

VOLUME 5(1) March 1985

Below are short overviews of the articles that appeared in this issue of VOLUME:

The Carotid Body: Structure and Function (Prof. Nicholas A. Saunders and Dr Leslie G. Olson)

This is an excellent review written by prominent academics who have published original research on ventilatory control and the effects of dopamine, a neural transmitter released from chemoreceptor cells in response to hypoxia. Professor Saunders, formerly a Dean at Monash University, is now Vice Chancellor of the University of Newcastle. Although this article was not intended to be exhaustive and there have been very significant advances in the neurophysiology of the carotid bodies over the past 21 years, it very nicely sets the scene for discussing the ultra-structure and neural transmitter content of the carotid body.

The carotid bodies are tiny sensory organs located at the bifurcation of the common left and right carotid arteries. Together with the aortic bodies (not discussed in this article) they make up the peripheral chemoreceptors and transmit neural signals to the respiratory centre in the brain via the glossopharyngeal and vagal nerves. Although the carotid bodies were first identified as distinct structures in the 18th century, it was not until 1927 that C. Heymans made the seminal finding that they were the major organ for sensing arterial PO₂. They found that the discharge rate of the nerve fibres within the carotid bodies increased with decreasing PaO₂ and that this influenced alveolar ventilation. So significant was this discovery that it led to them receiving the Nobel Prize. Saunders and Olson point out that variation in arterial blood gases that occur within each respiratory cycle and the carotid body discharge rate take place in parallel. This provides persuasive evidence that these organs have the capacity to regulate alveolar ventilation on a breath-by-breath basis in response to low oxygen levels in the arterial blood.

[The structure and function of the carotid bodies is extremely interesting and worthy of further comment – see below. I have also included comments about adaptation and acclimatisation to altitude as this throws some light on ventilatory response and the capacity of humans to adapt to their environment. I hope these brief comments are not only of interest but demonstrate the importance and relevance of the peripheral chemoreceptors to respiratory physiology.]

1) Additional Notes about the Carotid Bodies

- *The carotid bodies are one of the smallest organs in the body. In the above article the total mass was reported as “20 grams”, but I think this is incorrect - possibly by several orders of magnitude. I have seen these bodies in lambs and they are extremely small, requiring a microscope to see. Smith et al. (J. Pathol., 1982) report a more realistic size of 3 - 5 mm and a mass of only about 18 mg in man. The carotid bodies consist of cell clusters (type I (glomus) and type II cells), connective tissue, blood vessels, and nerve fibres. The cell clusters are separated by the connective tissue, which also extend around and contain the entire organ.*
- *The peripheral chemoreceptors consist of the carotid and aortic bodies. However, there are reports that other tissue with similar attributes may exist (i.e. paraganglion) within the thorax (Eaton and Howe, Cell Tissue Res., 1983) and abdomen (Deane et al., Acta Anat., 1973). The aortic bodies, which are located in*

the walls of the aorta, appear to account for only about 5-10% of the total ventilatory response to progressive hypoxaemia. However, relatively little is really known about the aortic bodies. I presume that this is because, unlike the carotid bodies whose tissue is assessable with anatomically defined borders, the aortic body tissue is very diffuse, making them extremely difficult to study. Thus, the vast majority of research has been carried out on the carotid bodies, particularly with respect the mechanism of oxygen sensing.

