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CROSSTALK

CrossTalk proposal: Elevated loop gain is a consequence of obstructive sleep apnoea

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Before addressing this question it is necessary to define loop gain (LG) in the context of obstructive sleep apnoea (OSA). In a closed loop system, such as the breathing system, a perturbation in the controlled loop component (the respiratory apparatus, or 'plant') elicits changes in the feedback (blood gas tensions) received by the controller (respiratory centres), which in turn effects a compensatory response in the plant. The initial response may partially correct the blood gas changes, with the residual changes being gradually corrected later. This is a stable response. However, the initial response may result in over-correction of the gas changes ('overshoot') such that they are better than what existed before the perturbation. The ventilatory apparatus is then inhibited through the same changes in blood gas tensions that resulted in the initial response, and a second hypopnoea results. If the second hypopnoea is less severe than the original one, the disturbance in gas tensions will also be less severe, eliciting a lesser response and a less severe hypopnoea results, and so on. Ultimately, the system stabilizes. If the overshoot results in such improvement in gas tensions that the second hypopnoea is more severe than the initial one, the cycle can perpetuate indefinitely. LG is the ratio of the initial response to the initial perturbation. A LG of <1.0 is consistent with stable breathing while a LG >1.0 results in perpetual cycling.

LG is determined by: (a) how much blood gas tensions deteriorate before the controller can reverse the trend (maximal changes), and (b) how much the controller will respond to these maximal changes ('controller gain') (Khoo *et al.* 1982; Younes, 1989; Younes *et al.* 2001). Maximal changes are determined by the time course of changes in gas tensions after the onset of hypopnoea ('plant gain'; related to lung volume, mixed venous gas tensions, and other factors) and the time it takes to elicit a ventilatory response ('Delay'). The longer the Delay, the greater the maximal changes and the higher the plant gain. Controller gain is determined by the sensitivity of respiratory centres to blood gas changes, which is also time dependent; the longer the P_{CO_2} change lasts the greater the response to the same P_{CO_2} change (Cunningham *et al.* 1986). Thus, both components of LG increase as a function of 'response delay'.

When respiratory mechanical impedance is fairly constant, such as in normal subjects or in patients with a stable upper airway (OSA on continuous positive airway pressure (CPAP)), Delay is strictly a function of the lung–carotid circulatory delay. Furthermore, because respiratory impedance is 'constant' it affects the initial perturbation and subsequent response equally. In this case, LG is a function of the relatively short circulatory delay ($\sim$7 s), and the relatively low (because of the short Delay) plant and controller gains. Under such conditions recurrent apnoeas or hypopnoeas occur when circulatory delay is abnormally long (heart failure), plant gain is high (low lung volume, poor mixed venous blood gas tensions, etc.) and/or high ventilatory responses to CO_2 and hypoxia. LG under such conditions predominantly reflects the behaviour of chemoreceptor-mediated feedback loops and I will refer to this as 'Chemical LG'.

In OSA, the repetitive nature of the events is consistent with a LG that is >1.0. This high LG cannot be analysed in the same way as in central apnoeas because the delay between event onset and initiation of ventilatory response is not the lung–carotid delay, but the time taken for upper airway (UA) dilator muscles to open the airway (event duration). Furthermore, respiratory mechanics during and following the obstructive phase are vastly different. Event duration (up to 100 s) is invariably longer than circulation delay ($\sim$7 s; Younes *et al.* 2007); progressive increase in effort occurs well before the airway opens (Remmers *et al.* 1978; Onal & Lopata, 1982; Berry & Gleeson, 1997), and the mechanisms that determine this duration are extremely complex (Younes, 2008; White & Younes, 2012; Younes *et al.* 2012). As the obstruction continues, plant gain increases and controller gain increases up to the level of respiratory pressure generation. Thus potential LG continues to increase, but actual LG is zero because there is no ventilatory response. At opening, potential LG may be very high, but it cannot be fully realized unless UA opens completely, which is not usually the case (snoring and flow limitation usually continue during the open phase). The net (actual) LG in OSA is determined by the potential LG at the end of obstruction (a function of event duration) as attenuated by the residual high impedance during the open phase. This net LG is what determines whether the cycle will repeat.

In summary, there is no doubt that UA instability and the resulting lengthy Delay (event duration > circulatory delay) is the main mechanism of increased LG in OSA. Thus, the increased LG in OSA is, in large measure, the result of the obstructive event itself. What might be debated is

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whether Chemical LG is increased and, if so, whether this contributes to OSA severity and whether the increase was the result or cause of the disease. To evaluate Chemical LG in these patients it is necessary to measure it when UA is stable, for example by measuring ventilatory responses during wakefulness or while the patient is asleep on CPAP. Measurements of ventilatory responses during wakefulness yielded highly conflicting results (see Loewen *et al.* 2009 for review). These studies used chemical challenges that do not reflect the situation in OSA. In OSA the chemical challenge is brief stimulation by a mixture of hypoxia and hypercapnia (asphyxia), whereas ventilatory response studies during wakefulness used re-breathing or steady-state exposures. By contrast, when measured during sleep, directly by proportional assist ventilation (Younes *et al.* 2001; Wellman *et al.* 2004) or indirectly from dynamic ventilatory responses to brief changes in inspired gases (Younes *et al.* 2007; Loewen *et al.* 2009), Chemical LG was somewhat elevated in OSA patients, but the increase is insufficient to cause instability in the absence of unstable UA (Younes *et al.* 2001; Wellman *et al.* 2004). Hence, central apnoea develops infrequently in patients while on CPAP.

