Editorial

Re-awakening the carotid bodies after anaesthesia: managing hypnotic and neuromuscular blocking agents

M. Raju[1] and **J. J. Pandit**[2]

1 Erasmus Scholar, 2 Consultant, Nuffield Department of Anaesthesia, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Correspondence to: J. J. Pandit
Email: jaideep.pandit@dpag.ox.ac.uk
Accepted: 29 June 2019
Keywords: carotid body; chemoreflexes; Hypoxia; neuromuscular blockade; respiration

Neuromuscular blocking drugs (NMB) are used in just under half of all general anaesthetics in the UK [1]. However, they have their own unintended effects, especially during early recovery from surgery. We now know that one of these is the risk of accidental awareness during general anaesthesia, which occurs almost exclusively in patients who are paralysed with NMBs [2]. Accidental awareness during recovery arises from too early re-awakening from hypnotic effects of anaesthesia coupled with delayed reversal of paralysis [2]. Postoperative respiratory effects of residual neuromuscular blockade are another well-known side-effects, self-evident if the diaphragm or intercostal muscles are weak or if there is a degree of upper airway collapse [3]. Such clinically detectable paralysis after surgery is at worst evidenced by dyspnoea, agitation, obvious weakness and, if the vocal cords are also partially paralysed, difficulty speaking or coughing (and this last can lead to atelectasis or aspiration). Together these can create a dangerous and frightening situation for patients. Indeed, personal histories from the UK's 5th National Audit Project (NAP5) report suggest that these respiratory symptoms can be interpreted by patients as a perception of having been accidentally awake 'during anaesthesia' [2].

A distinct and different respiratory effect of NMBs is, perhaps, less widely known but is very well established: the specific depression of chemoreflex control of breathing. The peripheral arterial chemoreceptors, located in the carotid bodies, are normally responsible for the rapid response to changing partial pressures of O_2 and CO_2 (hypoxia and hypercapnia, respectively). In humans, the aortic bodies are vestigial, and the central chemoreceptors are not relevant to our discussion because their response time is slow and NMBs, in any case, do not cross the blood brain barrier. In a series of ground-breaking studies in the 1990s, Eriksson's group demonstrated that neuromuscular blockade in volunteers depressed the acute ventilatory response to hypoxia and also to hypercapnia, at subclinical doses that did not depress baseline minute ventilation [4]. This underlines the important distinction in the physiology of the respiratory control system between, on the one hand 'baseline activity' and on the other hand, 'responsiveness'. The former is the innate drive to breathe, representing the 'central rhythm generator' activity of respiratory centre neurones (itself, in part, driven by 'feedforward' mechanisms such as volitional effort). The responsiveness, on the other hand, represents the unconscious 'feedback' part of the control system; the strength of the reflex being measured by its 'gain' or 'sensitivity'. Baseline activity and responsiveness are separate entities and can be influenced differentially. The clinical significance is that a normal resting minute ventilation cannot be taken to imply that the patient can reliably respond appropriately with hyperventilation to a stimulus like hypoxia. Hypoxaemia can arise for several reasons peri-operatively and being unable to respond to it can lead to adverse consequences [5]. This more subtle impairment of chemoreflex function, in addition to clinically evident hypoventilation, may underlie emerging concerns that high dosing of NMBs intra-operatively might adversely influence outcomes [6].

In this issue of *Anaesthesia*, Christensson et al. recruited volunteers with untreated obstructive sleep apnoea (OSA), administered rocuronium (to a train-of-four,

TOF, level ~0.7) and then made them hypoxic and hypercapnic [7]. Neuromuscular blockade was not reversed but allowed to wear off naturally, and respiratory measurements were taken at baseline and at TOF ~0.7 and > 0.9. Their important finding was that, even when TOF 0.7 did not impair baseline ventilation or cause symptomatic muscle weakness, the acute hypoxic ventilatory response was significantly depressed (but in this patient group, the hypercapnic ventilatory response was not). One of the challenges of studying ventilatory control in patients with OSA is that measured expired minute ventilation may be reduced by upper airway collapse and, hence, not reflect the output of the respiratory 'central rhythm generator'. Christensson et al. elegantly overcame this challenge by using background continuous positive airway pressure (CPAP), which they confirmed itself did not influence ventilatory or chemoreflex measurements. In this article, we discuss the implications of these results.

