Reappraisal of systemic venous chemoreceptors- might venous chemoreceptros have been controlling breathing all the time?

Parkes, Michael

DOI:
10.1113/EP086561

Document Version
Peer reviewed version

Citation for published version (Harvard):
Parkes, M 2017, 'Reappraisal of systemic venous chemoreceptors- might venous chemoreceptros have been controlling breathing all the time?', *Experimental Physiology*, vol. 102, no. 12, pp. 1567–1583. https://doi.org/10.1113/EP086561

Title Page

Reappraisal of systemic venous chemoreceptors- might they explain breathing matching metabolic rate in humans?

author
M.J.Parkes

Address for correspondence

School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT and NIHR/Wellcome Trust Birmingham CRF - University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2TH

Phone
+44 (0) 121 414 6977

email
m.j.parkes@bham.ac.uk

word count 6454
150 references

Running head systemic venous chemoreceptors and breathing in humans

Key words control of breathing, systemic venous chemoreceptors, exercise

New findings

What is the topic?
One of the major unanswered questions in physiology is explaining how breathing matches metabolic rate. Venous chemoreceptors seem to have been dismissed since the 1960s.

What advances does it highlight?
New evidence shows that their apparent dismissal needs reappraisal:

- the paper on which this depends has more than one interpretation and another obtained the opposite result.
- previous search ignored all locations between skeletal muscle and the right heart.
- Oxygen sensors other than the arterial chemoreceptors do exist. Heymans *et al.*, originally demonstrated some residual breathing response to hypoxia in sino-aortic denervated animals. Similar results occur in humans.

Reappraisal of systemic venous chemoreceptors- might they explain breathing matching metabolic rate in humans?

Abstract (242 words)
One of the major unanswered questions in physiology is explaining how breathing matches metabolic rate. The existence in humans of venous chemoreceptors that might control breathing seeems to have been dismissed since the 1960s. New evidence has emerged showing that this apparent dismissal needs reappraisal. First, the paper in humans on which this depends has more than one interpretation. Moreover a previous paper obtained the opposite result and is not cited. Secondly, previous search for venous chemoreceptors failed to examine all venous locations between skeletal muscle and the right heart and lungs. Thirdly, oxygen sensors other than the arterial chemoreceptors do exist. Heymans himself originally demonstrated some residual breathing response to hypoxia in sino-aortic denervated animals. Others confirm a residual breathing response to hypoxia in mammals including humans. There is now considerable interest in the importance of afferent feedback in controlling the cardiovascular and respiratory systems. Moreover, it is now clear that arterial, aortic and central chemoreceptors have no role in explaining breathing matching metabolic rate. These together provide a timely reminder that venous chemoreceptors remain ideal candidates still to be considered as metabolic rate sensors explaining matching in humans. First, this is because venous PO_2 and PCO_2 levels do change appropriately in proportion to metabolic rate, so a metabolic rate signal sufficient to drive breathing may already exist. Secondly, chemoreceptor-like anatomical structures are present in the systemic venous system but remain unexplored. Finally, no extant experimental evidence precludes their existence.

introduction

Many scientific reviews outline the major difficulty in providing any coherent explanation of one of the simplest and vital control systems in physiology: how well breathing matches metabolic rate (the rate of oxygen consumption) between rest to maximum exercise (Dejours, 1964;Comroe, 1964;Comroe, 1974;Ward, 1994;Dempsey *et al.*, 1995;Waldrop *et al.*, 1996;Forster & Pan, 1997;Dempsey & Whipp, 2003;Prabhakar & Peng, 2004;Poon *et al.*, 2007;Forster, 2007;Forster *et al.*, 2012;Kumar & Prabhakar, 2012;Parkes, 2013;Forster, 2014;Paterson, 2014;Dempsey *et al.*, 2014). There are difficulties too in the proposal that matching is explained only by combining more than one mechanism, either additively or multiplicatively (Cunningham, 1987;Comroe, 1974;Parkes, 2013;Paterson, 2014).

After nearly 100 years of research, either a completely new discovery awaits us, or there may be better interpretations of published data.

The simplest assumption is that there is a metabolic rate (oxygen) sensor somewhere and that this ultimately controls breathing. The systemic veins (and or in skeletal muscle itself) are the obvious site to locate the metabolic rate sensor(s). It has long been known (Bock *et al.*, 1928) that in humans the partial pressure of oxygen in systemic venous blood (PvO_2) falls linearly (figure 1b) in proportion to metabolic rate (Mitchell *et al.*, 1958;Edwards *et al.*, 1972;Casaburi *et al.*, 1989;Sun *et al.*, 2001) and that of carbon dioxide ($PvCO_2$) rises linearly (figure 1a) in proportion to metabolic rate. These changes are sustained as long as metabolic rate is raised. Moreover there are two reasons why the CNS does not need simultaneous measures of both arterial and venous blood gases to measure metabolic rate; first, the CNS could safely assume normal arterial partial pressures of oxygen and carbon dioxide (PaO_2 and $PaCO_2$) because PaO_2 does not fall and $PaCO_2$ does not rise during exercise (figure 1a &b) and secondly, it is already known that removal of such arterial measurements (carotid arterial chemoreceptor denervation) has little effect on breathing matching metabolic rate during exercise in humans (Wasserman *et al.*, 1975b;Honda *et al.*, 1979a). So combining the venous blood gas signal alone with knowledge of cardiac output could enable the CNS to estimate metabolic rate continuously for matching.

The idea of metabolic rate sensors in the systemic venous system is implied at least as early as 1886 and was last resurrected by Riley *et. al.,* (Dutton *et al.*, 1960;Riley *et al.*, 1960;Armstrong *et al.*, 1961;Riley, 1963;Riley *et al.*, 1963). Despite the undisputed existence of such an obvious metabolic rate signal, the particular problem is that nobody has yet succeeded in demonstrating whether it is used *i.e.*, that venous chemoreceptors either do or do not exist. One negative study in humans (Dejours *et al.*, 1955) is often cited. Dejours wrote the series of reviews (Dejours, 1962;Dejours, 1963;Dejours, 1964) cautiously proposing that "*such chemoreceptors do not seem to exist*"

and to which many articles defer.

But Dejours *et al.*,(1955) is directly contradicted by a previous study (Mills, 1944) that is not cited. Since neither study has been independently validated,

"*absence of evidence is not evidence of absence*" (Sagan, 1980)

and the better judgement is "inconclusive". In which case, venous chemoreceptors could explain matching all the time, but we fail to see them.

Failure of carotid & aortic (arterial) or central chemoreceptors to explain matching.

Corneille Heymans won the 1938 Nobel prize in Physiology or Medicine for the discovery of arterial chemoreceptors. These have dominated all thinking about the control of breathing ever since. Yet 3 sets of experiments in humans show that they cannot act as metabolic rate sensors (Forster *et al.*, 2012;Kumar & Prabhakar, 2012;Parkes, 2013;Parkes, 2014;Forster, 2014;Dempsey *et al.*, 2014).

1) figures 1 & 2 show that the arterial chemoreceptors are in the wrong location to measure metabolic rate, as they receive no known blood borne signal related to metabolic rate *(*$PaCO_2$ fails to rise and PaO_2 fails to fall during exercise),

2) their severest stimulation by hypoxia, to levels that can cause unconsciousness, fails to increase breathing to anywhere near the levels seen at maximum exercise (Dripps & Comroe, 1947;Parkes, 2013),

3) bilateral denervation of carotid chemoreceptors has remarkably little effect on breathing in humans at rest or during exercise (Lugliani *et al.*, 1971;Wasserman *et al.*, 1975b;Honda *et al.*, 1979a),

Even evidence for arterial chemoreceptors routinely acting as "mismatch sensors", or "fine tuning" breathing if it ever fails to match metabolic rate, is not easily obtained (Dripps & Comroe, 1947;Lambertsen *et al.*, 1953;Dejours *et al.*, 1958;Forster & Pan, 1994;Parkes, 2013). Neither is there evidence in humans that aortic or central chemoreceptors could be the metabolic rate sensor, because they too receive no blood borne (or other) signal linked to metabolic rate.

Arterial chemoreceptors undoubtedly do provide rapid warning about the chemical composition of blood supplying the brain. **But even when hypoxia stimulates breathing, this has only limited benefit. This hyperventilation itself uses up more oxygen. Moreover all it achieves is raising alveolar PO_2 by 1 mmHg for every 1 mmHg that it lowers alveolar PCO_2 (Luft, 1965). So at best it can only increase the partial pressure gradient driving oxygen from the lungs into the blood stream by about 27 mmHg (Malconian et al., 1993).** There is also much interest in their potential in driving maladaptive cardiorespiratory outcomes (*e.g.*, hypertension) in disease. But something else is responsible for measuring metabolic rate. Recent experimental evidence continues to emphasise important roles for chemoreceptor feedback, now from muscle (Cui *et al.*, 2011;Kaufman, 2012), and of afferent feedback from both muscle and the peripheral vasculature, in driving both the cardiovascular and respiratory systems (Paterson, 2014;Haouzi, 2014;Dempsey *et al.*, 2014). Yet apparently because of the Dejours reviews, the possibility that venous chemoreceptors might account for some of these intriguing observations is not currently considered.

