REVIEW-SYMPOSIUM

Rethinking O_2, CO_2 and breathing during wakefulness and sleep

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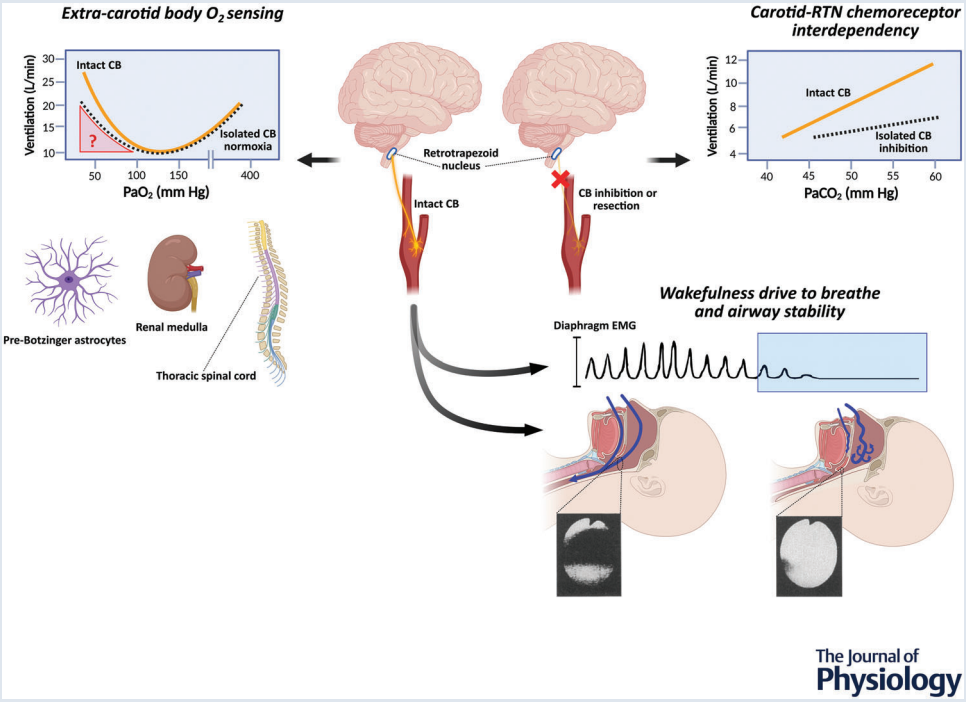

Abstract We have examined the importance of three long-standing questions concerning chemoreceptor influences on cardiorespiratory function which are currently experiencing a resurgence of study among physiologists and clinical investigators. Firstly, while carotid chemoreceptors (CB) are required for hypoxic stimulation of breathing, use of an isolated,

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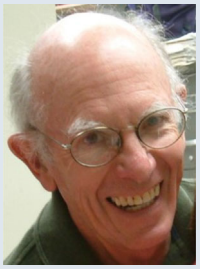
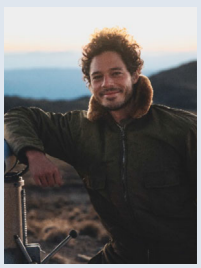

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extracorporeally perfused CB preparation in unanaesthetized animals with maintained tonic input from the CB, reveals that extra-CB hypoxaemia also provides dose-dependent ventilatory stimulation sufficient to account for 40–50% of the total ventilatory response to steady-state hypoxaemia. Extra-CB hyperoxia also provides a dose- and time-dependent hyperventilation. Extra-CB sites of O_2-driven ventilatory stimulation identified to date include the medulla, kidney and spinal cord. Secondly, using the isolated or denervated CB preparation in awake animals and humans has demonstrated a hyperadditive effect of CB sensory input on central CO_2 sensitivity, so that tonic CB activity accounts for as much as 35–40% of the normal, air-breathing eupnoeic drive to breathe. Thirdly, we argue for a key role for CO_2 chemoreception and the neural drive to breathe in the pathogenesis of upper airway obstruction during sleep (OSA), based on the following evidence: (1) removal of the wakefulness drive to breathe enhances the effects of transient CO_2 changes on breathing instability; (2) oscillations in respiratory motor output precipitate pharyngeal obstruction in sleeping subjects with compliant, collapsible airways; and (3) in the majority of patients in a large OSA cohort, a reduced neural drive to breathe accompanied reductions in both airflow and pharyngeal airway muscle dilator activity, precipitating airway obstruction.