Depression of hypoxic chemoreflex

There are several competing theories of how oxygen is sensed in the carotid body, but one suggested sequence of events is as follows (Fig. 1) [8]. Hypoxia closes background K+ (TASK) channels in the type-1 glomus cells. These leak channels normally serve to maintain membrane potential and hypoxia-induced closure depolarises the glomus cell membrane, which in turn opens voltage-gated Ca^{2+} channels leading to Ca^{2+} influx. The raised intracellular Ca^{2+} (the magnitude of which is proportional to the magnitude of hypoxic stimulus) promotes fusion of neurotransmitter-containing vesicles with the cell membrane. Neurotransmitter exocytosis, and then binding onto specific receptors on the postsynaptic terminal, leads to action potentials in the afferent glossopharyngeal nerve, the frequency of which are proportional to the strength of hypoxic stimulus. The carotid body is rich in neurotransmitters: acetylcholine (ACh), gamma aminobutyric acid (GABA), substance P, dopamine and other catecholamines, adenosine nucleotides, serotonin, enkephalins, neuropeptide Y, calcitonin gene-related peptide, galanin, endothelins and some others are all implicated. Animal studies using an isolated carotid body-nerve preparation have confirmed that non-depolarising neuromuscular blockade inhibits this response to hypoxia [9]. However, nicotinic antagonism does not inhibit the response of the isolated glomus cell to hypoxia [10] and these results together indicate that the action of drugs like rocuronium is at the synapse, not directly on the glomus cell and, in turn, that ACh is a clinically-relevant neurotransmitter at this junction [11].

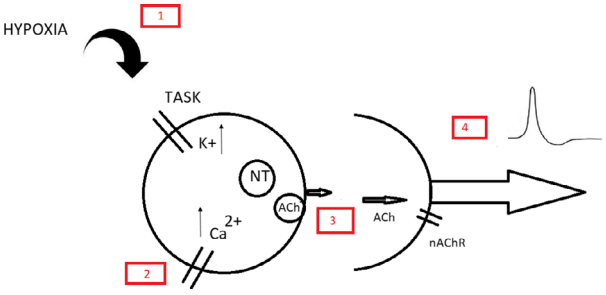

Figure 1 Schematic for oxygen sensing at type-1 glomus cell of carotid body. (1) Hypoxia closes background K+ (TASK) channels, which normally permit background leak of K+ outside the cell; K+ is thus retained in the cell, causing depolarisation. (2) Depolarisation opens voltage-gated Ca^{2+} channels, leading to Ca^{2+} influx. (3) This causes fusion of vesicles containing neurotransmitters (NT) with the cell membrane and acetylcholine (ACh; the likely clinically-relevant neurotransmitter) is released into the synaptic cleft. (4) ACh binds to specific nicotinic receptors (nAChR) causing action potentials in the afferent glossopharyngeal neve, which travel to the respiratory centre. Volatile anaesthetics block the oxygen sensing by TASK channels at step (1). Propofol inhibits glomus cell response by an as yet undefined mechanism (possibly inhibiting voltage-gated Ca^{2+} channels at (2); see reference [14]). Neuromuscular blockade prevents binding of ACh at nAChR at (4).

Christensson et al. report that, when TOF returned to near-normal > 0.9 in their subjects with OSA, acute hypoxic ventilatory response was also restored. However, the effect was variable across individuals and, recently, it has been reported in healthy volunteers, that even near-complete TOF reversal with sugammadex still leaves some individuals with a depressed acute hypoxic ventilatory response (A. Dahan, personal communication). How is it possible that hypoxic response can be depressed by NMBs, even when there is little or no muscle weakness? The human carotid body expresses nicotinic subunits α3, α7 β2 of the pentameric neuronal subtype ACh receptor; skeletal muscle expresses α1, β1, γ, δ or ε subunits. In the latter, up to ~75% of these receptors must be occupied before there is detectable twitch tension reduction. However, in the carotid body, receptors are blocked dose dependently [11]. This difference in receptor structure, and hence in sensitivity to agents, explains why, in some individuals, acute hypoxic ventilatory response is reduced even when neuromuscular function has largely recovered.

However, NMBs are not the only drugs known to depress the peripheral chemoreflex. Very low residual concentrations (<0.1 minimum alveolar concentration) of general anaesthetics (hypnotics) profoundly depress acute hypoxic ventilatory response in humans [12] and this has

been confirmed in human studies [13], animal work [14] and single cell and single channel recordings (cell attached patch clamping of isolated glomus cells) [15, 16]. This research has also established that general anaesthetics prevent the closing of TASK channels by hypoxia with a specific order of potency: halothane > enflurane > isoflurane > sevoflurane, with desflurane being similar in (minimal) depressive potency with sevoflurane [17]. Inhalational anaesthetic agents hence inhibit the whole pathway presented in Fig. 1. Propofol also depresses the isolated glomus cell hypoxic response but by a unique non-TASK, non-nicotinic, non-GABA, non-5-HT mechanism [10]. In other words, the combination of residual general anaesthetics directly depressing the glomus cell by various mechanisms and of NMBs depressing the synapse, is potentially synergistic in profoundly depressing the overall hypoxic response. In clinical practice there may be further depressive synergism with residual concentrations of other agents such as benzodiazepines [18] and opioids [19] which act, not at the carotid body, but more centrally in the nervous system to depress ventilation.

