Editorial

The role of loop gain in predicting upper airway surgical outcomes—what do we know?

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Obstructive sleep apnea (OSA) is a multifactorial disorder characterized by at least three primary phenotypes. The first phenotype is associated with mechanical impairments of the upper airway leading to increased collapsibility of the upper airway. The second phenotype is defined by a low arousal threshold which contributes to unstable ventilatory control. The third phenotype is defined by a high loop gain which also contributes to unstable ventilatory control during sleep (1,2). Loop gain by definition includes both "plant" (i.e., lung volume, gas exchange rate, circulatory delay) and "controller" (i.e., chemoreflex) gain components (3). An overall loop gain of less than 1 is typical of a stable respiratory control system (4). Unfortunately, due to the multitude of phenotypic impairments, optimal treatment for OSA has yet to be established.

The current gold standard treatment for OSA is continuous positive airway pressure (CPAP). While a considerable number of patients experience measurable benefits from this treatment, adherence remains poor, approximately 50% (3). Primary barriers to adherence include a poor mask fit, nasal congestion, sleep disturbances, and air leaks, leading to a poor perception of the device and discomfort (3,5). Upper airway surgery presents an alternative for patients who cannot tolerate CPAP, and could have significant implications for improving sleep fragmentation and associated co-morbidities in OSA patients. The surgical treatment of OSA dates back to 1969 and predicting the success of the procedure has been considered dependent on the severity of upper airway anatomical abnormalities responsible for turbulent airflow (6,7). Yet, the results remain ambiguous with a success rate between 16–83% (8).

There are at least three possible reasons to explain surgical failures in OSA patients, as outlined by Joosten and colleagues (9), (I) the anatomical abnormality is too severe to be rectified by surgery; (II) the surgical procedure does not target the site of collapse; and (III) the presence of non-anatomical traits might be principally responsible for the patient's apnea. One or more of the non-anatomical factors (i.e., arousal threshold, upper airway collapsibility, and high loop gain) are present in 69% of OSA patients, resulting in varying phenotypes (1). Consequently, the focus of Joosten and colleagues' investigation was to determine the impact of non-anatomical features, loop gain and arousal threshold, on the rate of success of surgery in patients with OSA (9).

Loop gain

The authors classified OSA patients as "responders" to surgery, if the apnea-hypopnea index (AHI) was reduced by ≥50% compared to baseline and the AHI was <10 events/hour following surgery. Twelve of 46 participants were

deemed responders to surgery. At baseline and following surgery, the non-responders had a significantly higher loop gain compared to responders. The results indicated that an increased loop gain in the non-responders continued to contribute to the initiation of apnea despite anatomical modifications that occurred following surgery. Nevertheless, further studies are required to examine if a relatively small average difference in loop gain that was reported between the responders and non-responders (0.38 *vs.* 0.48) could be responsible for the difference in the change in AHI that was reported between groups following surgery. Indeed, loop gains below 1 are typically considered to indicate a relatively stable system (4). In such a system, the magnitude of the response to an apnea should be sufficiently small enough to allow ventilation to quickly return to a stable pattern. A higher loop gain, usually greater than 1, has been identified as one of the causes for the waxing and waning pattern that is characteristic of an unstable ventilatory control pattern during wakefulness and sleep. Thus, whether a relatively small increase in loop gain, within a stimulus/response range that is typically considered to be stable, has the degree of impact on the AHI reported in the present study requires further investigation employing a larger number of participants, coupled with measures of upper airway collapsibility. Indeed, previous investigations have suggested that loop gain does not play a significant role in patients with either a highly or less collapsible airway (4,10).