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Abstract figure legend The carotid body (CB) is the primary contributor to the hypoxic ventilatory response. However, experimental unanaesthetized animal models that anatomically isolate and maintain normal CB tonic activity retain a ventilatory response to extra-CB systemic hypoxia that amounts to 40–50% of the intact model (left panel). O_2-sensitive sites in: (1) Pre-Bötzinger astrocytes, (2) renal medulla, and (3) thoracic spinal cord, may contribute to the extra-CB ventilatory response to whole-body hypoxia. The CB also contributes to CO_2 sensing at the retrotrapezoid nucleus (RTN) in the medulla (middle and right panels). Isolated CB inhibition with extra-corporeal hyperoxic/hypocapnic perfusate, or CB resection, both suppress the ventilatory response to CO_2 and decrease eupnoeic ventilation by 35–45%, providing evidence for a hyperadditive interaction between peripheral and central chemoreflexes. In the majority of obstructive sleep apnoea patients, a decreased central drive to breathe precedes airway obstruction, indicating that the central drive to breathe and chemosensitivity contribute to airway stability; complete closure of the upper airway is shown at the nadir of the oscillating drive to breathe (bottom panel).

Introduction

It is vital to life that breathing is tightly regulated so as to maintain levels of circulating and tissue O_2 and CO_2 within narrow limits during all states of wakefulness and sleep and to minimize the work required of the respiratory muscles to achieve this aim (Del Negro et al., 2018; Otis et al., 1950). Our review provides a brief perspective on three often overlooked problems concerned with pivotal yet controversial roles that CO_2 and O_2 play in the control of breathing. These include: (1) extra-carotid chemoreceptor (CB) contributions to O_2 sensing; (2) chemoreceptor interdependence contributions to CO_2 sensing and the eupnoeic drive to breathe; and (3) the contribution of chemoreception to the control of breathing and upper airway stability in sleep. These questions have special relevance to commonly used practices of quantifying chemoreceptor sensitivity and to the pathogenesis and treatment of cardiorespiratory diseases and obstructive sleep apnoea (OSA).

Extra-carotid body contributions to O_2 sensing

Since the 1930s, with the discovery of carotid chemoreceptor function by Nobel laureate Cornielle Heymans, it has been well established that the carotid chemoreceptors are the body's primary O_2 sensor for purposes of ventilatory and sympathetic nervous system regulation. Well-defined neural pathways begin in O_2-sensing CB glomus cells. Sensory pathways then project via the nucleus of the solitary tract (NTS) to the medullary respiratory pattern generator neurons that determine phrenic motor output and to ventrolateral medulla (RVLM) neurons that determine sympathetic outflow. Hypothalamic and CO_2-sensitive retrotrapezoid neurons

(RTN) are also included in this extended chemoreceptor pathway (King et al., 2012; Ruyle et al., 2019; Zera et al., 2019).

Extra-carotid body hypoxaemia. The first problem we explore in our review is concerned with the role of O_2 sensing outside of the carotid chemoreceptors. In order to determine whether significant O_2 sensing for cardiorespiratory control occurs outside the CB, two experimental approaches have been utilized, namely bilateral CB denervation (CBX) and CB isolation. CBX is commonly accompanied by ventilatory depression in response to acute hypoxia in anaesthetized animals (Melton et al., 1988; Neubauer et al., 1990). However, in awake or sleeping animals or humans with bilateral CBX, acute hypoxia either does not consistently change ventilation ($\dot{V}_E$) or increases it to a small fraction of that observed in the CB-intact state (Curran et al., 2000; Dahan et al., 2007; Timmers et al., 2003). A major limitation of using CBX as a means of quantifying its contribution to ventilatory control in an otherwise healthy animal or human is that substantial remodelling of the control system occurs over the days and weeks following CBX (Bisgard et al., 1980; Dahan et al., 2007). Another limitation of CBX is that once CBs are denervated we are unable to manipulate their input to determine their influence on the responsiveness to additional stimuli or on other structures in the extended chemoreceptor pathway.

An alternative experimental approach developed by the late Gerry Bisgard for use in unanaesthetized goats and later in awake and sleeping canines avoids both of these limitations (Fig. 1*A*). This approach employs denervation of one CB with the remaining CB vascularly isolated from the systemic and central circulations. The composition of the isolated CB perfusate is controlled by an extra-corporeal perfusion circuit (Curran et al., 2000; Daristotle et al., 1991).

In the Bisgard preparation, when the isolated CB's PO_2 and PCO_2 are controlled at normal (normoxic, normocapnic) levels, systemic hypoxaemia provides a fast-onset, dose-dependent hyperventilation, as shown by the following evidence:

- In Fig. 1*B*, in the sleeping canine with the isolated CB maintained normoxic, moderate levels of systemic poikilocapnic hypoxaemia are shown to elicit a fast-onset hypocapnia hyperventilation and a rise in blood pressure and heart rate (Curran et al., 2000).
- Over 5 min periods of extra-CB hypoxaemia, a dose-response hyperventilation occurred (not shown). At a systemic P_aO_2 of 38 mmHg, steady-state $\dot{V}_E$ increased 20% above normoxic control and P_aCO_2 fell 4 mmHg which compared to a 40% increase in $\dot{V}_E$ and a 10 mmHg fall in P_aCO_2 with whole-body hypoxia. These hyperventilatory responses to extra-CB hypoxaemia with the CB tonic input maintained at normoxic levels were not observed in the sleeping canine with bilateral CBX (Curran et al., 2000).
- In Fig. 1*C*, using the Bisgard preparation in the awake goat, again with isolated CB held normoxic, systemic eucapnia was now maintained (via increasing $FICO_2$) during the steady-state application of extra-CB systemic hypoxaemia. When the feedback inhibition of hypoxic-driven ventilatory drive via hypocapnia was prevented during moderate degrees of steady-state extra-CB hypoxaemia, a more than doubling of eupnoeic $\dot{V}_E$ was elicited and the ventilatory response to extra-CB hypoxaemia approximated 40–50% of the whole-body eucapnic hypoxic response (Daristotle et al., 1991).

Further studies of moderate isocapnic extra-CB systemic hypoxia combined with hypoxic stimulation of the isolated CB in awake goats also showed: (1) tidal volume (V_T), breathing frequency (fB) and $\dot{V}_E$ responses to isolated CB hypoxic stimulation were similar whether the systemic circulation was maintained normoxic or hypoxic; (2) based on measurements of respiratory muscle EMG, isolated CB hypoxic stimulation with systemic normoxia or hypoxia elicited similar recruitments of diaphragm and both intercostal and abdominal expiratory muscles; and (3) these breathing pattern and respiratory muscle recruitment patterns were nearly identical to those elicited by whole-body normoxic hypercapnia (Smith et al., 1993).

Extra-CB hyperoxia. Transiently applied hyperoxia suppresses the CB discharge almost completely, resulting in transient hypoventilation and a suppression of sympathetic nerve activity below normoxic control levels (Prasad et al., 2020) (Fig. 1*D*). However, prolonged hyperoxia beyond 2 min elicits a dose- and time-dependent increase in V_T, fB and $\dot{V}_E$ resulting, for example, in a 30% increase in $\dot{V}_E$ and a 3–4 mmHg arterial hypocapnia after 20 min exposure to 0.75 F_IO_2 in intact healthy humans (Becker et al., 1996). Further, much greater V_T and ventilatory responses to 3–60 min of hyperoxia are achieved when accompanying inhibitory influences are removed: (1) when eucapnia is maintained in CB-intact humans, $\dot{V}_E$ increased 1.6-fold more than normoxic control at 0.5 F_IO_2 and 2.2-fold at F_IO_2 0.75 (Becker, 1996) and unlike following transient hyperoxia (Fig. 1*D*), $\dot{V}_E$ remains greater than control even after several minutes of return to normoxia; (2) when CBs are denervated in awake cats, rodents and goats, systemic hyperoxia beyond 2–3 min duration elicits hyperventilation sufficient to reduce P_aCO_2 6–10 mmHg (Gautier et al., 1986; Miller & Tenney, 1975; Olson et al., 1988); and (3) when the isolated CB is maintained normoxic and systemic eucapnia is also maintained in awake goats using the Bisgard