- The carotid bodies defend against arterial hypoxaemia by increasing alveolar ventilation. They do this by generating nerve impulses in response to low arterial PO_2 – that is, they transduce a PO_2 signal to electrical signals - which are received by the neurons in the brain that regulate breathing. The carotid bodies are especially capable of responding to PO_2 rather than oxygen content because they are highly vascular and blood flow is very high relative to their mass and oxygen consumption. Thus, little oxygen is extracted from the arterial blood (ie PO_2 difference between arterial blood and carotid tissue is very small) so the PO_2 of the carotid tissue remains very close to arterial levels. Whilst both the carotid and aortic chemoreceptors are stimulated by hypoxaemia, there is evidence, albeit limited, that the aortic bodies respond to arterial oxygen content rather than purely PaO_2 (i.e. they respond to [effective] Hb concentration and PO_2)! This conclusion is based on the work of Lahiri et al., (J. Appl. Physiol., 1981) who found that an increase in carboxyhemoglobin concentration produced significant stimulation of aortic bodies, but had no effect on the output of the carotid body.
- The carotid bodies also augment ventilation in response to an increase in arterial PCO_2 and reduction in pH. However, most (about 80%) of the CO_2 induced response is via the central chemoreceptors located on the ventral surface of the medulla (Heeringa et al., Respir. Physiol., 1979; Loeschcke et al, Pflugers Arch., 1979). The circulation time from the lungs to the carotid bodies is only about 6 seconds, which is a lot shorter than the circulation time to the central respiratory centre. This, together with the carotid body's rapid response time (small mass, high blood flow) enables it to respond to hypoxaemia first.
- Whilst the neurophysiological changes within the carotid bodies that enable the transduction (and transmission) of PaO_2 to an electrical signal is poorly understood, it is worth reminding ourselves that “every neuron in the brain senses oxygen and changes its activity in response to hypoxia” (Neubauer and Sunderram, J. Appl. Physiol., 2004). This is perhaps not surprising given that oxygen is needed for many biochemical reactions. However, the ‘general’ neuronal response to hypoxia (and hypercapnia and acidosis) is depression, rather than excitation as seen in the peripheral chemoreceptors. It is becoming clear that potassium and calcium channels within the carotid body tissue (i.e. type I (glomus) cells) are important in the transduction process. The process appears to be: i) hypoxia causes depolarisation of the glomus cells by inhibiting the oxygen sensitive potassium channels; ii) this leads to an intracellular influx of calcium ions; and iii) the increase in calcium causes the release of neurotransmitters which causes the nerves to be fired (Bairam and Carroll, Resp. Physiol. Neurobiol., 2005).
- When the PaO_2 falls acutely, particularly below about 60 mmHg, the neural discharge from the carotid bodies to the respiratory centre increases causing stimulation of ventilation. (Actually, the net hypoxic stimulation depends on the

balance between the stimulating peripheral and inhibitory central chemoreceptors.) The hypoxic ventilatory response is hyperbolic with respect to the partial pressure of oxygen, but linear with respect to SaO_2 . Thus, the point where ventilation begins to rise sharply occurs at the point where the SaO_2 on the oxyhaemoglobin dissociation curve begins to fall rapidly (ie about 60 mmHg). However, in a given individual the hypoxic ventilatory response depends on whether $PaCO_2$ is kept constant or allowed to fall due to the hypoxic stimulation of ventilation (hyperventilation). The combination of a low PaO_2 and high $PaCO_2$ results in synergistic stimulation of ventilation i.e. the total ventilatory response is greater than the sum of each component.

- Acclimatization to altitude occurs relatively quickly (hours to weeks), whereas adaptation occurs more slowly (decades or generations). Chronic exposure to hypoxia has been shown to increase the mass of the carotid body due to increased blood volume and angiogenesis (formation of new blood vessels). During short-term visits to altitude there is a strong ventilatory response but as exposure continues over several years this response appears to become blunted (see note on pregnancy below). However, this observation is by no means uniform and may depend to some extent on the population studied. For example, Tibetans who have resided at altitude for many more generations than Andean or Rocky Mountain residents, maintain a higher resting minute ventilation (ie they have a stronger ventilatory drive), and have less intrauterine growth restriction at equivalent altitudes. Tibetans also have less pulmonary vasoconstriction, lower Hb concentrations and are less susceptible to mountain sickness than Andeans. These observations suggest Tibetans have a biological advantage compared to newcomers as a consequence of their longer generational period of time at high altitude. It is of interest to note that generally high altitude residents have a higher $PaCO_2$ than fully acclimatized newcomers to altitude.
- It is well established that the carotid bodies size and response to oxygen tension is not fully developed at birth. Growth and maturation of the carotid bodies occurs over the first postnatal weeks. I initially found this difficult to understand given that growth of this organ is stimulated by hypoxia and depressed by hyperoxia because even at sea level the foetus develops in a very low oxygen environment (PO_2 only 25-35 mmHg). However, perhaps it makes sense given that an increase in ventilation due to hypoxic stimulation in the foetus will have no effect on PO_2 and indeed would consume valuable energy. Nevertheless, at birth the carotid bodies are relative insensitive to hypoxia. Consequently, ventilatory response to hypoxia in the young infant and adult human are quite different. The net effect of hypoxia on ventilation depends on the balance between the peripheral (stimulatory) and central (inhibitory) effects. In the adult, the peripheral chemoreceptors dominate and they stimulate ventilation in response to hypoxia. However, in the infant the central effects play the major role and they effectively suppress ventilation as $PaCO_2$ falls as a result of hypoxic hyperventilation. Based on this mechanism it has been proposed that chronic exposure to hypoxia early in life may blunt the response to acute hypoxia by resetting or altering the maturation of the central, inhibitory effects. This suggests that exposure to chronic hypoxia from birth may prevent or inhibit the development of the adult response to acute hypoxia, thus leaving the central effects to exert a potentially dangerous and inhibitory influence. Theoretically, this could severely diminish the infant's capacity to mount an appropriate and sustained ventilatory response

to hypoxia and this mechanism may play a role in sudden infant death syndrome at low altitudes.