Chemoreceptor-like anatomical structures exist in the venous system

Carotid chemoreceptors belong to a general class of anatomical structures, known as paraganglia- groups of neurons outside the CNS believed to derive from the sympathetic nervous system (Bock, 1982). All paraganglia are believed to be chemoreceptors for O_2 and CO_2, but the function of almost all of them is unknown. They are almost invisible to the naked eye and their characteristic chromaffin granules are not easily

visible even with a light microscope (Bock, 1982). Intriguingly, the carotid bifurcation in humans is not the only location where paraganglia are found (Comroe, 1964;Bock, 1982). Not only are paraganglia found in the human aortic arch (Comroe, 1964), these apparently having no respiratory function in humans (Parkes, 2013), but also around the vagus nerves, some veins and pelvic viscera (Bock, 1982). They may be even more widespread in the systemic venous system, but we have no anatomical means yet of addressing this in humans using only post mortem material. Yet encouragingly, even in 2016, there is precedent for the discovery of new organs (Coffey & O'Leary, 2016).

In mammals other than humans, there has always been dispute (Bock, 1982) between the anatomical and functional identification of venous chemoreceptors. For example, an anatomical study in cats published in Nature (Hughes, 1965;Comroe, 1974) claimed to have discovered pulmonary chemoreceptors for systemic, mixed venous blood. A letter disputed this (Coleridge *et al.*, 1966). Later, one functional study failed to detect chemoreceptor-like activity when recording from some pulmonary vagal afferent nerves in anaesthetized cats (Coleridge *et al.*, 1967), despite an earlier functional study claiming to have found them (Duke *et al.*, 1963). There is early work in anaesthetized dogs and more recently rats, describing afferent neurones with chemoreceptor-like activity (*i.e.*, stimulated by hypoxia), originating in the abdomen (*i.e.*, outside the classical carotid and aortic regions), that are capable of stimulating breathing (Bean, 1952;Howe *et al.*, 1981;Child *et al.*, 1990;Howe, 1990). But none of these studies are definitive nor have been pursued further.

Stimulation as the main tool to search for functional venous chemoreceptors

The classical scientific approaches to search for venous chemoreceptors are recording, ablation and stimulation (Walshe, 1951;Cohen & Wang, 1959;Stein & Stoodley, 2006;Parkes, 2013).

Nobody yet has "recorded" the sensitivity to hypoxia and hypercapnia of paraganglia other than those of the arterial chemoreceptors in the carotid bifurcation and aortic arch (Torrance, 1996). Such descriptions of the properties of the arterial chemoreceptors are invaluable. But if venous chemoreceptors exist, the range and time course of blood gas changes to which they are exposed are very different. So their responses too would be very different. Presently "recording" can only be established indirectly from sampling the composition of venous blood. Figure 1 confirms that the operating range to which venous chemoreceptors would be exposed is very different and, more importantly, that appropriate changes in both PO_2 and PCO_2, in proportion to changes in metabolic rate, are already present.

"Ablation" is difficult; venous chemoreceptors have not been found so we do not know what nervous structures to ablate. If widespread, we may guess that their afferent pathways might include the spinal cord in addition to some cranial nerves. So "ablation" here can consider the implications for their existence of experiments in humans involving spinal anaesthesia and paraplegia.

So far "stimulation" (applying hypoxia, hypercapnia, asphyxia or occlusion cuffs) is the principal scientific approach used to search for venous chemoreceptors.

Some of the basic principles for evaluating experimental evidence (Parkes, 2013) also need reiteration here, in particular the need for independent verification of the key experiments (at least 2 citations for each), for validation of negative results and to put stimulation experiments in the context of maximum metabolic rate

being at ~ 5.6 $LO_2.min^{-1}$ (~1.9kW) in exercise (~400W of external work, with maximum breathing at ~100-150 $L.min^{-1}$. Here, the useful terminology for quantifying breathing is as minute ventilation ($\dot{V}e$) in litres per minute ($L.min^{-1}$), for exercise and metabolic rate are as $L\ O_2.min^{-1}$ or in watts (W), with external work as watts of external work (W_{ew}) and for variance in the data as ± standard error of the mean (SEM).

Initial but misleading preconceptions about venous chemoreceptors

In order to achieve matching, the control system needs a sensor to measure metabolic rate (rate of O_2 consumption) continuously. This would then drive breathing appropriately between rest and maximum exercise. What is known about chemoreception to O_2 and CO_2 in general is derived principally from studying carotid chemoreceptors. This has led to the obvious preconception that venous chemoreceptors must have similar properties *i.e.*, that stimulation of one discrete population of chemoreceptors (for humans, only the carotid chemoreceptors), at one bilateral location (the carotid bifurcation), produces a substantial and rapid stimulation of breathing (typically within ~ 1 second (Cropp & Comroe, 1961)).

Applying this preconception to systemic venous chemoreceptors proposes that one population - located only at or near the right atrium and or in pulmonary artery- could estimate metabolic rate of the whole body by sampling the composition of mixed venous blood and stimulating breathing immediately. It should be easy to reveal this population, by testing whether appropriate stimuli applied here stimulate breathing substantially and immediately. The failure of such "easy experiments" to produce unambiguous and positive results (a stimulation of breathing) revealing them has contributed to the apparent dismissal of venous chemoreceptors. But this preconception is misleading. There are many reasons that would account for such negative results while remaining consistent with the existence of venous chemoreceptors.

The ideal stimulus, its duration and location, to reveal venous chemoreceptors

Venous chemoreceptors could have three properties radically different from this preconception of one population at one location. These were not taken into account in the original evaluation of these "easy experiments" (*e.g.,* (Dawes & Comroe, 1954)) and would explain why venous chemoreceptors could be much more difficult to find.

First, venous chemoreceptors might instead be located at multiple locations along the systemic venous side, anywhere between each skeletal muscle and the right heart (figure 2). So the ideal stimulus would need to be applied at as many locations as possible from muscle to the right heart to produce a big (and therefore detectable) stimulation of breathing. The CNS would derive metabolic rate by adding or multiplying these many chemoreceptor signals with appropriate weighting. This would provide the ideal graded stimulation of breathing that perfectly matched the number of metabolically active muscles and would explain how breathing matches metabolic rate so well. This would also explain why venous chemoreceptors are so difficult to find experimentally: because there are few at any one location, they are difficult to reveal. Even maximal

stimulation at just one location (or ablation at one location) might barely increase (or ablation barely decrease) breathing sufficiently to be noticed.

Secondly, we accept the importance of the rapid breathing response (within 1 second) to carotid chemoreceptor stimulation. This is because if arterial blood gas levels ever do change in a threatening direction, this represents an immediate threat to the brain. But the breathing response to venous chemoreceptor stimulation may not, and need not, be so rapid because of a combination of two factors:

1) the metabolic rate of the whole body (and consequently venous blood gas levels) does not normally change within 1 second, so their natural stimulus could take more time to build up,

2) it may take longer for the CNS to integrate the inputs from multiple venous chemoreceptor sites (also, venous chemoreceptors might just respond more slowly).

So the duration of ideal stimulus for venous chemoreceptors should be much longer than 1 second. Providing a sustained stimulus that is isolated solely to the venous side from muscle to the right heart, is technically not straightforward and has not yet been attempted. Furthermore, this duration issue also exposes the difficulty in interpreting the "easy" and classic studies infusing hypoxic or hypercapnic venous blood at the right atrium (e.g., (Cropp & Comroe, 1961;Sylvester *et al.*, 1973)). If a slow breathing increase in response to venous chemoreceptor stimulation overlapped with the more rapid breathing response once such blood reached the arterial chemoreceptors, the arterial chemoreceptor response would "interpretatively" mask any venous chemoreceptor response. Thus the observed response may not represent solely that of arterial chemoreceptors and distinction of these two possibilities requires repeating these experiments after arterial chemoreceptor denervation.

Thirdly, since both $PvCO_2$ and PvO_2 always change as metabolic rate changes (*i.e.*, in the direction of asphyxia), the ideal stimulus to reveal venous chemoreceptors should be simultaneously to lower PvO_2 and to raise $PvCO_2$ to their levels at maximum exercise. It is already known that changing both simultaneously is a better stimulus than the simple sum of either alone to the arterial chemoreceptors (Torrance, 1996) and to increase breathing (Nielsen & Smith, 1951;Cormack *et al.*, 1957;Lloyd, 1965;Bernards *et al.*, 1966;Swanson & Bellville, 1974;Comroe, 1974;Teppema & Dahan, 2010). But this ideal stimulus has not yet been applied systematically in the search for venous chemoreceptors.

These 3 points could explain why venous chemoreceptors have not yet been seen: applying the wrong stimulus at the wrong location and for the wrong duration.

The residual stimulation of breathing by hypoxia in sino-aortically denervated animals

If arterial chemoreceptor denervation completely abolishes all stimulation of breathing by hypoxia (*i.e.*, if the breathing increase is now zero in every subject), then venous chemoreceptors cannot be the metabolic rate (oxygen) sensor. But it has always been known that there is still a residual stimulation of breathing by hypoxia after arterial chemoreceptor denervation. Its mechanism has never been explained.

