Comments on the CrossTalk proposal and opposing view: Elevated loop gain is a consequence of obstructive sleep apnoea

Respiratory chemoreflex considerations

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The issue of whether elevated loop gain is a consequence of obstructive sleep apnoea (OSA) is important and the authors are to be commended for raising it in this CrossTalk proposal (Orr et al. 2014; Younes, 2014). A major aspect of loop gain is the respiratory chemoreflex response and overnight changes were assessed in OSA and non-OSA subjects using rebreathing tests (Duffin, 2011) in the evening and morning, just before and after sleep (Mahamed et al. 2005). The sub-threshold ventilation or wakefulness drive was unchanged overnight in both groups, but the rate of rise of CO2 during rebreathing, an index of metabolism, was lower in the morning in both groups. A decrease in metabolism during sleep acts to increase plant gain, but in the non-OSA group the ventilatory recruitment threshold was lower in the morning, offsetting the increase in plant gain to leave loop gain unchanged. Such a change in ventilatory recruitment threshold during sleep would act as a protective effect. In the OSA group, however, while the ventilatory recruitment threshold was unchanged overnight, the chemoreflex sensitivity was increased in the morning. This increased controller (feedback) gain combined with the increased plant gain (only slightly offset by the sensitivity increase) resulted in an increase in loop gain in the morning. The question is why, as this CrossTalk addresses.

To answer this question, overnight changes in the respiratory chemoreflexes from evening to morning were assessed in 11 healthy volunteers, using rebreathing tests as in the previous OSA study, on 2 nights a week apart (Diep, 2006). During one night they were subjected to 20 s hypoxic exposures, at a rate of 30/h while sleeping (stage determined from polysomnograph readings), and during the other night 20 s air exposures; the order was randomized. The hypoxic exposures night produced the same overnight changes seen in the OSA group, while the air exposures night produced the same changes as in the non-OSA group. These findings therefore support the idea that the hypoxic episodes experienced by OSA patients are responsible for their overnight chemoreflex sensitization, and consequent increase in loop gain and decrease in stability. In this respect OSA patients are no different from normal subjects, and so measuring the chemoreflexes in OSA patients may provide treatment guidance (Wang et al. 2013).

One aspect not discussed in the CrossTalk is the possible changes in cerebral blood flow control in OSA patients. Cerebral blood flow is remarkably sensitive to arterial CO2 (Battisti-Charbonney and al., 2011), and since the central chemoreceptors lie within the brain environment, their CO2 stimulus is affected by cerebral blood flow (Xie et al. 2006; Ainslie & Duffin, 2009). Indeed, changes in cerebral blood flow reactivity to CO2 have been implicated in the breathing instability observed in subjects during altitude acclimatization (Burgess et al. 2013). These authors had also tested this aspect in an OSA subject and found that oral indomethacin, which reduced cerebrovascular reactivity, also exacerbated this subject’s OSA (Burgess et al. 2010). Abnormalities in cerebral perfusion have been noted in OSA patients (Yadav et al. 2013; Shiota et al. 2014), and pressure autoregulation also appears to be different (Urbano et al. 2008). The cerebrovascular aspect of OSA therefore deserves further investigation, possibly using the powerful technique of magnetic resonance imaging (Wang et al. 2008; Sobczyk et al. 2014) to measure differences in the distribution of cerebrovascular reactivity between OSA and non-OSA subjects.

References


Diep D, Eckert DJ & Grunstein RR (2013). Drug effects on ventilatory control and upper airway physiology related to sleep apnea. Respir Physiol Neurobiol 188, 257–266.


**Additional information**

**Competing interests**

None declared.

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**Au contraire, the case is not closed**

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Younes suggested that a high chemical loop gain (CLG) is not inherent in patients with obstructive sleep apnoea (OSA), based solely on the work completed by Loewen and colleagues (Loewen et al. 2009). This study established that CLG was reduced following treatment, which suggests that factors linked to OSA (e.g. intermittent hypoxia, arousal) contribute to high CLG. However, the finding does not eliminate the possibility that high CLG is in part due to an inherent trait, since loop gain following treatment could have remained higher than values in appropriately matched controls, which were not included in the study. In contrast to Younes’ argument, Orr and colleagues argue that stimuli linked to OSA in combination with inherent factors could contribute to high CLG. We support this argument based on work completed in our laboratory. We have shown previously that intermittent hypoxia has a role in enhancing chemoreflex sensitivity in individuals with sleep apnoea (Khodadadeh et al. 2006; Gerst et al. 2011; Mateika & Syed, 2013). More recently, employing a constant routine protocol, we found that chemoreflex sensitivity was higher and the carbon dioxide reserve lower during non-rapid eye movement sleep in the morning compared to the evening and afternoon, despite the elimination of breathing events with continuous positive airway pressure (El-Chami et al. 2014a; El Chami et al. 2014b). This latter finding indicates that high CLG may be both a cause and consequence of OSA.

**References**


El Chami M, Syed Z, Shaheen D, Ivers B, Badr MS, Lin HS & Mateika J (2014b). The carbon dioxide reserve is reduced and chemoreflex sensitivity is increased in the morning compared to the evening and afternoon in participants with sleep apnea. *FASEB J* 28, 1178.7.


**Additional information**

**Competing interests**

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**Loop gain: a cautionary tale**

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The distinction between ‘chemical’ and ‘actual’ loop gain that Younes (2014) has introduced in this debate is useful conceptually, but the notion requires a bit of fine-tuning. Loop gain analysis is based on the premise that the non-linear equations characterizing the ventilatory control system can be linearized by determining its response to small perturbations around a given equilibrium state (Khoo, 2000). But this premise breaks down when the system includes a collapsible upper airway which behaves essentially like an on–off switch (i.e. a ‘hard non-linearity’). A more intuitive way to think about this is to consider an ‘effective’ controller curve that combines the properties of the (largely linear) chemical controller with the on–off characteristic of the upper airway (see figure at https://drive.google.com/file/d/0B7ORewaU5PMjZC1ld1jhQkF1c2c/edit?usp=sharing). In one possible scenario (Younes et al. 2007), the upper airway reopens without arousal, with ventilation jumping from zero to V1, once chemical drive exceeds the recruitment threshold (P(UAreopening)). Another possibility is that when the arousal threshold (< P(UAreopening)) is exceeded, ventilation jumps abruptly from zero to V2 (> V1). If V1 or V2 subsequently lower P(CO2) to below P(UAreopening), recurrent episodes of obstructive apnoea could follow. Note that, in the vicinity of either threshold, the effective controller gain (and thus local loop gain) becomes essentially infinite, but controller gain at higher P(CO2) could be high or low. Thus, consistent with previous model simulations (Khoo et al. 1991), recurrent obstructive apnoea can occur in low-gain or high-gain systems through different mechanisms of instability.

**References**


**Additional information**

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