- It is of particular interest to note that females native to high altitudes (e.g. Andeans) where the inspired PO_2 is chronically low, frequently relocate to lower altitudes (termed out-migration) to give birth and remain there for several months before returning. This lesson was learnt by several countries (e.g. Spanish and British) after they invaded and occupied high altitude countries. To their horror they found that their own offspring frequently died soon after birth, and no doubt soon practiced out-migration. Yes, there are lots of lessons to be learnt by observing local practices and customs. Another relevant example is the Japanese breathhold pearl divers long ago learnt from experience (with no knowledge of physiology!) that their chance of surviving a dive was improved if they whistled before each dive!.
- Increased resting ventilation and enhanced carotid body drive to ventilation in response to hypoxaemia occurs during pregnancy and is probably associated with increased levels of progesterone and estrogen. It is worth noting that the blunted ventilatory response of high altitude residents, referred to above, has been observed to disappear during pregnancy in Peruvian women thus allowing them to mount a heightened ventilatory response during gestation. This suggests that hypoxic ventilatory drive can be rapidly reversed.
- The yak has successfully adapted to residence at altitudes in excess of 4,500m despite belonging to the same genus as the domestic cow, which is well known for its exaggerated pulmonary vasoconstrictor response. The yak has smaller pulmonary arteries and attenuated endothelial cells than the cow and has a blunted vasoconstrictor response, all of which result in a reduction in the blood-gas barrier and improved oxygenation.
- The carotid bodies have been implicated in the diving response (see review by Foster and Sheel, *Scand. J. Med. Sci. Sports*, 2005).
- Removal of the carotid bodies in humans has been performed as an experimental treatment for asthma and COPD. In fact, 50 years ago these peripheral chemoreceptors were thought to cause asthma. Resection of the carotid bodies in asthmatic and patients with COPD results in a blunted hyperventilatory response to breathing low inspired oxygen mixtures and increased exercise induced hypoxaemia (although to what extent this is due to their obstructive ventilatory defect, is unclear). This is very interesting as it suggests that these peripheral sensors play an important role in protecting against exercise-induced hypoxaemia. I wonder whether this could at least in part explain reports of arterial desaturation in some apparently healthy but not super-fit people (particularly females) towards the end of a bout of intense exercise? Perhaps we should consider whether the carotid body is normal or not in these individuals as presumably these people have a normal cardio-respiratory system? Also, perhaps we could predict those who would desaturate during exercise by assessing their capacity to mount a ventilatory response to inhaling hypoxic mixtures at rest? It may be of interest to also determine whether the siblings of those who do desaturate have increased risk of SIDS? **DPJ**.

2) **Should Students be Exposed to Low Inspired Oxygen Concentrations?**

For our more experienced members I would be very interested to hear their views on the value and safety of student practicals in which students breathe gas mixtures containing low inspired oxygen concentrations.

From a quantitative perspective I have always found the mechanisms underlying the control of ventilation difficult to understand. This is despite having some experience in the 1990s in designing and running student practicals on the effect of hypoxia and hypercapnia on ventilation. I raise this in the context of the “carotid body” because last month my opinion was sought as to the relevance and safety of such practicals and, in particular, whether acute inhalation (say over a few minutes) of 7% oxygen should be banned. Reading between the lines I was being asked whether or not such practicals should be banned, and whether from safety point of view, I could recommend a lower inspired oxygen concentration limit?

In summary, my conclusions were as follows:

- To my knowledge there is no recommended lower oxygen limit for such a practical.*
- **Should students be allowed to inspired mixtures down to 7% oxygen?** My comment on this was (abbreviated): It would be unsafe for students to breathe a gas mixture containing only 7% oxygen as this would lead to profound hypoxaemia irrespective of the degree of compensatory hyperventilation. Perhaps not coincidentally, breathing this level of oxygen is equivalent to an altitude close to the summit of Mt Everest! I estimate that the inspired PO₂ (wet) of a mixture containing only 7% oxygen (at sea level) is 43 mmHg and this would result in an arterial PO₂ of only 15-30 mmHg depending on the level of hyperventilation. This corresponds to an arterial blood oxygen saturation of <50%, at best.*
- **Students should not be allowed to inspire a gas mixture containing less than 11.0% oxygen.** My rationale was that this concentration of oxygen is equivalent to breathing air at an altitude of about 5,150 meters (16,900 feet) which is about 1,200 meters higher than the city of La Paz (see below). Breathing a gas mixture containing 11% oxygen (at sea level) should decrease the blood oxygen level sufficiently to produce sufficient hypoxaemia to induce a ventilatory response in most people without significant clinical risk. After all it is of no value performing this practical if the inspired oxygen concentration is not reduced sufficiently to induce a ventilatory response. Also, ventilatory response to hypoxic mixtures varies widely between people*