Heymans described this residual response in his original discovery of the arterial chemoreceptors (Heymans *et al.*, 1930) (see figure 3) and deliberately confirmed it subsequently in unanesthetized dogs

(Cordier & Heymans, 1935;Bouckaert *et al.*, 1938). While others have not seen this, neither were they looking for it (Wright, 1936;Gernandt, 1946;Bjurstedt, 1946;Dumke *et al.*, 1941)). But many other independent studies confirm the existence of a residual response (Selladurai & Wright, 1932;Marshall & Rosenfeld, 1936;Gesell & Moyer, 1937;Smyth, 1937;Davenport *et al.*, 1947;Schmidt, 1932;Jongbloed, 1936;Comroe, 1939;Schmidt & Comroe, 1940;Moyer & Beecher, 1942;Watt *et al.*, 1943;Decharneux, 1934):

"an increase in respiration sometimes occurred during systemic anoxemia even after denervation of the carotid and aortic chemoreceptors" (Comroe, 1939)

"Heymans et al found…..that section of the sinus and depressor nerves changed the violent hyperpnea and marked hypertension produced by nitrogen inhalation into a very slight respiratory stimulation and a relatively small rise in blood pressure……..

….. instances are not lacking … of a distinct anoxemic hyperpnea remaining after section of the sinus and depressor nerves.." (Schmidt & Comroe, 1940)

They were also fully aware of its importance in suggesting chemoreceptors, other than arterial, mediate the stimulation of breathing by hypoxia. Thus:-

" in unanesthetized dogs ....after denervation ...depression of depth and rate... was succeeded by acceleration of rate. Therefore known chemoreceptor reflexes cannot be responsible for all the increase in rate during prolonged anoxia" (Watt *et al.*, 1943)

"and after removal of all known chemoreceptors by additional section of the aortic nerves, anoxemia still produced the same acceleration …... If all means of peripheral chemical excitation are thus removed how then was acceleration produced?....." (Gesell & Moyer, 1937)

"*The possibility that the stimulation of respiration attending hypoxia, in the absence of carotid and aortic and possibly pulmonary chemoreceptor innervation, may be due to unknown chemoreceptive mechanisms cannot be ruled out by these experiments*" (Moyer & Beecher, 1942)

"some mechanism other than the carotid and aortic bodies causes delayed tachypnea in lightly anaesthetized or unanesthetized animals. Another mechanism may also be involved in the hyperpnea of chronic anoxemia….This could represent central stimulation by anoxia (concomitant with central depression), reflex stimulation from an unidentified group of peripheral chemoreceptors ……." (Comroe, 1964).

Later, its description disappears (Cropp & Comroe, 1961;Sylvester *et al.*, 1973). But it resurfaces (Comroe, 1974;Miller & Tenney, 1975;Gautier & Bonora, 1980) and there is allusion in Teppema & Dahan (2010) .

One possibility is that this residual breathing response to hypoxia is mediated by venous chemoreceptors. Its effect on breathing may appear small only because the ideal stimulus, duration and location to reveal venous chemoreceptors have yet to be applied.

The residual stimulation of breathing by hypoxia in humans after arterial chemoreceptor denervation

The common misconception that in humans only carotid chemoreceptors (Parkes, 2013) mediate the breathing response to hypoxia arises from the belief that hypoxia supposedly produces no increase (i.e. an increase in breathing of zero) after carotid chemoreceptor denervation in humans (Lugliani *et al.*, 1971;Honda

et al., 1979b;Dahan *et al.*, 2007). And because temporary sinoaortic anaesthetic blockade in just 2 subjects (Guz *et al.*, 1966) apparently produces no further deficits in breathing than carotid chemoreceptor denervation alone, (thereby eliminating any stimulation of breathing by aortic chemoreceptors in humans (Lugliani *et al.*, 1971;Honda *et al.*, 1979b;Parkes, 2013;Wasserman *et al.*, 1994).

But for 2 reasons this is a misconception. First, some studies do confirm the presence of some residual breathing sensitivity (or an enhancement of kinetics) to hypoxia in bilaterally carotid chemodenervated patients (Swanson *et al.*, 1978;Whipp *et al.*, 1994;Bellville *et al.*, 1979;Guz *et al.*, 1966;Wade *et al.*, 1970;Honda *et al.*, 1979b;Honda, 1992). Furthermore, this arises too quickly to be caused by central chemoreceptors (Swanson *et al.*, 1978).

Secondly, in most of these studies the level of hypoxia applied may not always have been intense enough to reveal definitively whether or not this residual response exists. The inspired oxygen level apparently needs to be lowered to <9% (Dripps & Comroe, 1947;Comroe, 1964), *i.e.*, apparently to a PaO_2 of ~<40 mmHg (Parkes, 2013) before substantial stimulation of breathing is evident. But in chemo-denervation studies such levels levels of hypoxia may not always have been applied (Lugliani *et al.*, 1971;Honda *et al.*, 1979b;Dahan *et al.*, 2007).

Some (*e.g.*, (Honda *et al.*, 1979b)) suggest that this residual stimulation in humans might be due to regrowth and re-innervation of carotid chemoreceptor tissue. But such regrowth is impossible when residual stimulation is detected immediately after sinoaortic denervation (Schmidt & Comroe, 1940). Furthermore, explaining the residual stimulation by the presence of additional chemoreceptors (*e.g.*, venous chemoreceptors) is as valid as by re-innervation of denervated chemoreceptors. There is no experimental evidence yet to distinguish between these two explanations.

How does CO_2 stimulate breathing after arterial chemoreceptor denervation?

Central chemoreceptors for CO_2 do exist and their stimulation does stimulate breathing (Heymans *et al.*, 1930;Cordier & Heymans, 1935;Dejours, 1962;Ballantyne & Scheid, 2000).

There is also a common mis-attribution that all breathing responses to raised PCO_2 (hypercapnia) remaining after arterial chemoreceptor denervation are caused solely by central chemoreceptors. This is a mis-attribution because nobody yet has confirmed that ablation of central chemoreceptors abolishes this remaining breathing response to hypercapnia (Spode & Schlaefke, 1975;Schlaefke *et al.*, 1974;Schlaefke *et al.*, 1979;Schlaefke, 1981;Whipp, 1983). Neither can central chemoreceptors account for the continued matching of breathing with metabolic rate after bilateral carotid denervation in humans, because they have no means of sensing metabolic rate.

This mis-attribution has two important implications for venous chemoreceptors. First, it implies, without ever establishing, that venous chemoreceptors cannot mediate any of the stimulation of breathing by raised PCO_2. Secondly, it creates an interpretative problem that discourages further "stimulation" experiments to search for venous chemoreceptors using their ideal stimulus of combined hypoxia and hypercapnia and after arterial chemoreceptor denervation. Any detectable stimulation of breathing is attributed solely to CO_2

stimulating central chemoreceptors. Whereas it could equally represent some stimulation of venous chemoreceptors. This misconception continues to hinder the search for venous chemoreceptors.

How would we know if we had discovered venous chemoreceptors?

The ideal stimulation experiment would be to induce in resting subjects for a sustained period the venous PO_2 and PCO_2 levels attained during maximum exercise, without simultaneously changing their systemic arterial levels. At present, this is technically too difficult to achieve, the nearest being the sudden release of occlusion cuffs, described below. (It might also be useful to change both systemic venous and arterial PO_2 in carotid sinus denervated patients, but this straightforward experiment is yet to be undertaken).

The ideal positive result is that such stimulation increases breathing to the levels of maximum exercise (*e.g.*, $\geq$100 $L.min^{-1}$ in humans), followed up by independent confirmation and appropriate outcomes from "ablation" and "recording" experiments (Parkes, 2013).

How would we know if we had established that venous chemoreceptors don't exist?

The ideal negative is to show zero change in breathing following the ideal venous stimulus and or a complete abolition of any increase in breathing by denervation of arterial and central chemoreceptors. There are two common approaches that fail to validate the negative result; -the "hyperoxia argument"- abolishing any response by applying hyperoxia is inadequate (because this might simply weaken any venous chemoreceptor response); and the "response time argument"- demonstrating breathing increases only after the stimulus could have reached the carotid or central chemoreceptors (because a breathing response to their stimulation might just overlap with a slower breathing response to venous chemoreceptor stimulation).

The following paragraphs show how stimulation experiments in both humans and in other mammals fail to establish the existence of venous chemoreceptors, but neither do they establish that venous chemoreceptors do not exist.

Inconclusive stimulation experiments in animals for cardiopulmonary venous chemoreceptors

The early literature (with animals- *ie.*, not humans- and with anaesthesia), that could not find venous chemoreceptors, is inconclusive because these "easy experiments" were incomplete and focussed only on the right heart and pulmonary arteries (Aviado & Schmidt, 1955;Dawes & Comroe, 1954;Cropp & Comroe, 1961;Comroe, 1974). They did not undertake a systematic and exhaustive search for them by applying the ideal stimulus, duration and location between muscle and the right heart. Thus:-

1) Heymans originally discovered the carotid chemoreceptors in dogs only by accident (Heymans, 1967) and his research thereafter appears to have concentrated on these, rather than searching for more.

2). Even this early literature (Aviado & Schmidt, 1955;Dawes & Comroe, 1954;Cropp & Comroe, 1961;Comroe, 1974;Sylvester *et al.*, 1973) contains ambiguities that indicate something else might be present. For instance Aviado & Schmidt (1955) describe (their page 261) *"a respiratory component of the* [vena cava] *infusion reflex…Dogs responded by stimulation of respiratory rate and minute volume as long as the vagi were intact. These observations have been confirmed…… and denied…… …if accepted….is like that of chemoreceptor stimulation"*. Later studies confirm a small stimulation of breathing (*e.g.*, by ~ 1 $L.min^{-1}$) in anaesthetized animals by obstruction of the inferior vena cava (Haouzi *et al.*, 1995;Haouzi *et al.*, 2005;Haouzi & Bell, 2010). The proposed mechanism includes involvment of distension of the veins (Haouzi, 2014). It is also possible that venous chemoreceptors make a contribution.