Clinical implications

Clinical outcome studies have found an increased incidence of postoperative desaturation when NMBs are used [20]. If residual neuromuscular blockade is depressive to hypoxic response, then it is logical to reverse it. The choice of reversal agent and timing of administration are, therefore, relevant. There are some theoretical reasons why sugammadex should reverse NMBs more completely than neostigmine. One is that the dose of neostigmine is limited, as excessive dosing can exacerbate paralysis. A second is that even in therapeutic doses some studies report that neostigmine can induce muscle weakness [21]. In contrast, reversal of rocuronium-induced paralysis appears quicker and more complete with sugammadex with fewer adverse outcomes [22].

Monitoring is relevant, as it influences the optimum timing of reversal. Administration of reversal is generally most effective when paralysis is partial as opposed to deep, and depth of paralysis can only be estimated with quantitative neuromuscular function monitoring. Notwithstanding debates around the optimum stimulus type or muscle group used, it is notable that the Association of Anaesthetists' standards of monitoring mandate nerve stimulator monitoring when NMBs are used [23]. There is emerging evidence that quality improvement strategies to record TOF and reverse neuromuscular blockade appropriately can reduce postoperative pulmonary complications [24]. Moreover, the advice is to maintain neuromuscular blockade as light (as many twitches, or as high a TOF) as possible while facilitating surgery or avoid them altogether. This lesson originally emanated from NAP5, where it was realised that traumatic experiences resulted primarily from the awareness of being paralysed, not from the awareness of surgery or even of experiencing pain [2]. Minimising depth of paralysis may allow a patient to signify their awareness. Thus, NMB management is important not only for good restoration of muscle power but also to limit respiratory and, perhaps unexpectedly, psychological side-effects.

The known synergy of NMB-induced depression of hypoxic response with other agents requires us to consider which agents to use in patients at high risk of respiratory complications, like those with OSA. In addition to opioid-sparing techniques, the physiological data make it logical to use agents with less depressive properties to acute hypoxic ventilatory response like sevoflurane, desflurane (or propofol in a total intravenous technique). Advantageously, these are also the agents generally most rapidly eliminated from the body. Additionally, agents like doxapram can be used in clinical practice to stimulate breathing immediately post-surgery. Doxapram is now known to act in a manner akin to hypoxia at the TASK channel of the carotid body glomus cell [25]. However, if postoperative depression of carotid body function arises due to the multimodal action of several drugs themselves acting at multiple sites, then simplistic antagonism at one site (TASK) may not be sufficient, but recent research is focussing on other, specific agents that could stimulate breathing in rational ways [25].

Eikermann has referred to the 'hidden universality of neuromuscular block' [26], by which he had in mind that even patients we believe are fully reversed from NMBs may, in fact, still be partially paralysed. 'Universality' of neuromuscular blockade could apply also in the sense in which NMBs affect not only the musculature but also the respiratory control system. Thus, we need to view complete reversal from neuromuscular blockade as a necessary, but not sufficient end-point for ensuring reversal of hypoxic depression. If there is still detectable paralysis, we can also be sure there will be hypoxic chemoreflex depression.

Many years ago, Knill and Gelb summarized their pioneering work on low-dose anaesthetic effects in inhibiting carotid body function as demonstrating that the 'watchdogs were sleeping' [13]. The very organs tasked to defend us from hypoxaemia remained silenced by residual hypnotics at the time they were, arguably, needed most, in the immediate postoperative period. The careful work of Christensson et al., and others, reminds us that to re-awaken the 'watchdogs', we need to carefully manage

neuromuscular blockade – not just anaesthesia reversal – for a safe recovery.

Acknowledgements

No competing interests declared.