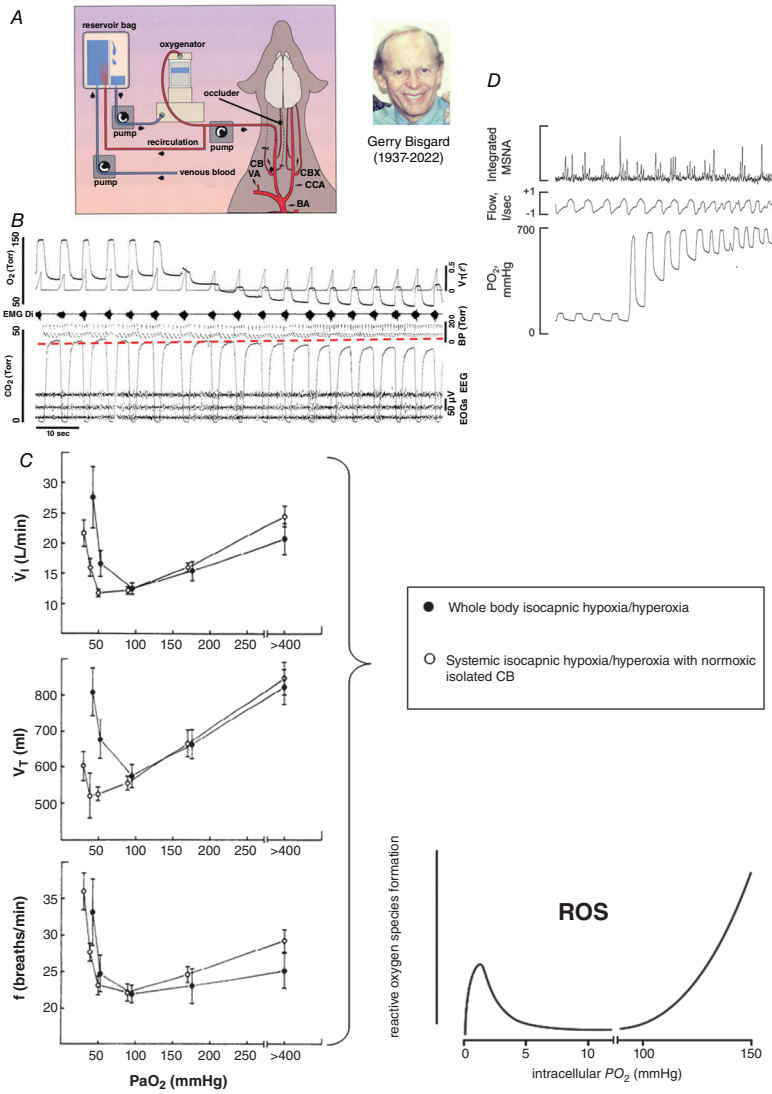

Figure 1. Extra-CB hypoxia/hyperoxia stimulation of breathing
A, the Bisgard preparation was developed for use in unanaesthetized goats to allow extra-corporeal perfusion of the carotid chemoreceptor (CB) isolated from the systemic and CNS circulations. Curtis Smith adapted the Bisgard preparation for use in the awake and sleeping canine. Details on animal handling and surgical procedures along with evidence supporting isolation of the CB from the CNS, the physiological characteristics of the preparation, and reproducibility of findings are contained in Curran et al. (2000), Daristotle et al. (1991) and Smith et al. (2015). Although the rodent is currently used in the great majority of investigations of cardiorespiratory regulation, the use of larger animals was required in order to adequately isolate and perfuse the carotid body and to allow repeated blood sampling in the same animal in the unanaesthetized state. Use of anaesthesia or decortication has marked depressant effects on breathing and chemoreceptor responsiveness and therefore should be avoided in studies attempting to quantify chemoreceptor gains. The canine proved to be especially appropriate for repeated study in the quiet awake and sleeping states following several weeks of training using the same animal handler and employing an air-conditioned, soundproof room. Reproduced with permission from Curran et al. (2000) and Smith et al. (2015). *B*, effects of extra-CB poikilocapnic hypoxaemia using the Bisgard preparation in sleeping canines. The isolated CB was held normoxic and normocapnic while extra-CB hypoxaemia was produced via reduced inspired fractions of O_2 (F_IO_2). Note the gradual reduction in F_IO_2 and $PETO_2$ below normoxic levels beginning at breath #8. Over the ensuing 40 s as $PETO_2$ was reduced to below 65 mmHg, breathing frequency (fB) increased by 2 bpm, $\dot{V}_E$ rose 8–10% and $PETCO_2$ was progressively reduced 2–3 mmHg below air-breathing control (noted by dashed line) and heart rate and blood pressure gradually rose by 11 bpm and 6 mmHg, respectively. Reproduced with permission (Curran et al., 2000). *C*, extra-CB isocapnic hypoxaemia/hyperoxia. Using the Bisgard preparation in the awake goat with isolated CB held normoxic and normocapnic, while 5 min of steady-state extra-CB eucapnic hypoxaemia (P_aO_2, 100–35 mmHg) and extra-CB eucapnic hyperoxia (P_aO_2, 100–500 mmHg) were superimposed by changing F_IO_2 and adding F_ICO_2 sufficient to maintain P_aCO_2 at normoxic control levels. The extra-CB eucapnic hypoxaemic ventilatory response occurred predominantly via increased fB, while the ventilatory response

to whole-body eucapnic hypoxaemia occurred via both increased fB and tidal volume (V_T). The extra-CB and whole-body steady-state eucapnic hyperoxic ventilatory responses both occurred via increases in fB and V_T. Also shown is the correspondence of the biphasic ventilatory stimulation to extra-CB isocapnic hypoxaemia/hyperoxia with changes in the production of reactive oxygen species (ROS). Modified and reproduced with permission from Daristotle et al. (1991) and Gourine & Funk (2017). *D*, ventilatory and integrated muscle sympathetic nerve activity (MSNA) in response to transient hyperoxia in the CB-intact healthy human. Note the simultaneous reduction in fB and airflow rate as well as the reduction in MSNA frequency as $PETO_2$ exceeds ∼300 mmHg during brief exposure to F_IO_2 1.0. Also note the almost immediate return of $\dot{V}_E$ and MSNA to control levels upon restoration of normoxia. Reproduced with permission (Prasad et al., 2020).

preparation, extra-CB steady-state hyperoxia more than doubled eupnoeic $\dot{V}_E$ (Fig. 1*C*). Clearly, as cautioned many decades ago, accumulated evidence has demonstrated that even relatively mild levels of hyperoxia of short duration present much more complex and substantial effects on ventilatory control beyond just those on CB suppression (Dripps & Comroe, 1947).