3). To interpret the results of cyanide or phenyl diguanide infusions in these "easy experiments" (Dawes & Comroe, 1954;Comroe, 1974), the "response time argument" was applied, whose weakness is explained above.

Inconclusive stimulation experiments for venous chemoreceptors in animals between muscle and the right atrium

Some cross circulation experiments did find evidence for the existence of venous chemoreceptors (breathing increased in anaesthetized resting [recipient] dogs when venous blood from the hind legs of "exercised" [donor] dogs was returned to the recipient's iliac vein (Kao & Ray, 1954;Riley, 1963)). But these were done under anaesthesia, at low "exercise" intensities (Forster & Pan, 1997), the crucial time intervals are not reported and results are not consistent between different experiments (Kao, 1956;Kao, 1963;Kao *et al.*, 1963;Kao *et al.*, 1964;Kao, 1974;Forster & Pan, 1997).

Attempts have also been made in anaesthetized (Wasserman *et al.*, 1975a) or unanaesthetized animals (Yamamoto & Edwards, 1960;Phillipson *et al.*, 1981a;Phillipson *et al.*, 1981b;Phillipson *et al.*, 1981c), to test whether raising only systemic $PvCO_2$ can stimulate breathing without raising $PaCO_2$ (and hence without involving arterial and central chemoreceptors). One purpose was to test the possibly that breathing might be controlled just from CO_2 (the "CO_2 flow" hypothesis). But another equally valid possibility is that such experiments partially stimulate venous chemoreceptors. Indeed if so, the better experiment would be to simultaneously raise systemic $PvCO_2$ and lower systemic PvO_2- the ideal venous chemoreceptor stimulant (and again without altering $PaCO_2$ or PaO_2). In any event, the interpretation of the results of such experiments remains controversial (Dempsey *et al.*, 2014). The arterial blood sampling regimes were not frequent enough to establish convincingly that no $PaCO_2$ rise occurred and arterial chemoreceptor denervation was not always applied. Interestingly, some acknowledged that they were unable to rule out venous chemoreceptors.

Inconclusive stimulation experiments in humans for venous chemoreceptors within skeletal muscle

Venous chemoreceptors might exist even within skeletal muscle (and within other organs), since muscle contributes most to the increased metabolic rate of exercise. It has been known since the 1930s (Alam & Smirk, 1937;Coote *et al.*, 1971;Rowell *et al.*, 1976;Rowell & O'Leary, 1990;Fisher & White, 2004) that

stimulation of chemoreceptors within skeletal muscle increases blood pressure (a " pressor response"). The receptors mediating this pressor response are termed here "muscle metabolo-receptors" to distinguish them from putative muscle/venous chemoreceptors that might stimulate breathing. These muscle metabolo-receptors are revealed by inflating an occlusion cuff wrapped round exercising limbs during exercise to trap metabolites within the muscle. When the exercise is stopped but the cuff remains occluded ("post exercise occlusion"), the trapped metabolites stimulate muscle metabolo-receptors that in turn sustain a pressor response at or above its exercise level until the cuff is released (see figure 3 of (Rowell *et al.*, 1976)).

Applying the same technique should also reveal if muscle metabolites stimulate breathing. The cuff could be inflated either during exercise (ideally at high -but not maximum- intensity), or after maximum exercise stops ("post-exercise occlusion"). A positive result occurs if occlusion further stimulates breathing during exercise and or sustains breathing post exercise at its exercise level for as long as occlusion is maintained. (The further importance of releasing the post exercise occlusion cuff is considered later).

The problem however is in validating the negative result– no stimulation of breathing- to establish muscle chemoreceptors cannot stimulate breathing. A major difficulty is in ensuring no blood leaked round the cuff and hence weakened the stimulation. This may well occur since the pressor response can decrease while cuff inflation is maintained (Crisafulli *et al.*, 2008). There are two reasons why the negative result is not validated simply by confirming that post exercise occlusion sustains some sort of pressor response:

1) if some of the trapped metabolites had leaked out, the remnant might be sufficient to provoke a pressor response but insufficient to produce a detectable effect on breathing.
2) the venous chemoreceptors that stimulate breathing might be different chemoreceptors from muscle metabolo-receptors and hence the pressor response does not reflect their response.

The key validation, (yet to be applied), is to demonstrate complete retention of a tracer (a dye or CO_2 itself) within the occluded limb, or that CO_2 production at the mouth is decreased by exactly the amount expected from the total amount of CO_2 produced (but trapped) within the limb.

Overall, the occlusion studies on humans during exercise are inconclusive (Dempsey *et al.*, 2014). Some find no effect on breathing (Asmussen *et al.*, 1943;Dejours *et al.*, 1957;Rowell *et al.*, 1976) or an increase (Comroe & Schmidt, 1943;Sargeant *et al.*, 1981) or a decrease (Barman *et al.*, 1943).

11/12 studies report that occlusion fails to stimulate breathing during exercise and or fails to sustain breathing post-exercise at its exercise levels (Wiley & Lind, 1971;Rowell *et al.*, 1976;Fordyce *et al.*, 1982;Innes *et al.*, 1989;Haouzi *et al.*, 1993;Scott *et al.*, 2000;Haouzi *et al.*, 2001;Fukuba *et al.*, 2007;Lykidis *et al.*, 2010;Olson, 2010;Bruce & White, 2012;Bruce & White, 2015). Only one found breathing was sustained post-exercise by arm occlusion (Piepoli *et al.*, 1995). But this was not confirmed with post-exercise leg occlusion (Scott *et al.*, 2000).

Recently some (Lykidis *et al.*, 2010;Bruce & White, 2012;Bruce & White, 2015), but not all (see figure 1 in Olson *et al.*, 2010), have observed a small increase in breathing ($4 – 7$ $L.min^{-1}$) if cuff occlusion is combined with raising the end tidal partial pressure of carbon dioxide ($PetCO_2$) by ~7 mmHg in healthy subjects. There are a number of possible explanations for this.

Possibly the unnatural stimulus of raising PCO_2 (which does not occur as metabolic rate increases) just exaggerates the breathing response to exercise. This is supported by the absence of this small stimulation if only the occluded limb is exposed to the raised PCO_2 (Bruce & White, 2015).

Another possibility is that raising $PetCO_2$ compensates for incomplete muscle occlusion (*i.e.,* for cuff leakage) and thereby at last provides a sufficiently intense stimulus to reveal a detectable increase in breathing. In any event, increases in breathing greater than 4 – 7 $L.min^{-1}$ need to be demonstrated before accepting the presence within muscle of chemoreceptors capable of making an important contribution to controlling breathing.

Inconclusive stimulation experiments for venous chemoreceptors in humans between muscle and the right heart

Here the basic stimulation technique is to release venous blood (to release the post-exercise occlusion cuff) containing trapped metabolites and or drugs known to stimulate carotid chemoreceptors directly (*e.g.,* cyanide, (Anichkov & Belenkii, 1963;Comroe, 1964;Winder *et al.,* 1933)) and to measure the size and timing of any increased breathing. Ideally all 4 limbs are exercised at maximum intensity before all are occluded (to maximise the mass of trapped metabolites and hence any effect on breathing). If a convincing increase in breathing occurs after cuff release and before such blood could have reached the carotid chemoreceptors, then venous chemoreceptors must exist. But they may still exist even if breathing is stimulated only after this blood passes through the carotid chemoreceptors. There are two contradictory studies.

Mills et al., (1944) produced the first functional evidence that venous chemoreceptors might exist in humans. They applied a cuff for 10-15 minutes round one or two rested limbs. In 11/13 subjects, sudden release of the cuff produced a substantial stimulation of breathing (to a remarkable 16 – 92 $L.min^{-1}$ as measured in 2 subjects). Indeed the stimulation was so intense that the resulting hypocapnia "*was sometimes so vigorous as to produce paraesthesia*" (*i.e.,* $PaCO_2$ levels < 20 mmHg). This occurred "*within at most 4.2 sec*" which is too fast for the blood transport time as measured at rest (~19 sec) from limbs to the carotid chemoreceptors (Robb & Weiss, 1933;Dejours *et al.,* 1955;Winning *et al.,* 1986). Furthermore, in some subjects, the chemoreceptor stimulant sodium cyanide was injected into the muscle distal to the occlusion just before release. On release (see figure 4), "*the hyperpnea was always diphasic*.." [in two subjects occurring at 2 and 11-13 sec] with the first phase again being too fast to have stimulated carotid chemoreceptors. Astonishingly, nobody has ever attempted to confirm these remarkable results.

Instead, and without reference to Mills, Dejours *et al.,* (1955) had just 4 subjects perform and bilateral leg exercise at low intensity (only $14W_{ew}$), with the leg cuffs inflated for 2 minutes as exercise ended. Post exercise release of the cuff resulted in deoxygenated blood reaching the carotid region (earlobe) 17 seconds later (range 13 – 21 seconds) and in none did breathing increase until a mean of 2.5 ±1 seconds after this (range 0.9 – 6.4 seconds). Figure 5 shows the results from one subject. Dejours cautiously concluded "……*seems to show the absence of ventilatory chemoreceptors situated along the path of the venous blood to the level of the vena cava of the right heart"* [my translation]

But there is more than one interpretation. Venous chemoreceptors could still exist but have a longer latency. Without carotid chemoreceptor denervation, this possiblity cannot be ruled out. Neither are these results compatible with Mills et al., (1944). Nor has anyone directly confirmed Dejours's results. Nor has anyone (Winning *et al.*, 1986) confirmed Dejours's methodological claim, remarkable with apparatus of unspecified response time available in 1955, that they could even measure accurately the time course of the arrival at the earlobe of deoxygenated blood suddenly released from the leg!