References

1. Sury MR, Palmer JH, Cook TM, Pandit JJ. The state of UK anaesthesia: a survey of National Health Service activity in 2013. *British Journal of Anaesthesia* 2014; **113**: 575–84.
2. Pandit JJ, Andrade J, Bogod DG, et al. The 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. *Anaesthesia* 2014; **69**: 1089–101.
3. Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesthesia and Analgesia* 2010; **111**: 120–8.
4. Eriksson LI. Reduced hypoxic chemosensitivity in partially paralysed man. A new property of muscle relaxants? *Acta Anaesthesiology*. *Scandinavica* 1996; **40**: 520–3.
5. Ward DS, Karan SB, Pandit JJ. Hypoxia: developments in basic science, physiology and clinical studies. *Anaesthesia* 2011; **66** (Suppl. 2): 19–26.
6. McLean DJ, Diaz-Gil D, Farhan HN, et al. Dose-dependent association between intermediate-acting neuromuscular-blocking agents and postoperative respiratory complications. *Anesthesiology* 2015; **122**: 1201–13.
7. Christensson E, Ebberyd A, Hårdemark Cedborg AA, et al. Hypoxic ventilatory response after rocuronium induced partial neuromuscular block in men with obstructive sleep apnoea. *Anaesthesia* 2019; in press.
8. Buckler KJ. TASK channels in arterial chemoreceptors and their role in oxygen and acid sensing. *Pflügers Archiv* 2015; **467**: 1013–25.
9. Wyon N, Joensen H, Yamamoto Y, Lindahl SG, Eriksson LI. Carotid body chemoreceptor function is impaired by vecuronium during hypoxia. *Anesthesiology* 1998; **89**: 1471–9.
10. O'Donohoe PB, Turner PJ, Huskens N, Buckler KJ, Pandit JJ. Influence of propofol on isolated neonatal rat carotid body glomus cell response to hypoxia and hypercapnia. *Respiratory Physiology and Neurobiology* 2019; **260**: 17–27.
11. Jonsson M, Gurley D, Dabrowski M, et al. Distinct pharmacologic properties of neuromuscular blocking agents on human neuronal nicotinic acetylcholine receptors: a possible explanation for the train-of-four fade. *Anesthesiology* 2006; **105**: 521–33.
12. Knill RL, Gelb AW. Peripheral chemoreceptors during anesthesia: are the watchdogs sleeping? *Anesthesiology* 1982; **57**: 151–2.
13. Pandit JJ, Moreau B, Donoghue S, Robbins PA. Effect of pain and audiovisual stimulation on the depression of acute hypoxic ventilatory response by low-dose halothane in humans. *Anesthesiology* 2004; **101**: 1409–16.
14. Karanovic N, Pecotic R, Valic M, et al. The acute hypoxic ventilatory response under halothane, isoflurane, and sevoflurane anaesthesia in rats. *Anaesthesia* 2010; **65**: 227–34.
15. Pandit JJ, Buckler KJ. Differential effects of halothane and sevoflurane on hypoxia-induced intracellular calcium transients of neonatal rat carotid body type I cells. *British Journal of Anaesthesia* 2009; **103**: 701–10.
16. Pandit JJ, Winter V, Bayliss R, Buckler KJ. Differential effects of halothane and isoflurane on carotid body glomus cell intracellular Ca2 + and background K+ channel responses to hypoxia. *Advances in Experimental Medicine and Biology* 2010; **669**: 205–8.
17. Pandit JJ. The variable effect of low-dose volatile anaesthetics on the acute ventilatory response to hypoxia in humans: a quantitative review. *Anaesthesia* 2002; **57**: 632–43.
18. Nagyova B, Dorrington KL, Robbins PA. Effects of midazolam and flumazenil on ventilation during sustained hypoxia in humans. *Respiration Physiology* 1993; **94**: 51–9.
19. Berkenbosch A, Teppema LJ, Olievier CN, Dahan A. Influences of morphine on the ventilatory response to isocapnic hypoxia. *Anesthesiology* 1997; **86**: 1342–9.
20. Kirmeier E, Eriksson LI, Lewald H, et al. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. *Lancet Respiratory Medicine* 2019; **7**: 129–40.
21. Kent NB, Liang SS, Phillips S, et al. Therapeutic doses of neostigmine, depolarising neuromuscular blockade and muscle weakness in awake volunteers: a double-blind, placebo-controlled, randomised volunteer study. *Anaesthesia* 2018; **73**: 1079–89.
22. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. *Cochrane Database of Systematic Reviews* 2017; **8**: CD012763.
23. Checketts MR, Alladi R, Ferguson K, et al. Recommendations for standards of monitoring during anaesthesia and recovery. *Anaesthesia* 2016; **71**: 85–93.
24. Rudolph MI, Chitilian HV, Ng PY, et al. Implementation of a new strategy to improve the peri-operative management of neuromuscular blockade and its effects on postoperative pulmonary complications. *Anaesthesia* 2018; **73**: 1067–78.
25. O'Donohoe PB, Huskens N, Turner PJ, Pandit JJ, Buckler KJ. A1899, PK-THPP, ML365, and Doxapram inhibit endogenous TASK channels and excite calcium signaling in carotid body type-1 cells. *Physiology Reports* 2018; **6**: e13876.
26. Eikermann M. Hidden universality of residual neuromuscular block. *British Journal of Anaesthesia* 2016; **116**: 435–6.