In addition to the primary finding (i.e., the impact of surgery on the AHI is less in patients with increased loop gain), the authors also reported that loop gain was similar both before and after surgery in responders and non-responders. The authors contend that this finding indicates that loop gain is genetically predisposed in patients with OSA, because loop gain remained unaltered despite significant reductions in the AHI. However, despite reporting that average loop gain did not change following surgery, a positive correlation between the change in AHI and the change in loop gain following surgery was evident. Based on this latter result, the absence of an average change in loop gain likely reflects a differential response in loop gain to changes in the AHI following surgery. Otherwise, a positive correlation would not be possible. In other words, in some participants loop gain increased after surgery and in others loop gain decreased after surgery, as shown in Figure 2 of the manuscript (9). Thus, in most subjects, loop gain did not remain unaltered following surgery. The reasons for the disparate response in loop gain remains to be determined. Nonetheless, the premise that loop gain is genetically predisposed requires further investigation. The possibility that loop gain might be dependent on factors that influence AHI is supported by recent findings from our laboratory. We showed that despite the elimination of intermittent hypoxia with nasal CPAP, increases in controller gain, coupled to a decrease in the carbon dioxide reserve, during non-rapid eye movement sleep were evident in the early morning compared to the evening and afternoon (11). In other words, independent of genetic predisposition, multiple variables might influence loop gain, even those that are independent of OSA. Future studies manipulating variables that could potentially influence measures of loop gain (i.e., circadian rhythm) and arousal threshold are required to determine if enhanced loop gain is a cause or consequence of sleep apnea.

Arousal threshold

The authors also reported that participants were more easily aroused (i.e., lower arousal threshold) from respiratory related events following surgery. The change in the arousal threshold was significantly greater in the responders compared to the non-responders following surgery. Thus, the results imply that elevations in the arousal threshold might be initiated by sleep apnea and that upper airway surgery not only improves the AHI but also modifies the arousal threshold so that it impacts on the AHI to a lesser extent. However, this conclusion requires further investigation given that the same authors (12) and others (1,13) previously reported that a lower arousal threshold was coupled to increases in the AHI. Indeed, one might anticipate that a decrease in the arousal threshold coupled to repeated arousals would be accompanied by an increase in the AHI because (I) an insufficient time is available for respiratory stimuli to recruit the upper airway muscles to stabilize the airway before arousal; (II) arousal can lead to dynamic ventilatory instability promoting subsequent airway collapse and perpetuation of apneas and hypopneas; and (III) because sleep fragmentation could prevent the individual from achieving slow wave sleep which typically is associated with a more stable airway. Indeed, given this latter point it would have benefitted readers if modifications in sleep architecture were presented for both the responders and non-responders (i.e., rather than being pooled). Given that this did not occur it is difficult to determine the impact that modifications of the arousal threshold had on sleep architecture for each group. Nonetheless, based on the pooled data, modifications in the arousal threshold had little

impact on sleep architecture and the number of respiratory arousal related events. If the severity of sleep apnea impacts the arousal threshold, one would anticipate that more time in the deeper stages on non-rapid eye movement would have been evident (14) and the number of respiratory arousal related events would have been altered post-surgery, which was not the case. Indeed, both an absolute and standardized decrease (i.e., standardized to total sleep time) in N2 was evident following surgery. Nevertheless, despite the discrepant findings between the present study and previous investigations, the results indicate that post-surgical decreases in the arousal threshold do not appear to counteract the benefits of upper airway surgery on the AHI.

Future research

Joosten and colleagues' findings (9) can be used as a blueprint for the development of future research studies. These studies include the investigation of variables that impact loop gain and their role in determining surgical outcome measures. Similarly, studies focused on the arousal threshold will ultimately determine those variables linked to OSA that might impact the arousal threshold. Results from these studies could lead to future investigations focused on interventions that are guided by an understanding of individual phenotypic physiological properties and the role these properties have in the pathogenesis of sleep apnea. Likewise, these studies could significantly improve treatment of individuals suffering from OSA and could increase the sensitivity of stratifying patients into responders and non-responders. Lastly, given that the present investigation was retrospective and included multiple forms of surgeries, larger studies focused on a given surgery are necessary to confirm the results obtained in this study.

Summary statement

The results obtained from Joosten and colleagues (9) provide new information on the role that loop gain and arousal threshold has in determining the success of upper airway surgery. Ultimately, these findings will be used to select patients with the highest probability for successful surgery. The results highlight the importance of understanding a patient's baseline physiology in order to determine if surgical alternatives to CPAP treatment will be successful. Moreover, understanding the role that ventilatory control instability has in OSA pathogenesis will prevent patients from undergoing futile surgery and associated complications. Lastly, the authors provide information that may lead to new therapies targeting loop gain that will increase the number of positive surgical outcomes in OSA patients. These findings are important discoveries that require additional confirmation from prospective large-scale studies.

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Footnote

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