Instead of this discrepancy provoking new experiments to distinguish between Mills and Dejours, it was Dejours who wrote the series of reviews (Dejours, 1962;Dejours, 1963;Dejours, 1964) cautiously proposing that

"*such chemoreceptors do not seem to exist*"

Whereas, despite Mills et al., (1944) being published in a mainstream journal, this has been cited so rarely since that it is reasonable to describe it as new evidence. (Even when cited, (Ross *et al.*, 1962) no confirmatory experiments were undertaken).

Subsequent studies in dogs confirm that cyanide stimulates breathing by stimulating something at an unknown location other than the arterial or central chemoreceptors. Levine *et al.*, (1975) found that intra-aortic cyanide stimulates breathing (by 228%) in 8 anaesthetized dogs even after bilateral sinoaortic denervation in 4 of them (independently confirming (Winder *et al.*, 1933)). This stimulation cannot be due to cyanide directly stimulating the head, brain, arterial or central chemoreceptors because it still stimulated breathing (by 163%) in 5 dogs when their heads were vascularly isolated from the rest of their body. This could be explained by cyanide stimulating venous chemoreceptors.

Many subsequent papers in humans confirm that cuff release produces a sudden increase in breathing (Rowell *et al.*, 1976;Fordyce *et al.*, 1982;Innes *et al.*, 1989;Haouzi *et al.*, 1993;Haouzi *et al.*, 2001;Fukuba *et al.*, 2007), without providing a complete or the same explanation, nor reference to Mills et al., (1944).

Inconclusive ablation experiments for a venous chemoreceptor spinal afferent pathway in humans

If venous chemoreceptors exist in peripheral veins, one obvious afferent pathway to the brain is via the spinal cord. If they are the crucial metabolic rate sensors and use this afferent pathway exclusively, this predicts that, if the spinal cord is blocked and the muscle below the cord can somehow be "exercised", breathing should now fail to increase in proportion to metabolic rate. Again, experiments so far are inconclusive (Dempsey *et al.*, 2014).

Fernandes *et al.*, 1990 had 6 subjects exercise at 57% of $\dot{V}O_2$ max on a bicycle ergometer and up to exhaustion (~238±30 W_{ew}). They found that maximum metabolic rate (1kW) and breathing (116 ±11 $L.min^{-1}$) were not significantly different between control and those with epidural anaesthesia at L3/L4. But the fact that they could continue pedalling at all shows that the spinal cord was not completely blocked! It is naïve to assume that epidural anaesthesia blocks all afferent but no efferent pathways. Furthermore, while pain sensation (to pin pricks) was lost, they demonstrated residual activity in one subconscious sensory pathway (their figure 1 shows persistence of an "attenuated" pressor response to leg ischaemia). So it is not certain that all sensory pathsways were blocked and hence that venous chemoreceptors cannot exist.

Similarly, if breathing increased normally in paraplegics during electrically evoked "exercise" of the limbs below the spinal break, this too would oppose the existence of a spinal afferent pathway from venous chemoreceptors that drives breathing. Evidence for such "exercise" stimulating breathing has been presented in humans (Adams *et al.*, 1984;Brice *et al.*, 1988;Brown *et al.*, 1990) and in other mammals under anaesthesia, see (Haouzi *et al.*, 2005;Levine, 1979;Cross *et al.*, 1982). But there two problems:-

1) the intensity of such artificial exercise is too low to be definitive (increasing breathing by only 2 – 4 L air .min^{-1}! (Adams *et al.*, 1984;Brice *et al.*, 1988;Brown *et al.*, 1990)

2) warmed blood returning from the exercising muscles will cross the spinal break and thermal conduction may stimulate spinal thermoreceptors, whose stimulation could then explain the stimulation of breathing (Hales *et al.*, 1970).

Two other related techniques are similarly inconclusive. All that can be deduced from the fact breathing still increases during modest exercise in humans after heart or heart lung transplantation (Banner *et al.*, 1988), or in those with left to right cardiac shunts (Storey & Butler, 1963), is that venous chemoreceptors may not exist solely in the cardiopulmonary region.

The definitive studies still to be undertaken

It is straightforward to resolve the venous chemoreceptor question in humans (to distinguish between Mills et al., (1944) and Dejours *et al.*, (1955)). Bilateral carotid chemoreceptor denervation is still performed (Dahan *et al.*, 2007). Definitive occlusion cuff-release experiments using the scientific method outlined above could be done on such patients. How fast (in relation to limb-carotid conduction time) and by how much does release of an occlusion cuff round 4 maximally exercised limbs (preferably also containing a dye and or cyanide) stimulate their breathing both <u>before and after</u> denervation?

In such patients it should also be possible to establish whether any residual breathing sensitivity to hypoxia is due to arterial, venous or other chemoreceptors. What is the size of any stimulation of their breathing at suitable FiO_2 levels below 9%? By how much is their breathing at rest stimulated if both their $PvCO_2$ and PvO_2 levels are changed to those seen during maximum exercise?

Conclusions

On the one hand, venous chemoreceptors cannot be discovered if they do not exist. But this has not been established definitively. If it is, the mystery deepens of how to explain breathing matching metabolic rate without involving arterial, central or venous chemoreceptors. The many more complex hypotheses attempting to explain this (Dejours, 1964;Comroe, 1964;Comroe, 1974;Ward, 1994;Dempsey *et al.*, 1995;Waldrop *et al.*, 1996;Forster & Pan, 1997;Dempsey & Whipp, 2003;Prabhakar & Peng, 2004;Poon *et al.*, 2007;Forster, 2007;Forster *et al.*, 2012;Kumar & Prabhakar, 2012;Parkes, 2013;Forster, 2014;Paterson, 2014;Dempsey *et al.*, 2014) then require fresh ideas to investigate them.

On the other, venous chemoreceptors may not have been found because the wrong stimulus has been applied at wrong location for wrong duration. If the ideal experiments ever reveal them, there is no

inconsistency with current scientific literature. The many more complex hypotheses then become unnecessary. Venous chemoreceptors may have been present all the time but we fail to see them.

Acknowledgements.

I am most grateful to the late Professor Alan Howe for his encouragement in preparing this review and to staff at the Radcliffe Science Library, University of Oxford and from Andrew Dakin in Medical Illustrations, Queen Elizabeth Hospital Birmingham for help in reproducing figure 3.

Conflict of interest.

The views expressed are those of the author and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health.

Reference List

Adams, L., Frankel, H., Garlick, J., Guz, A., Murphy, K., & Semple, S.J. (1984). The role of spinal cord transmission in the ventilatory response to exercise in man. J Physiol (Lond) 355, 85-97.

Alam, M. & Smirk, F.K. (1937). Observations in man upon a blood pressure arising reflex from the voluntary muscle. J Physiol (Lond) 92, 372-383.

Anichkov, S.V. & Belenkii, M.L. (1963). Pharmacology of the carotid body chemoreceptors. Pergamon Press Litd, Oxford.

Armstrong, B.W., Hurt, H.H., Blide, R.W., & Workman, J.M. (1961). The humoral regulation of breathing. Science 133, 1897-1906.

Asmussen, E., Christensen, E.H., & Nielsen, M. (1943). Humoral or neuronal control of respiration during muscular work. Acta Physiol Scand 36, 160-167.

Aviado, D.M. & Schmidt, C.F. (1955). Reflexes from stretch receptors in blood vessels, heart and lungs. Physiol Rev 35, 247-300.

Ballantyne, D. & Scheid, P. (2000). Mammalian brainstem chemosensitive neurones: linking them to respiration *in vitro*. J Physiol (Lond) 525.3, 567-577.

Banner, N.R., Guz, A., Heaton, R., Innes, J.A., Murphy, K., & Yacoub, M.H. (1988). Ventilatory and circulatory responses at the onset of exercise in man following heart or heart-lung transplantation. J Physiol (Lond) 399, 437-449.

Barman, J.M., Moreira, M.F., & Consolazio, F. (1943). The effective stimulus for increased pulmonary ventilation during muscular exertion. J Clin Invest 43, 53-56.

Bean, J.W. (1952). Intestine in reflex chemical control of breathing. Am J Physiol 171, 522-527.

Bellville, J.W., Whipp, B.J., Kaufman, R.D., Swanson, G.D., Aqleh, K.A., & Wiberg, D.M. (1979). Central and peripheral chemoreflex loop gain in normal and carotid body-resected subjects. J Appl Physiol 46, 843-853.

Bernards, J.A., Dejours, P., & Lacaisse, A. (1966). ventilatory effects in Man of breathing successively CO2-free, CO2-enriched and CO2-free gas mixtures with low, normal or high oxygen concentration. Resp Physiol 1, 390-397.

Bjurstedt, A.G.H. (1946). interaction of centrogenic and chemoreflex control of breathing during oxygen deficiency at rest. Acta Physiol Scand Suppl 12, suppl 38, 1-88.

Bock, A.V., Vancaulaert, C., Dill, D.B., Folling, A., & Hurxthal, L.M. (1928). Studies in muscular activity. III. Dynamical changes occurring in man at work. J Physiol (Lond) 66, 136-161.