Mechanisms and sites of extra-CB hypoxia/hyperoxia sensing

The search for extra-CB sites and mechanisms of O_2 sensing for the control of breathing and sympathetic nerve activity has gained considerable attention in recent years. In the case of hypoxia-induced excitation, three potential sites have been discovered:

(1) A central stimulating effect of hypoxia on breathing appears to be mediated by the actions of ATP released from activated astrocytes intermingled with medullary respiratory networks responsible for generation of respiratory and presympathetic neural activity (Gourine & Funk, 2017; Marina et al., 2015).
(2) A highly hypoxic-sensitive renal medulla is capable of activating renal afferent fibres in dorsal root ganglia that project to the ipsilateral horn where they synapse with neurons projecting via the NTS to RVLM cardio-respiratory cells (Kopp, 2015; Patinha et al., 2017).
(3) In a reduced rodent preparation, ventilation and sympathetic nerve activity were stimulated via local hypoxia applied at the level of the thoracic spinal cord (Barioni et al., 2022).

Mechanisms of extra-CB, hyperoxic-induced hyperventilation have traditionally been attributed to CO_2 accumulation in the brain's extracellular fluid, secondary to cerebral vascular constriction and/or a loss of carbamino CO_2 from oxygenated Hb and a reduction in HbO_2 buffering capacity, i.e. the Haldane effect (Becker et al., 1996; Lambertsen et al., 1953). On the other hand, recent findings in healthy humans have shown no significant change in jugular venous (jv) PCO_2 during the increased ventilation accompanying moderate steady-state poikilocapnic hyperoxia (Fernandes et al., 2021). Isocapnic, steady-state hyperoxia also showed no increase in jugular venous PCO_2 at moderate levels of hyperoxia (P_aO_2, 320 mmHg) and an average 2.3 ± 1.7 mmHg increase in $P_{jv}CO_2$ during more severe hyperoxia (P_aO_2 430 mmHg) (Ainslie et al., 2014). Thus, using $P_{jv}CO_2$ measures as a marker of at least the direction of change in brain ECF and medullary chemoreceptor PCO_2, these limited data to date reveal that substantial, dose-dependent hyperoxic-induced increases in $\dot{V}_E$ occur with either no or inconsistent coincident increases in an apparent central CO_2 stimulus. On the contrary, as referenced above in unanaesthetized CBX animals, the substantial hypocapnic hyperventilation (-6–10 mmHg P_aCO_2) accompanying hyperoxia of three or more minutes' duration points to an alkaline – rather than acid – brain ECF under these conditions. Finally, it seems unlikely that sustained brain hypercapnia secondary to the hyperoxic-induced Haldane effect would persist to explain the substantial residual hyperventilation and arterial hypocapnia which remains for more than 15–20 min following the reduction of HbO_2 saturation to normoxic levels (Becker et al., 1996). A more definitive quantitation of an obligatory role for central hypercapnia in hyperoxic hyperventilation might benefit from an experimental model with Hb lacking the capability for regulating CO_2 release in response to HbO_2 saturation.

Another promising extra-CB stimulus to breathe may be found in alterations in redox state. Hyperoxic-induced reactive oxygen species (ROS) can react with various cellular targets including lipid bilayers, ion channels and various enzymatic systems, resulting in changes in membrane excitation, synaptic transmission, gene induction and cellular metabolism (Dean et al., 2004; Dröge, 2002). Evidence supporting these effects of ROS on ventilatory control include: (1) the positive correlation between systemic and medullary ROS production with the biphasic ventilatory responses to extra-CB hyperoxia and hypoxaemia (Fig. 1*C*) (Dean et al., 2004; Gourine & Funk, 2017); (2) the lingering stimulation of $\dot{V}_E$ which persists for many minutes following cessation of steady-state hyperoxia; (3) stimulation of RTN CO_2-sensitive chemoreceptor neurons via hyperoxia-induced ROS (Mulkey et al., 2003); and (4) the attenuation of the hyperventilatory response to hyperoxia achieved within the initial minutes of hyperoxia exposure via experimental blunting of ROS production and accumulation in humans (Fernandes et al., 2021).

