and 24-h cortisol profile was obtained. This design allowed for baseline comparisons of cortisol rhythm between apnoeics and controls; and within-subject comparisons of cortisol rhythm following CPAP.

The study determined that OSA (AHI 38.5, minimum oxygen saturation measured by pulse oximetry 82%) was associated with increased 24-h cortisol levels compared to controls (7.99 *versus* 7.10 $\mu g \cdot dL^{-1}$; p=0.04). This difference was slightly amplified after adjusting for variables such as age, BMI, anxiety/depression scales and smoking status. There was no shift in the circadian pattern of cortisol release nor in the daytime cortisol level. In terms of sleep, OSA was associated with impaired sleep architecture, increased wake after sleep onset (WASO) and a shift from stage N2 to stage N1 sleep. As expected, CPAP improved AHI and sleep architecture. CPAP also normalised 24-h cortisol (decrease from 7.89 to 7.25 $ng \cdot mL^{-1}$; p<0.01) and induced a non-statistically significant trend in decreased nighttime and daytime cortisol levels. Multiple regression analysis revealed an association between 24-h cortisol and logAHI (r^2=0.19, β=0.23, p=0.01). A trend correlation was noted between 24-h cortisol and WASO and (r=0.23, p=0.05). Similar findings were observed in both men and women.

We applaud this study for addressing the important question of whether OSA activates the HPA axis, and for approaching this question in a rigorous manner. The relation between HPA activity and sleep is complex, and potentially influenced by sleep architecture/duration, circadian rhythm, sex, age and mood disorders [4]. Previous related studies lacked serial blood sampling, control groups or attention to confounding variables [19]. When one considers the varied clinical manifestations of OSA and heterogeneous HPA responses to stress in general [14], it is striking that OSA had a measurable impact on cortisol levels. Perhaps certain OSA patients are more prone to HPA activation. If so, who might these "responders" be? Kritikou *et al.* [20] determined that cortisol elevation was not related to minimal oxygen saturation, but was associated with WASO and logAHI, parameters that reflect disturbed sleep. These exploratory analyses are consistent with evidence that cortisol surges during transient nocturnal awakenings [21, 22]. It would therefore also be interesting to see whether subjective sleep quality, sleepiness, or insomnia were also predictors of cortisol elevation in their study.

Kritikou *et al.* [20] point out that untreated OSA was associated with a ∼15% increase in 24-h cortisol. In absolute terms, 24-h cortisol differences between OSA and controls were ∼1 $\mu g \cdot dL^{-1}$, while CPAP lowered the value by 0.6 $\mu g \cdot dL^{-1}$. Salivary cortisol levels transiently increase by 50–75% within 30 min after spontaneous awakening in healthy subjects. The "Trier Social Stress Test" involves giving a speech and performing mental arithmetic in front of an audience, and leads to a rapid ∼10 $\mu g \cdot dL^{-1}$ (∼70%) increase in serum cortisol with a return to baseline after 90 min [23]. Thus, HPA activation in this study could be characterised as modest, but prolonged. Perhaps a sustained cortisol elevation of this magnitude could have deleterious health consequences. Mechanisms linking OSA to cardio-metabolic dysfunction are still unclear [24] and cortisol could certainly play a role. In particular, cortisol fosters abdominal adiposity and insulin resistance [8] and sensitises adipose tissue to lipolysis [25]. Central obesity, insulin resistance and free fatty acid elevation are features of OSA [26, 27].

In conclusion, Kritikou *et al.* [20] elegantly show that 24-h cortisol is increased by OSA and decreased by CPAP. Further studies will be needed to determine the clinical significance of this elevation. In the meantime, Walter Cannon and Hans Seyle would likely agree: OSA is stressful.

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