Bock, P. (1982). The paraganglia. Springer-Verlag, Heidelberg.

Bouckaert, J.J., Heymans, C., & Samaan, A. (1938). The role of carotid sinus and vagal chemoreceptors in the respiratory and vasomotor effects of hypoxaemia in anaesthetized and normal dogs. J Physiol (Lond) 94, 4-P.

Brice, A.G., Forster, H.V., Pan, L.G., Funahashi, A., Hoffman, M.D., Murphy, C.L., & Lowry, T.F. (1988). Is the hyperpnea of muscular contractions critically dependent on spinal afferents? J Appl Physiol 64, 226-233.

Brown, D.R., Forster, H.V., Pan, L.G., Brice, A.G., Murphy, C.L., Lowry, T.F., Gutting, S.M., Funahashi, A., Hoffman, M., & Powers, S. (1990). Ventilatory response of spinal cord-lesioned subjects to electrically induced exercise. J Appl Physiol 68, 2312-2321.

Bruce, R.M. & White, M.J. (2012). Muscle afferent activation causes ventilatory and cardiovascular responses during concurrent hypercapnia in humans. Exp Physiol 97, 208-2018.

Bruce, R.M. & White, M.J. (2015). The ventilatory response to muscle afferent activation during concurrent hypercapnia in humans: central and peripheral mechanisms. Exp Physiol 100, 896-994.

Casaburi, R., Daly, J.A., Hansen, J.E., & Effros, R.M. (1989). Abrupt changes in mixed venous blood gas composition after onset of exercise. J Appl Physiol 67, 1106-1112.

Child, B., Hedley, R.J., & Howe, A. (1990). reflex respiratory responses to abdominal intravascular sodium cyanide in the anaesthetized rat. J Physiol (Lond) 423, 27P.

Coffey, J.C. & O'Leary, D.P. (2016). The mesentery: structure, function, and role in disease. The Lancet Gastroenterology & Hepatology 1, 238-247.

Cohen, M.I. & Wang, S.C. (1959). Respiratory neuronal activity in pons of cat. J Neurophysiol 22, 33-50.

Coleridge, H.M., Coleridge, J.C.G., & Howe, A. (1966). Aorticopulmonary glomus tissue in the Cat. Nature 211, 1187.

Coleridge, H.M., Coleridge, J.C.G., & Howe, A. (1967). A search for pulmonary arterial chemoreceptors in the cat, with a comparision of the blood supply of the aortic bodies in the new-born and adult animal. J Physiol (Lond) 191, 353-374.

Comroe, J.H. (1939). The location and function of the chemoreceptors of the aorta. Am J Physiol 127, 176-191.

Comroe, J.H. (1964). The peripheral chemoreceptors. In Handbook of Physiology, Respiration, section 1 eds. Fenn, W.O. & Rahn, H., pp. 557-583. American Physiological Society, Washington,D.C.

Comroe, J.H. (1974). Physiology of Respiration, an introductory text. Year Book Publishers, Chicago.

Comroe, J.H. & Schmidt, C.F. (1943). Reflexes from the limbs as a factor in the hypernea of muscular exercise. Am J Physiol 138, 536-547.

Coote, J.H., Hilton, S.M., & perez-Gonzalez, J.F. (1971). The reflex nature of the pressor response to muscular exercise. J Physiol (Lond) 215, 789-804.

Cordier, M.D. & Heymans, C. (1935). Le centre respiratoire. Ann de Physiol 11, 535-771.

Cormack, R.S., Cunningham, D.J.C., & Gee, J.B.L. (1957). The effect of carbon dioxide on the respiratory response to want of oxygen in Man. Q J Exp Physiol 42, 303-319.

Crisafulli, A., Milia, R., Lobina, A., Caddeo, M., Tocco, F., Concu, A., & Melis, F. (2008). Haemodynamic effect of metaboreflex activation in men after running above and below the velocity of the anaerobic threshold. Exp Physiol 93, 447-457.

Cropp, G.J.A. & Comroe, J.H. (1961). Role of mixed venous blood PCO2 in respiratory control. J Appl Physiol 16, 1029-1033.

Cross, B.A., Davey, A., Guz, A., Katara, P.G., McClean, M., Murphy, K., Semple, S.J.G., & Stidwill, R. (1982). The role of spinal cord transmission in the ventilatory response to electrically induced leg exercise in the anaesthetised dog. J Physiol (Lond) 329, 37-55.

Cui, J., Leuenberger, U.A., Blaha, C., King, N.C., & Sinoway, L.I. (2011). Effect of P2 receptor blockade with pyridoxine on sympathetic response to exercise pressor reflex in humans. J Physiol (Lond) 589, 685-695.

Cunningham, D.J.C. (1987). Studies on arterial chemoreceptors in man. J Physiol (Lond) 384, 1-26.

Dahan, A., Nieuwenhuijs, D., & Teppema, L. (2007). Plasticity of Central Chemoreceptors: Effect of Bilateral Carotid Body Resection on Central CO_2 Sensitivity. PLoS Med 4, e239.

Davenport, H.W., Brewer, G., Chambers, A.H., & Goldschmidt, S. (1947). The respiratory responses to anoxemia of unaesthetized dogs with chronically denervated aortic and carotid chemoreceptors and their causes. Am J Physiol 148, 406-416.

Dawes, G.S. & Comroe, J.H. (1954). Chemoreflexes from the heart and lungs. Physiol Rev 34, 167-201.

Decharneux, G. (1934). L'influence de l'altltude sure la respiration de deux chiens prives de leurs sinus carotidiens. C R Soc Biol (Paris) 116, 352-354.

Dejours, P. (1962). Chemoreflexes in breathing. Physiol Rev 42, 355-358.

Dejours, P. (1963). The regulation of breathing during muscular exercise in Man. A neuro-humoral theory. In The regulation of human respiration eds. Cunningham, D.J.C. & Lloyd, B.B., pp. 553-547. Blackwells, Oxford.

Dejours, P. (1964). Control of respiration in muscular exercise. In Handbook of Physiology, Respiration, section 1 eds. Fenn, W.O. & Rahn, H., pp. 631-648. American Physiological Society, Washington,D.C.

Dejours, P., Labrousse, Y., Raynaud, J., Girard, F., & Teillac, A. (1958). Stimulus oxygene de la ventilation au repos et au cours de l'exercise musculaire, a basse altitude (50m) chez l'homme. Rev Franc Etudes Clin Biol 3, 105-123.

Dejours, P., Mithoefer, J.C., & Raynaud, J. (1957). Evidence against the existence of specific ventilatory chemoreceptors in the legs. J Appl Physiol 10, 367-371.

Dejours, P., Mithoefer, J.C., & Teillac, A. (1955). Essai de mise en evidence de chemorecepteurs veineux de ventilation. J Physiol (Paris) 47, 160-163.

Dempsey, J.A., Forster, H.V., & Ainsworth, D.M. (1995). Regulation of hyperpnea, hyperventilation, and respiratory muscle recruitment during exercise. In regulation of Breathing eds. Dempsey, J.A. & Pack, A.I., pp. 1065-1132. Marcel Dekker, new York.

Dempsey, J.A. & Whipp, B.J. (2003). The respiratory system. In Exercise Physiology, people and ideas ed. Tipton, C.M., pp. 138-187. American Physiological Society, Oxford.

Dempsey, J.A., Blain, G.g.M., & Amann, M. (2014). Are type III–IV muscle afferents required for a normal steady-state exercise hyperpnoea in humans? J Physiol (Lond) 592, 463-474.

Dripps, R.D. & Comroe, J.H. (1947). The effect of the inhalation of high and low oxygen concentrations on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation (oximeter) of normal individuals. Am J Physiol 149, 277-291.

Duke, H.N., Green, J.H., Heffron, P.F., & Stubbens, V.W.J. (1963). Pulmonary chemoreceptors. Q J Exp Physiol 48, 164-175.

Dumke, P.R., Schmidt, C.F., & Chiodi, H. (1941). The part played by carotid body reflexes in the respiratory response of the dog to anoxemia with and without simultaneous hypercapnia. Am J Physiol 133, 1-20.

Dutton, R.E., Nath, S., & Riley, R.L. (1960). Reflex stimulation of pulmonary ventilation by mixed venous PCO_2. Fed Proc 19, 382.

Edwards, R.H., Denison, D.M., Jones, G., Davies, C.T.M., & Campbell, E.J.M. (1972). Changes in mixed venous gas tensions at start of exercise in man. J Appl Physiol 32, 165-169.

Fernandes, A., Galbo, H., Kjaer, M., Mitchell, J.H., Secher, N.H., & Thomas, S.N. (1990). Cardiovascular and ventilatory responses to dynamic exercise during epidural anaesthesia in man. J Physiol (Lond) 420, 281-293.

Fisher, J.P. & White, M.J. (2004). Muscle afferent contributions to the cardiovascular response to isometric exercise. Exp Physiol 89, 639-646.

Fordyce, W.E., Bennett, F.M., Edelman, S.K., & Grodins, F.S. (1982). Evidence in man for a fast neural mechanism during the early phase of exercise hyperpnea. Resp Physiol 48, 27-43.

Forster, H.V., Haouzi, P., & Dempsey, J.A. (2012). Control of breathing during exercise. Compr Physiol 2, 743-777.

Forster, H.V. & Pan, L.G. (1994). The role of the carotid chemoreceptors in the control of breathing during exercise. Med Sci Sports Exerc 328-336.