In summary, when CB tonic input is present, findings using the Bisgard isolated CB preparation in awake or sleeping animals suggest that extra-CB sources contribute as much as 40-50% to the ventilatory response to whole-body hypoxia. Thus, sensory input from the carotid chemoreceptors is required for ventilatory stimulation in response to both carotid and extra-carotid chemoreceptor hypoxaemia. In unanaesthetized animals or humans, extra-CB hypoxia shows no depressive effect on eupnoeic breathing or on the ventilatory response to CB stimulation. Extra-CB hyperoxia also presents a powerful drive to breathe in the unanaesthetized animal and human. This response to extra-CB hyperoxia mimics the breathing pattern and respiratory muscle recruitment characteristics of the hypercapnic ventilatory response. The use of even a few minutes of hyperoxia or hypoxia in testing ventilatory response sensitivities must recognize the complexity and substantial impact of the multiple sites and mechanisms of action beyond the traditional modes of chemoreception. Limited evidence to date – including the significant effects of experimental blockade of ROS production – points to a significant role for ROS production in mediating this dose-dependent hyperoxic hyperventilation, although some contribution from CO_2 accumulating in the brain's extracellular fluid via release of carbamino CO_2 from Hb cannot be ruled out.

Chemoreceptor interdependence

Two distinct sets of chemoreceptors with neuronal connections directly to medullary respiratory pattern generator and presympathetic neurons account for most of the ventilatory and sympathetic nerve responses to changes in arterial blood gases at the carotid chemoreceptor and to medullary extracellular fluid CO_2/H^+ acting at the level of the RTN (Fig. 2*A*). In addition to the independent effects of each set of chemoreceptors influenced by changes in their own immediate environments, we now consider the several lines of evidence that have also revealed the strong modulatory effects of carotid chemoreceptor input on central chemoreceptor gain. Based on the following evidence we propose that these interdependencies influence sensitivity to hyper- and hypocapnia at the medullary chemoreceptor as well as enhance the cardiorespiratory effects of tonic carotid chemoreceptor activity.

Interdependent effects on CO_2 chemosensitivity.

- Phox2b, a key gene product proliferating in early embryonic development of the autonomic nervous system is strongly expressed in neurons that are part of an uninterrupted chain in a circuit that includes the carotid chemoreceptors and their afferents plus NTS projections to the RTN – the latter being the major site of medullary H^+ sensing (Guyenet et al., 2016).
- In anaesthetized intact rodents, systemic hypoxaemia was shown to stimulate RTN CO_2-sensitive neurons. This hypoxic-induced stimulatory effect was blocked via CBX (Takakura et al., 2006).
- The nature of this chemoreceptor interdependence was demonstrated using the Bisgard preparation in the awake canine, where inhibiting the isolated, perfused CB with hyperoxic and/or hypocapnic blood markedly depressed the ventilatory response slope to extra-CB hypercapnia via reduced V_T, fB, mean inspiratory flow–tidal volume/inspiratory time (V_T/T_i), and diaphragm EMG (EMG_{di}). Conversely, stimulating the isolated CB with hypoxaemia or hypercapnia enhanced the extra-CB hypercapnic ventilatory response slope (see Fig. 2*B*) (Blain et al., 2010; Smith et al., 2015).
- Bilateral CBX in humans, canines and rodents studied within a few days of denervation, i.e. allowing minimal time for control system remodelling, confirm the hyperadditive effects shown with the Bisgard preparation by revealing significant reductions in: (1) the extra-CB hyperoxic/hypercapnic ventilatory response slope (Dahan et al., 2007; Getsy et al., 2020; Rodman et al., 2001) (see Fig. 2*C*); and (2) the ventilatory response to focal cerebral metabolic acidosis in awake goats (Hodges et al., 2005).
- The apnoeas induced following transient ventilatory overshoots during sleep require relatively small reductions in P_aCO_2 when both the CB and systemic transient hypocapnia were present, as normally occurs in the intact human or animal. These findings contrasted with the failure of apnoea to occur when even substantial transient hypocapnia was produced in sleeping canines at either the isolated central or CB sites of chemoreception (Smith et al., 2007).

Alternative models of chemoreceptor interdependence. Our proposal of a hyperadditive interdependence of carotid with medullary chemoreceptors is supported by findings in unanaesthetized canines, humans and rodents with physiological levels of cardiorespiratory chemosensitivity and employing anatomical isolation of the carotid chemoreceptors from the systemic circulation (Fig. 2*B* and *C*). Contrary to our proposal, additive and even hypoadditive interdependencies have been reported in reduced rodent preparations with isolation of brainstem and peripheral chemoreceptors, and in humans and anaesthetized rodents whose chemoreceptors were not anatomically isolated. The relative merits of these preparations have been debated in detail (Duffin & Mateika, 2013; Teppema & Smith, 2013; Wilson & Day, 2013).

