Editorial Commentary

Appeasing the Carotid Body After Chronic Intermittent Hypoxia

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I recall vividly a conversation with the late Professor C. John Dickinson DM, FRCP, ARCO (Professor of Medicine and Chairman of the Department of Medicine at St. Bartholomew’s Hospital, London, 1975–1992) who remarked that in the majority of cases cardiovascular pathology occurred at night while asleep. John’s great hypothesis was that a shortage of oxygen to the brain because of high cerebrovascular resistance, triggered hypertension, and that was worsened by the diurnal falls in blood pressure further compromising cerebral perfusion. Clearly, such a mechanism would be thoroughly agonised during sleep-disordered breathing.

Sleep-disordered breathing occurs in ≈1 in 5 men and 1 in 10 women aged between 50 and 70 years.1 With an increasing incidence between 14% and 55% over the past 2 decades, sleep-disordered breathing is growing into a huge clinical and economic problem. Associated with sleep-disordered breathing is narcolepsy, cardiovascular disease including heart failure and hypertension, autonomic imbalance, baroreceptor resetting, and inflammation. The causes of sleep apnea are partly dependent on whether the apneas are obstructive or central in origin but many patients have a combination of both. Continuous positive airway pressure has been shown to reduce peripheral chemosensitvity (as seen as a reduction in the hypoxic ventilatory response2) and abolish hypopneas and apneas in patients with obstructive sleep apnea.3 However, the associated hypertension, which is found in at least 50% of cases, is typically not ameliorated.4 Central sleep apneas are controlled using adaptive servo ventilation: a recent study by Cowie et al5 in heart failure patients with reduced left ventricular ejection fraction used adaptive servocontrolled inspiratory pressure and expiratory positive airway pressure (SERVE-HF). Unexpectedly, all-cause mortality and cardiovascular mortality were significantly higher relative to the control group. Thus, alternative strategies for the treatment of sleep-disordered breathing and associated cardiovascular disease are needed and an article recently published by Del Rio et al6 is most timely. They used a rat model of chronic intermittent hypoxia that generated modest hypertension and showed that once the hypertension was fully established, selective removal of the carotid body chemoreceptors bilaterally normalized arterial pressure. This parallels the classic earlier work of Fletcher et al7 who showed that in rats transection of the carotid sinus nerves prevented hypertension in response to chronic intermittent hypoxia. But Del Rio et al’s8 study documents new information of high clinical relevance. Importantly, and for the first time, they show that performing the intervention after the hypertension had developed was successful, suggesting that the carotid bodies are essential for the maintenance of hypertension accompanying chronic intermittent hypoxia, and not just its development. The significance of this from a clinical perspective is that patients obviously only present when they express the symptom. Thus, a treatment strategy that can alleviate an established hypertension has important clinical implications. In addition, the authors used radiotelemetry to allow high-fidelity blood pressure to be measured definitively in conscious rats; earlier studies used tail cuff or indwelling chronic catheters that can both cause stress and easily confound blood pressure data. They also provide evidence that autonomic balance is restored to the heart, which provides a plausible explanation for the reduction in arrhythmias induced by the chronic intermittent hypoxia.5 Baroreceptor reflex function, which was depressed by the chronic intermittent hypoxia, was markedly improved post carotid body ablation. Rescuing the baroreceptor reflex by improving its reflex gain and lowering its set point should not be underestimated as a potential mechanism for both the anti-hypertensive effect and the restoring autonomic balance after carotid body removal. Recent human trials have stimulated the selective removal of the carotid body chemoreceptors—so called hyperreflexia. This is portrayed by the augmented ventilatory response to hypoxia in the Del Rio et al study. As reported by McBryde et al8 in the spontaneously hypertensive rat, this hyperreflexia was accompanied by elevations in ongoing tonic drive emanating from the carotid body. The study by Del Rio et al9 shows that increased carotid body afferent tone must also exist and likely explains the enhanced tidal volume at rest and the presence of hypertension. These data are consistent with the recently proposed peripheral afferent activation hypothesis of

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hypertension, where sensitization and tonicity of afferent sensors, such as the carotid body and muscle/renal afferents, drive autonomic imbalance contributing to sympathetic excess and the ensuing hypertension (Figure).

Clinically, the question is whether carotid body ablation would be a safe way to alleviate sleep-disordered breathing (and the associated cardiovascular diseases) or might the apneic events worsen? The answer to this question might depend on whether the apneas are of central or obstructive in origin. There are some other considerations to mention: first, are carotid chemoreceptors involved in the initiation of an apneic event caused by over active peripheral chemoreception leading to a period of hyperventilation-induced hypocapnia that destabilizes the respiratory rhythm generator? (Figure). Second, are the carotid bodies important for the arousal from the apnea? If carotid bodies were ablated, would there be any compensation from central chemoreceptors? Because carotid bodies provide excitatory drive to the central chemoreceptors (Figure), it may be imperative to assess the activity of them and their apneic threshold before irreversible ablation of carotid bodies. Third, it is not easy to gauge the importance of carotid body chemoreceptors in respiratory dysfunction based on current animal models. In the Del Rio et al study, there is no evidence that chronic intermittent hypoxia induced breathing irregularities and, although proposed originally as a model of sleep apnea, this model has its limitations for understanding respiratory arrhythmias and sleep apnea per se. Do we need to add chronic intermittent hypoxia to an existing model of heart failure or hypertension to better mimic the human condition? Animal models displaying apneas such as the Rett syndrome mice, in which methyl CpG-binding protein 2 is knocked out, might better lend themselves as a model for understanding apneas and strategies for their rescue. Indeed, our data point strongly to excitability of respiratory neural elements causing postinspiratory apnea. There are 3 messages here: (1) there is a need for more detailed assessment of respiration—it is all too easy to measure inspiration only but the apnea is often caused by a dysfunction/prolongation of expiration (postinspiration and stage II expiration, Figure); (2) it is the strength of the postinspiratory neurone coupling to sympathetic neurones that appears exaggerated contributing to sympathetic over activity in hypertension, including chronic intermittent hypoxia (Figure); and (3) postinspiratory activity also drives upper airway adductors that could contribute to obstructive apneas (Figure). Thus, future studies should consider measuring expiratory and inspiratory activities.