Forster, H.V. & Pan, L.G. (1997). Control of breathing during exercise. In The Lung, 2 edn, eds. Crystal, R.G., West, J.B., Weibel, E.R., & Barnes, P.J., pp. 2001-2010. Lippincott-Raven, Philadephia.

Forster, H.V. (2007). Commentary on "Homeostasis of exercise hyperpnea and optimal sensorimotor integration: The internal model paradigm" by Poon et al. Resp Physiol Neurobiol 159, 18-20.

Forster, H.V. (2014). Recent advances in understanding mechanisms regulating breathing during exercise. J Physiol (Lond) 592, 429-431.

Fukuba, Y., Kitano, A., Hayashi, N., Yoshida, T., Ueoka, H., Endo, M.Y., & Miura, A. (2007). Effects of femoral vascular occlusion on ventilatory responses during recovery from exercise in human. Resp Physiol Neurobiol 155, 29-34.

Gautier, H. & Bonora, M. (1980). Possible alterations in brain monoamine metabolism during hypoxia-induced tachypnea in cats. J Appl Physiol 49, 769-777.

Gernandt, B.E. (1946). A study of the respiratory reflexes elicited from the aortic and carotid bodies. Acta Physiol Scand Suppl 11 suppl 35, 1-81.

Gesell, R. & Moyer, C. (1937). Factors which determine the rate and depth of breathing. Am J Physiol 119, 55-66.

Guz, A., Noble, M.I.M., Widdicombe, J.G., Trenchard, D., & Mushin, W.W. (1966). Peripheral chemoreceptor block in man. Resp Physiol 1, 38-40.

Hales, J.R.S., Kao, F.F., Mei, S.S., Wang, C., & Gretenstein, M. (1970). Panting in heated cross-circulated dogs. Am J Physiol 218, 1389-1393.

Haouzi, P., Chenuel, B., & Chalon, B. (2001). Control of breathing and muscle perfusion in humans. Exp Physiol 86, 759-768.

Haouzi, P., Chenuel, B., Haouzi, P., & Chenuel, B. (2005). Control of arterial PCO2 by somatic afferents in sheep. J Physiol (Lond) 569, 975-987.

Haouzi, P., Huszczuk, A., Gille, J.P., Chalon, B., Marchal, F., Crance, J.P., & Whipp, B.J. (1995). Vascular distension in muscles contributes to respiratory control in sheep. Resp Physiol 99, 41-50.

Haouzi, P., Huszczuk, A., Porszasz, J., Chalon, B., Wasserman, K., & Whipp, B.J. (1993). Femoral vascular occlusion and ventilation during recovery from heavy exercise. Resp Physiol 94, 137-150.

Haouzi, P. (2014). Tracking pulmonary gas exchange by breathing control during exercise: role of muscle blood flow. J Physiol (Lond) 592, 453-461.

Haouzi, P. & Bell, H.J. (2010). Respiratory Effects Of Changing The Volume Load Imposed On The Peripheral Venous System. Resp Physiol Neurobiol 171, 175-180.

Heymans, C. (1967). Pharmacology in old and modern medicine. Annual Review of Pharmacology & Toxicology 7, 1-13.

Heymans, C., Bouckaert, J.J., & Dautrebande, L. (1930). Sinus carotidien et reflexes respiratoires. II. Influences respiratoires reflexes de l'acidose, de l'alcalose, de l'anhydride, carbonique, de l'ion hydrogene et de l'anoxemie. Sinus carotidiens et echanges respiratoires dan les poumons et au dela des poumons. Archives Internationales de Pharmacodynamie et de Therapie 39, 400-450.

Honda, Y. (1992). Respiratory and circulatory activities in carotid body-resected humans. J Appl Physiol 73, 1-8.

Honda, Y., Myojo, S., Hasegawa, S., Hasegawa, T., & Severinghaus, J.W. (1979a). Decreased exercise hyperpnea in patients with bilateral carotid chemoreceptor resection. J Appl Physiol 46, 908-912.

Honda, Y., Watanabe, S., Hashizume, I., Satomura, Y., Hata, N., Sakakibara, Y., & Severinghaus, J.W. (1979b). Hypoxic chemosensitivity in asthmatic patients two decades after carotid body resection. J Appl Physiol 46, 632-638.

Howe, A. (1990). Aortic and abdominal glomera. In Control of the Cardiovascular and respiratory systems in health and disease eds. Kappagoda, C.T. & Kaufman, M.P., pp. 57-61. Plenum Press, New York.

Howe, A., Pack, R.J., & Wise, J.C.M. (1981). Arterial chemoreceptor-like activity in the abdominal vagus of the rat. J Physiol (Lond) 320, 309-318.

Hughes, T. (1965). Portal blood supply to glomus tissue and its significance. Nature 205, 149-151.

Innes, J.A., Solarte, I., Huszczuk, A., Yeh, E., Whipp, B.J., & Wasserman, K. (1989). Respiration during recovery from exercise: effects of trapping and release of femoral blood flow. J Appl Physiol 67, 2608-2613.

Jongbloed, M.J. (1936). Sur le role des sinus carotidiens et des nerfs aortiques dans la regulation de la respiration pendant la depression atmospherique. Ann de Physiol 12, 457-470.

Kao, F.F. (1956). Regulation of respiration during muscular activity. Am J Physiol 185, 145-151.

Kao, F.F. (1963). An experimental study ofthe pathways involved in exercise hyperpnoea employing cross-circulation techniques. In The regulation of human respiration eds. Cunningham, D.J.C. & Lloyd, B.B., pp. 461-502. Blackwells, Oxford.

Kao, F.F. (1974). The peripheral neurogenic drive:an experimental study. In Muscular exercise and the lung eds. Dempsey, J.A. & Reed, C.E., pp. 71-88. University of Wisconsin Press, Madison.

Kao, F.F., Michel, C.C., & Mei, S.S. (1964). Carbon dioxide and pulmonary ventilation in muscular exercise. J Appl Physiol 19, 1075-1080.

Kao, F.F., Michel, C.C., Mei, S.S., & Li, W.K. (1963). Somatic afferent influnece on respiration. Ann N Y Acad Sci 109, 696-711.

Kao, F.F. & Ray, L.H. (1954). Respiratory and circulatory responses of anesthetized dogs to induced muscular work. Am J Physiol 179, 249-254.

Kaufman, M.P. (2012). The exercise pressor reflex in animals. Exp Physiol 97, 51-58.

Kumar, P. & Prabhakar, N.R. (2012). Peripheral Chemoreceptors: function and plasticity of the carotid body. Compr Physiol 2, 141-219.

Lambertsen, C.J., Kough, R.H., Cooper, D.Y., Emmel, G.L., Loeschcke, H.H., & Schmidt, C.F. (1953). Comparison of relationship of respiratory minute volume to pCO_2 and pH or arterial blood and internal jugular blood in normal Man during hyperventilation produced by low concentrations of CO_2 at 1 atmosphere and by O_2 at 3.0 atmospheres. J Appl Physiol 5, 255-263.

Levine, S. (1975). Nonperipheral chemoreceptor stimulation of ventilation by cyanide. J Appl Physiol 39, 199-204.

Levine, S. (1979). Ventilatory response to muscular exercise: observations regarding a humoral pathway. J Appl Physiol 47, 126-137.

Lloyd, B.B. (1965). The interactions between hypoxia and other ventilatory stimuli. In Proc. int. Symp. cardiovasc. respir. Effects Hypoxia pp. 146-165. Karger, Basel/New York, Kingston, Ontario.

Luft, U.C. (1965). Aviation Physiology- the effects of altitude. In Handbook of Physiology, Section 3, volume II eds. Fenn, W.O. & Rahn, H., pp. 1099-1145. American Physiological Society, Washington DC.

Lugliani, R., Whipp, B.J., Seard, C., & Wasserman, K. (1971). Effect of bilateral carotid body resection on ventilatory control at rest and during exercise in Man. New Eng J Med 285, 1105-1112.

Lykidis, C.K., Kumar, P., Vianna, L.C., White, M.J., & Balanos, G.M. (2010). A respiratory response to the activation of the muscle metaboreflex during concurrent hypercapnia in man. Exp Physiol 95, 194-201.

Malconian, M.K., ROCK, P.B., REEVES, J.T., CYMERMAN, A., & HOUSTON, C.S. (1993). Operation Everest II: Gas tensions in expired air and arterial blood at extreme altitude. Aviat Space Environ Med 64, 37-42.

Marshall, E.K. & Rosenfeld, M. (1936). Depression of respiration by oxygen. J Pharm Exp Ther 57, 437-457.

Miller, M.J. & Tenney, S.M. (1975). Hypoxia-induced tachypnea in carotid-deafferented cats. Resp Physiol 23, 31-39.

Mills, J.N. (1944). Hyperpnoea in Man produced by sudden release of occluded blood. J Physiol (Lond) 103, 244-252.

Mitchell, J.H., Sproule, B.J., & Chapman, C.B. (1958). Factors influencing respiration during heavy exercise. J Clin Invest 37, 1693-1701.

Moyer, C.A. & Beecher, H.K. (1942). Central stimulation of respiration during hypoxia. Am J Physiol 136, 13-21.

Nielsen, M. & Smith, H. (1951). Studies on the regulation of respiration in acute hypoxia. Acta Physiol Scand 24, 293-313.

Olson, T.P. (2010). Influence of Locomotor Muscle Metaboreceptor Stimulation on the Ventilatory Response to Exercise in Heart Failure. Circ Heart Fail 3, 212-219.