Given the wide range of experiments already completed on this question of interdependence, we do not have a

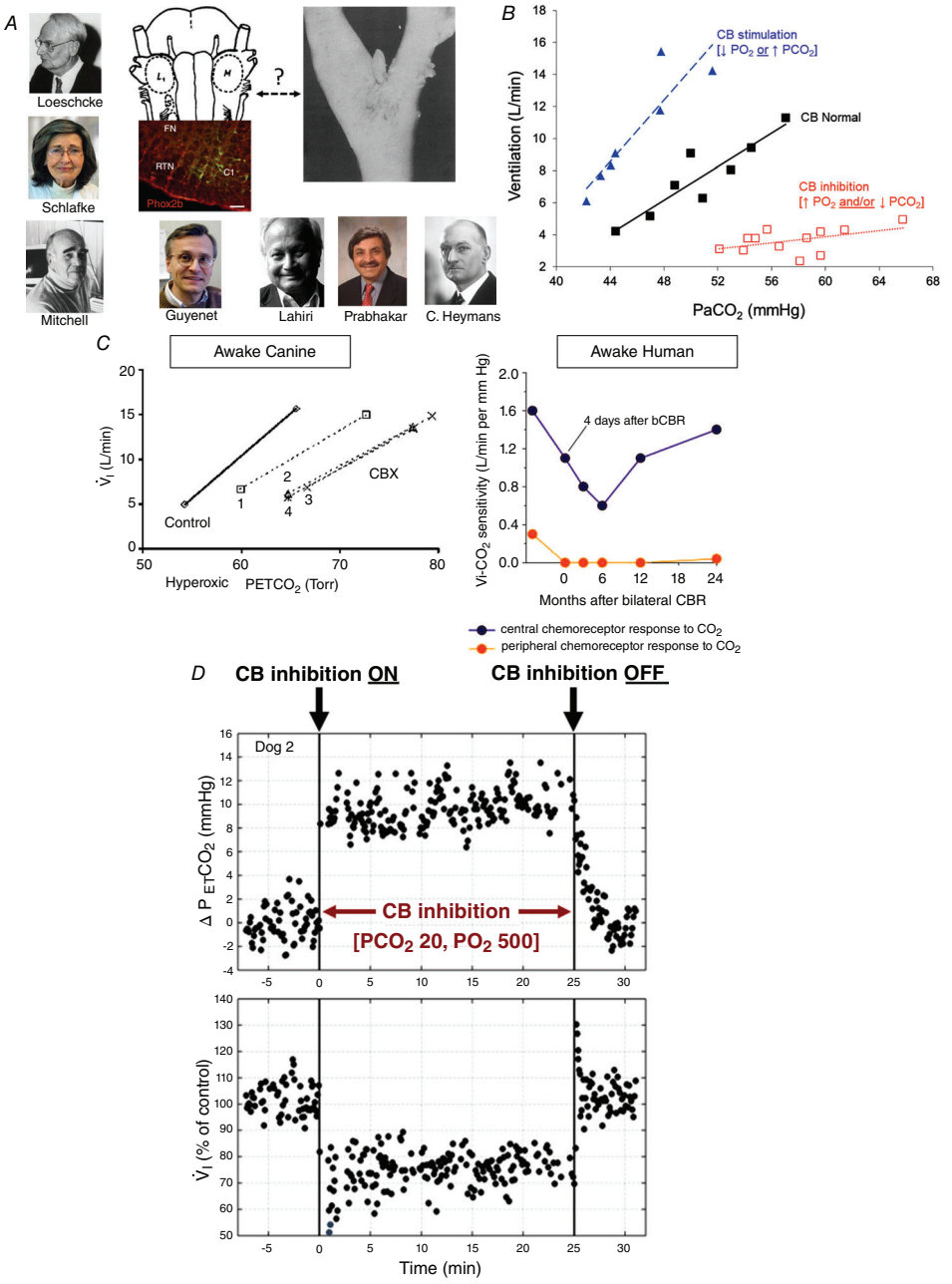

Figure 2. Carotid-medullary chemoreceptor interdependence
A, H^+-sensitive chemoreceptors were found to be located on the ventrolateral medullary surface by Hans Loeschke, Mariann Schlafke and Robert Mitchell in the mid-1960s. More recently, Patrice Guyenet and colleagues recorded from CO_2-sensitive neurons in the retrotrapezoid nucleus (RTN) – an area which is believed to serve as the major site of medullary H^+ sensing as well as an integrative site receiving synaptic input from the hypothalamus, lung stretch receptors, and the carotid chemoreceptors. Corneille Heymans was awarded the Nobel prize in 1938 for discovering the function of the CB and Nanduri Prabhakar has been instrumental over the past several decades in advancing our understanding of O_2 and CO_2-sensing mechanisms at the carotid chemoreceptor. The question posed in this illustration concerns the nature of the interdependence of central and peripheral chemoreceptors. Panels *B* and *C* support the view that carotid chemoreceptors exert a hyperadditive influence on central CO_2 sensitivity. Others using different approaches do not share this view (see text). *B*, using the Bisgard preparation in awake canines, Curtis A. Smith and colleagues showed that stimulating or disfacilitating input from the isolated CB via altering CB PO_2 and/or PCO_2 had marked hyperadditive effects on the ventilatory response to systemic hypercapnia. These hyperadditive effects of CB stimulation/disfacilitation on the central hypercapnic ventilatory response included hyperadditive effects on V_T, fB, V_T/T_i and EMG_{di}. Reproduced with permission from Blain et al. (2010) and Smith et al. (2015). *C*, when awake canines (Rodman et al., 2001) and humans (Dahan et al., 2007) were studied repeatedly over the initial few days immediately following bilateral CB denervation (CBX) the ventilatory