Does a somewhat increased Chemical LG aggravate the instability produced by abnormal UA mechanics? A higher Chemical LG would lead to a faster increase in respiratory effort during the obstruction. However, since UA opening via arousals (arousal threshold; Gleeson *et al.* 1990; Kimoff *et al.* 1994; Eckert & Younes 2014) or via reflex activation of pharyngeal dilators ('effective recruitment threshold'; Younes, 2008; White & Younes, 2012; Younes *et al.* 2012) occurs when a certain chemical drive is reached, the increased Chemical LG would reduce event duration but not result in higher chemical stimulus at the time of opening. This, *per se*, would not aggravate the instability. However, because of circulation delay, chemical drive continues to increase for 1–2 breaths beyond event termination. An above normal ventilatory response might, therefore, result in greater overshoot, increasing the chance of recurrence. Whether the higher controller gain in OSA contributes to OSA severity is currently debatable. Chemical LG correlates with apnoea severity only in patients with mild UA mechanical abnormality (Wellman *et al.* 2004). Oxygen breathing (Martin *et al.* 1982; Smith *et al.* 1984; Gold *et al.* 1985, 1986; Wellman *et al.* 2008) and acetazolamide (Sharp *et al.* 1985; Tojima *et al.* 1988; Whyte *et al.* 1988; Edwards *et al.* 2012), both of which attenuate Chemical LG, partially reduce the apnoea–hypopnoea index in some but not all patients. This is understandable since Chemical LG is only modestly elevated and only in some patients (Younes *et al.* 2001; Wellman *et al.* 2004, 2008; Edwards *et al.* 2012).

With respect to whether the increased Chemical LG in OSA is inherent or acquired as a result of OSA, there is little to discuss. There is only one study that directly addressed this issue. We studied dynamic ventilatory responses to asphyxia mimicking obstructive events during sleep before and several weeks after therapy with CPAP. There was a dramatic reduction in these responses following treatment (Fig. 1; Loewen *et al.* 2009). Thus, the high Chemical LG did not pre-exist. Case closed!

In summary, the high LG in OSA is due to OSA and not to high Chemical LG. The contribution of Chemical LG to OSA severity, if any, is modest and limited to some patients in whom Chemical LG is high.

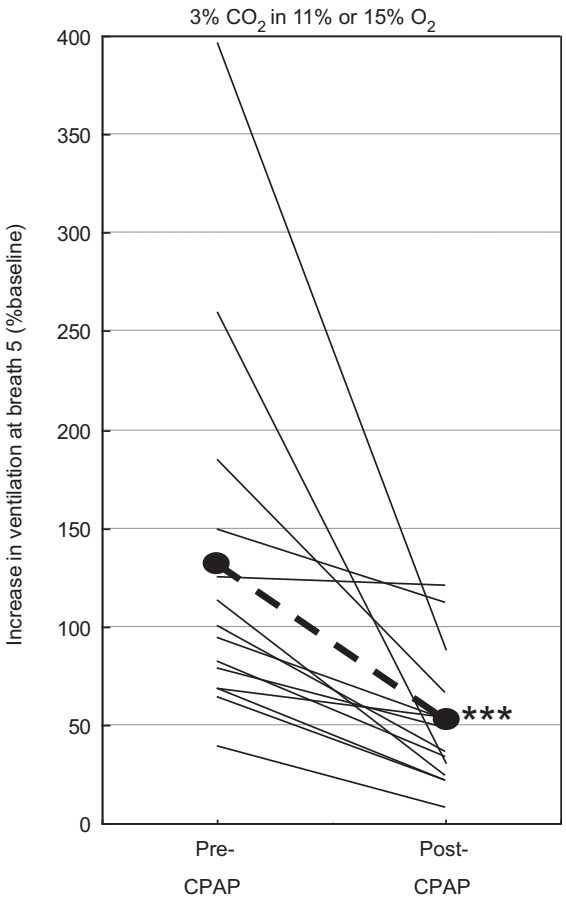

Figure 1. Change in dynamic ventilatory response to asphyxia after several weeks of CPAP therapy
Increase in ventilation 5 breaths after changing inspired gas from air to 3% CO_2 in 11% or 15% oxygen before and after several weeks of therapy with continuous positive airway pressure (CPAP). In both cases the patient was on optimal CPAP during the measurements. ***$P < 0.005$. Reproduced from Loewen *et al.* (2009).

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Additional information

Competing interests

None declared.