Parkes, M.J. (2013). Evaluating the Importance of the Carotid Chemoreceptors in Controlling Breathing during Exercise in Man. Biomed Research International 2013, 1-18.

Parkes, M.J. (2014). Have the carotid chemoreceptors anything to do with the control of breathing during exercise in Man? Physiol News 94, 22-25.

Paterson, D.J. (2014). Defining the neurocircuitry of exercise hyperpnoea. J Physiol (Lond) 592, 433-444.

Phillipson, E.A., Bowes, G., Townsend, E.R., Duffin, J., & Cooper, J.D. (1981a). Carotid chemoreceptors in ventilatory responses to changes in venous CO_2 load. J Appl Physiol 51, 1398-1403.

Phillipson, E.A., Bowes, G., Townsend, E.R., Duffin, J., & Cooper, J.D. (1981b). Role of metabolic CO2 production in ventilatory response to steady-state exercise. J Clin Invest 68, 768-774.

Phillipson, E.A., Duffin, J., & Cooper, J.D. (1981c). Critical dependence of respiratory rhythmicity on metabolic CO2 load. J Appl Physiol 50, 45-54.

Piepoli, M., Chua, T.P., & Coats, A.J. (1995). Exercise intolerance in patients with chronic heart failure. Eur Heart J 16, 1744-1745.

Poon, C.S., Tin, C., & Yu, Y. (2007). Homeostasis of exercise hyperpnea and optimal sensorimotor integration: The internal model paradigm. Resp Physiol Neurobiol 159, 1-13.

Prabhakar, N.R. & Peng, Y. (2004). Peripheral chemoreceptors in health and disease. J Appl Physiol 96, 359-366.

Riley, R.L., Dutton, R.E., Fuleihan, F.J.D., Nath, S., Hurt, H.H., Yoshimoto, C., Sipple, J.H., Permutt, S., & Bromberger-Barnea, B. (1963). regulation of respiration and blood gases. Ann N Y Acad Sci 109, 829-851.

Riley, R.L., Ross, R.S., & Armstrong, B. (1960). Pulmonary arterial PCO2 and ventilation in Man. Fed Proc 20, 431.

Riley, R.R. (1963). The hyperpnoea of exercise. In The regulation of human respiration eds. Cunningham, D.J.C. & Lloyd, B.B., pp. 524-534. Blackwell, Oxford.

Robb, G.P. & Weiss, S. (1933). A method for the measurement of the velocity of the pulmonary and peripheral venous blood flow in Man. Am Heart J 8, 650-670.

Ross, J.C., Hickam, J.B., & Frayser, R. (1962). Tourniquet hyperpnea and its modification by agents which alter cerebral blood flow. J Clin Invest 41, 269-280.

Rowell, L.B., Hermansen, L., & Blackmon, J.R. (1976). Human cardiovascular and respiratory responses to graded muscle ischemia. J Appl Physiol 41, 693-701.

Rowell, L.B. & O'Leary, D.S. (1990). Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. [Review] [92 refs]. J Appl Physiol 69, 407-418.

Sagan, C. (1980).
Cosmos: International Affairs in the Modern Age. Random House, New York.

Sargeant, A.J., Rouleau, J.L., Sutton, J.R., & Jones, N.L. (1981). Ventilation in exercise studied with circulatory occlusion. J Appl Physiol 50, 718-723.

Schlaefke, M.E. (1981). Rev Physiol Biochem Pharm 90, 171.

Schlaefke, M.E., Kille, J., Folgering, H., Herker, A., & See, W.R. (1974). Breathing without central chemosensitivity. In Central rhythmic and regulation eds. Umbach, W. & Koepchen, H.P., pp. 97-104. Hippokrates Verlag, Stuttgart.

Schlaefke, M.E., Kille, J.F., & Loeschcke, H.H. (1979). Elimination of central chemosensitivity by coagulation of a bilateral area on the ventral medullary surface in awake cats. Pflugers Arch 378, 231-241.

Schmidt, C.F. (1932). Carotid sinus reflexes to the respiratory centre 1. Identification. Am J Physiol 102, 94-118.

Schmidt, C.F. & Comroe, J.H. (1940). Functions of the carotid and aortic bodies. Physiol Rev 20, 115-157.

Scott, A.C., Francis, D.P., Davies, L.C., Ponikowski, P., Coats, A.J., & Piepoli, M. (2000). Contribution of skeletal muscle "ergoreceptors" in the human leg to respiratory control in chronic heart failure. J Physiol (Lond) 529.3, 863-870.

Selladurai, S. & Wright, S. (1932). Mode of action of respiratory stimulant: 1. Mode of action of oxygen lack. Q J Exp Physiol 22, 233-248.

Smyth, D.H. (1937). The study of the carotid sinus respiratory reflexes by means of chronic experiments. J Physiol (Lond) 88, 425-435.

Spode, R. & Schlaefke, M.E. (1975). Influence of muscular exercise on respiration after central and peripheral chemodenervation. Pflugers Arch 359, R49.

Stein, J.F. & Stoodley, C.J. (2006). Neuroscience, an introduction. Wiley, Chichester.

Storey, W.F. & Butler, J. (1963). Evidence that the PCO2 of mixed venous blood is not a regulator of ventilation during exercise. J Appl Physiol 18, 345-348.

Sun, X.G., Hansen, J.E., Stringer, W.W., Ting, H., & Wasserman, K. (2001). Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise. J Appl Physiol 90, 1798-1810.

Swanson, G.D. & Bellville, J.W. (1974). Hypoxic-hypercapnic interaction in human respiratory control. J Appl Physiol 36, 480-487.

Swanson, G.D., Whipp, B.J., Kaufman, R.D., Aqleh, K.A., Winter, B., & Bellville, J.W. (1978). Effect of hypercapnia on hypoxic ventilatory drive in carotid-body resected man. J Appl Physiol 45, 971-977.

Sylvester, J.T., Whipp, B.J., & Wasserman, K. (1973). Ventilatory control during brief infusions of CO2-laden blood in the awake dog. J Appl Physiol 35, 178-186.

Teppema, L.J. & Dahan, A. (2010). The Ventilatory Response to Hypoxia in Mammals: Mechanisms, Measurement, and Analysis. Physiol Rev 90, 675-754.

Torrance, R.W. (1996). Prolegomena. Chemoreception upstream of transmitters. In Frontiers in arterial chemoreception, volume 410. eds. Zapata, P. & Eyzaguirre, C., pp. 13-38. Plenum, New York.

Wade, J.G., Larson, C.P., Hickey, R.F., Ehrenfeld, W.K., & Severinghaus, J. (1970). Effect of carotid body endartectomy on carotid chemoreceptor and baroreceptor function in Man. New Eng J Med 283, 823-829.

Waldrop, T.G., Eldridge, F.L., Iwamoto, G.A., & Mitchell, J.H. (1996). Central neural control of respiration and circulation during exercise. In Handbook of Physiology, section 12. Exercise: regulation and integration of multiple systems eds. Rowell, L.B. & Shepherd, J.T., pp. 353-380. Oxford University Press, New York.

Walshe, F.M.R. (1951). On the interpretation of experimental studies of cortical motor function: with special reference to the "operational view" of experimental procedures. Brain 74, 18-266.

Ward, S.A. (1994). Assessment of peripheral chemoreflex contributions to exercise hypernea in humans. Med Sci Sports Exerc 26, 303-310.

Wasserman, K., Hansen, J.E., Sue, D.Y., Whipp, B.J., & Casaburi, R. (1994). Principles of exercise testing and interpretation.

Wasserman, K., Whipp, B.J., Casaburi, R., Huntsman, D.J., Castagna, J, & Lugliani, R. (1975a). Regulation of arterial PCO2 during intravenous CO2 loading. J Appl Physiol 38, 651-656.

Wasserman, K., Whipp, B.J., Kayal, S.N., & Cleary, M.G. (1975b). Effect of carotid body resection on ventilatory and acid base control during exercise. J Appl Physiol 39, 354-358.

Watt, J.G., Dumke, P.R., & Comroe, J.H. (1943). Effects of inhalation of 100% and 14% oxygen upon respiration of unanaesthetised dogs before and after chemodenervation. Am J Physiol 138, 610-617.

Whipp, B.J. (1983). ventilatory control during exercise in humans. Ann Rev Physiol 45, 393-413.

Whipp, B.J., Ward, S.A., Baum, V.C., & Winter, B. (1994). The influence of hyperoxia on ventilatory kinetics during moderate exercise in carotid-body-resected humans. J Physiol (Lond) 475, 20P.

Wiley, R.L. & Lind, A.R. (1971). Respiratory responses to sustained static muscular contractions in humans. Clin Sci 40, 221-234.

Winder, C.V., Winder, H.O., & Gesell, R. (1933). The seat of action of cyanide on pulmonary ventilation. Am J Physiol 105, 311-336.

Winning, A.J., Hamilton, R.D., Shea, S.A., & Guz, A. (1986). Respiratory and cardiovascular effects of central and peripheral intravenous injections of capsaicin in man: evidence for pulmonary chemosensitivity. Clin Sci 71, 519-526.

Wright, S. (1936). Further observations on the mode of action of oxygen lack on respiration. Q J Exp Physiol 26, 63-79.

Yamamoto, W.S. & Edwards, M.W. (1960). Homeostasis of carbon dioxide during intravenous infusion of carbon dioxide. J Appl Physiol 15, 807-818.