***I would be most interested to learn from readers comments and alternative (or supportive) views.** I recently discuss this with Dr Debbie Burton (Senior Lecturer, Charles Sturt University) and Peter Rochford (Head Scientist, Respiratory and Sleep Laboratories, Austin Health). Debbie informs me that she does not run such a practical but provides students with a video. This is an interesting option that makes a lot of sense. Peter responded as follows:*

“I have a view about hypoxic exposure for non-clinical purposes because we recently did a study involving induced hypoxia (SaO₂'s down to 70%) in normal subjects. As you can imagine, our ethics committee was interested in the attendant risks and we found it very difficult to find relevant published data on this, despite a fairly intensive search. There is data from studies on pilots and mountaineers (etc), but it is a problem applying it to your average normal subject being exposed to acute

hypoxia in the laboratory setting. The results of our study show that it is also not easy to predict SaO₂ from FiO₂ in an individual. We had two adverse events from 13 subjects where one subject briefly “passed out” and the other felt like passing out. These occurred when breathing a mixture containing 15% oxygen and the other 11%. We were unable to determine whether these were vaso-vagal episodes (the subjects had hoods over their heads and a lot of blood was being taken from an arterial line over 2-3 hours) or directly due to the effects of the hypoxia. Various features of the events suggest that they were likely to be vaso-vagal. What is safe for students is difficult to say. It would appear that any recommendation is a guess once you go below the sea level equivalent PiO₂ of a pressurized commercial aircraft cabin (normally FiO₂ >15%) where it is reasonable to presume that the risk is negligible in healthy individuals. If the aim is to give students first hand experience of the hypoxic ventilatory response, then only ‘modest’ falls in SaO₂ are only needed, perhaps no lower than 85%. From our data, most people achieve this with FiO₂ >12%.”

I agree that there is a very wide ‘normal’ hypoxic response making it particularly important when conducting such practicals to expose the subject to the hypoxic mixtures in a graded and progressive (incremental) manner. But it is very interesting that the normal ventilatory response to hypoxaemia is wide. One wonders whether such a wide sensitivity can be explained simply on the basis of hyperventilation! I guess this could be modelled fairly easily. DPJ]

Extended Abstracts

The following two abstracts presented at a one-day “Medical Aerosols” symposium held in Tokyo (April 1984) were republished in VOLUME with the permission of Dr Allen Gale, President of the International Society of Aerosols in Medicine:

On the Effects of Aerosol Bronchodilator and Some Problems of Ultrasonic Nebulisation – its Pharmacological Potency With or Without Positive Pressure.

Yukio Goto, Jun Harada, Yoshihiro Sugiura (Department of Anaesthesiology, Fukui Medical School, Fukui, Japan). In their study Goto et al compared the effect of administering bronchodilators (a β -agonist) via an ultrasonic nebuliser with and without 10 cmH₂O intermittent positive pressure breathing. They measured the diameter of the larger airways (and other morphometric indices) from photographs taken during bronchography in 17 patients. Excessive airway narrowing (referred to as “strangulation”), and airway dilation were quantified. Overall, Goto et al conclude that the delivery of nebulised bronchodilators is facilitated when combined with intermittent positive pressure breathing.

Effects of β -stimulant Aerosol on Respiration, Circulation and Metabolism – Experimental Studies of Inhalation Techniques on Canine Asthma Models.

Jun Harada, Yukio Goto (Department of Anaesthesiology, Fukui Medical School, Fukui, Japan). The aim of this study was to explore the most suitable protocol for administering nebulised medication for the treatment of acute asthma. A canine model was used in which asthma was experimentally induced by having the animals inhale an aerosol of the ascaris antigen for 10 minutes. The effect of an aerosol of β -agonist delivered by several different methods was then assessed.

[This is a very topical subject, even 22 years later! DPJ]

Modified Mouthpiece for Spirometry (David P. Johns)

This note describes modifying the end of a cardboard mouthpiece to reduce the likelihood of tongue occlusion. At the time of writing cardboard mouthpieces with a square end were in common use, particularly for spirometers such as the Vitalograph wedge bellows.

Mouth-Piece

This section contained an apology from the Editor for two errors that occurs in the previous edition of VOLUME and a letter from our President, Judy Roget. Judy advocated the Society critically examine the quality of lung function testing so we could inform guidelines.

Please contact me if you are interested in a copy of this or any other issue of VOLUME.

David P. Johns PhD, CRFS, FANZSRS

School of Medicine, University of Tasmania

david.johns@utas.edu.au

Tel: (03) 6226 4801