Ultimately, evidence for a role for carotid body ablation or its modulation in sleep-disordered breathing pathologies will need to come from human studies and these have begun. Carotid body resection has been used as a treatment

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**Figure.** A theoretical, simplified schematic diagram of the connections of the carotid body glomus cells to the cardiovascular and respiratory networks within the medulla oblongata. As portrayed by the color coding, we hypothesize that glomus cells are connected separately via the nucleus of the solitary tract (NTS) to dedicated reflex pathways, as previously suggested. We also propose that carotid body excites selective groups of medullary neurones, regulating cardiovascular and respiratory functions. In particular, we highlight the physiological response (kinesiology; dashed arrows): (1) the central chemoreceptive neurones in the retrotrapezoid nucleus (RTN) that have onward connections to the presympathetic neurones of the rostroventrolateral medulla (RVLM) and the ventral respiratory column (VRC) neurones to power the respiratory oscillator. We infer that RTN excitability depends, in part, on input from the glomus cells. (2) The postinspiratory (post-insp) neurones as drivers of sympathetic activity via the RVLM, cardiac vagal preganglionic vagal motoneurones, and laryngeal adductors located in the nucleus ambiguus (NA); (3) inspiratory (insp) VRC neurones driving preganglionic vagal bronchoconstrictors located in the NA. Pathology (solid lined arrows) results from increased sensitization/tonicity of the carotid body contributing to elevated chemical loop gain, resulting in hyperventilation-induced hypocapnia; this depresses the RTN, destabilizes the respiratory pattern generator during sleep causing central apnea (CSA), hypoxia, sympathoactivation, hypertension, cardiac arrhythmias (because of excessive simultaneous coactivation of cardiac sympathetic and cardiac vagal drives). With an excess glomic drive to glottal adductors and bronchioles, this may also agonise obstructive sleep apnea (OSA). These apneas cause intermittent hypoxia and hypocapnia providing positive feedback to the carotid body that may contribute to their sensitization and aberrant tonicity. Del Rio et al showed how disconnecting the carotid body afferent nerves running although the petrosal ganglion abolished the established hypertension and cardiac arrhythmias induced by chronic intermittent hypoxia. These data and the schematic single out the carotid body as a putative therapeutic target for several cardiovascular, respiratory, and pulmonary diseases.
for systolic heart failure and drug-resistant hypertension. In both these studies, direct evidence for reductions in muscle sympathetic activity was found. About sleep-disordered breathing, the data are limited in heart failure to a case study where unilateral carotid body resection was performed. This resulted in a reduction in central sleep apneas. In hypertensive patients where one carotid body was removed, there were no significant changes in the apnea–hypopnea index. All told, it may be that the type of apnea (central versus obstructive) will be important for determining both the efficacy and the appropriateness of adopting carotid body ablation/modulation as a therapeutic approach for the treatment of sleep-disordered breathing. Nevertheless, Del Rio et al have clearly shown the potential clinical benefit of carotid body denervation in a model of chronic intermittent hypoxia for the restoration of autonomic balance; this now adds to the clinical benefit of carotid body ablation/denervation seen in both animals and humans with heart failure and hypertension.

Important questions remain: why does sensitization occur in the carotid body and what are the molecular mechanisms that cause a sustained afferent drive in sleep-disordered breathing and cardiovascular diseases? Could a single mechanism exist across multiple disease states that explains this aberrant carotid body tone or are the mechanisms responsible diseasespecific? Is it possible that there are different mechanisms within the carotid body driving breathing versus autonomic pathologies perhaps based on distinct subsets of glomus cells connected to separate central reflex pathways (Figure) as we suggested previously. The chronic intermittent hypoxic model has shed light on numerous potential mechanisms. Important for translation is that any antagonist targeting identified mechanisms of carotid body sensitization must be rela-

tively selective and not induce unwanted side effects. Future research efforts should attempt to pharmacologically target the carotid body to appease its excitability, which would avoid the irreversibility issue of denervation or ablation, but preserve its physiological function. This remains an important future challenge, but based on the Del Rio et al study, it is likely to be a most clinically productive strategy.

To conclude, the Del Rio et al study on the role of the carotid bodies for the maintenance of the hypertension induced by chronic intermittent hypoxia in rats adds further credence to the rapidly emerging and topical opinion that this chemoreceptive site is contributing substantially to cardiovascular pathology and, therefore, opens future opportunities for therapeutic targeting, especially because it lies outside the central nervous system.

References


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