response slope to systemic hyperoxic hypercapnia was reduced by 30–70%. Also note in CBX humans the 'late' (presumably central) ventilatory response to hypercapnia fell over the initial 6 months post-CBX. Over the ensuing weeks and months, while the 'early' (presumably peripheral) CO_2 ventilatory response remained markedly reduced, the central CO_2 response gradually returned to control intact levels. This study uniquely included pre- and post-CBX longitudinal data in a small number of human patients, thereby allowing quantitation of the immediate and long-term effects of CBX on CO_2 responsiveness (Dahan et al., 2007). Modified and reproduced with permission from Dempsey, Xie et al. (2014). *D*, markedly inhibiting the isolated CB in the awake, air-breathing canine (via hyperoxic/hypocapnic CB perfusate) elicited an immediate 40–45% reduction in $\dot{V}_E$ and a 9–14 mmHg rise in P_aCO_2. Significant sustained reduction in V_T, fB, V_T/T_i, and EMG_{di} amplitude all accompanied the CB inhibition. Over the ensuing 25 min, $\dot{V}_E$ recovered only slightly despite a persistent substantial systemic and presumably CNS hypercapnic acidosis. Note the substantial overshoot of $\dot{V}_E$ above eupnoeic control when CB inhibition was suddenly removed revealing a strong drive to breathe induced by central hypercapnia that was prevented via inhibition of the isolated CB. Reproduced with permission (Blain et al., 2009).

specific proposal for the use of one model over others in arriving at a definitive resolution. However, given our own substantial experience as well as the wealth of available information bearing on this complex question, we now recommend a few principles as guides to future consideration of this fundamental problem. Firstly, the use of *both* central superimposed on a background of peripheral chemostimulation/disfacilitation *and* peripheral superimposed on a background of central stimulation/disfacilitation should be conducted in the *same* preparation to determine whether the 'order' of chemoreceptor perturbations is a determining factor in the nature of chemoreceptor interdependence. Secondly, reduced or anaesthetized preparations with markedly depressed ventilatory responsiveness to chemoreceptor stimuli and the potential for 'saturation' of respiratory motor output to multiple chemoreceptor and extra-chemoreceptor stimulation should be avoided in these experiments where the primary aim is to quantify changes in gain to multiple combined stimuli (Eldridge et al., 1981; Gourine et al., 2005; Melton et al., 1988). Thirdly, if intact preparations, i.e. without anatomical separation of peripheral and central chemoreceptors, are used (e.g. Milloy et al., 2022; Tin et al., 2012), then the use of systemic hypercapnia (via increased $FICO_2$) will stimulate *both* central *and* peripheral chemosensitive sites to varying degrees (Fig. 2*C*). Thus, interpretation of findings obtained in this intact preparation should consider that the ventilatory response to the superimposition of hypoxia (on systemic hypercapnia) is likely a reflection primarily of well-established hypoxic/hypercapnic interactive effects (Lahiri & DeLaney, 1975; Teppema et al., 2010) rather than the influence of peripheral–central interdependence. Fourthly, species may differ – at least between rodents and larger animals including humans – in the relative importance of peripheral *vs.* central chemoreception in the drive to breathe (Guyenet & Bayliss, 2022) as well as in the strength of the hypercapnic/hypoxic interactive effect (see *Discussion* (Tin et al., 2012)). These differences likely have an important bearing on comparing study findings. Finally, the recently described capability for selective ablation or optogenetic stimulation of CO_2-sensitive neurons in the RTN in awake rodents might provide another unique model permitting independent manipulation of chemoreceptor stimuli in a physiological, responsive setting (Souza et al., 2023).

Tonic CB contributions to eupnoea. Use of the Bisgard preparation in unanaesthetized animals has also revealed a major contribution of tonic CB activity plus peripheral–central chemoreceptor interdependence on the drive to breathe during normal air-breathing eupnoea. Note in Fig. 2*C* that with CB inhibition achieved via perfusion of the isolated CB with hyperoxic/hypocapnia blood, eupnoeic $\dot{V}_E$ was immediately and markedly reduced. Thereafter, systemic hypercapnia and acidosis persisted with only minor compensatory increases in $\dot{V}_E$ until the CB inhibition was removed (Blain et al., 2009). This substantial influence of removing CB tonic activity on the eupnoeic drive to breathe during air-breathing appears to reflect a dual effect, i.e. directly on the medullary respiratory pattern generator and indirectly on suppression of central CO_2 chemosensitivity (also see Fig. 2*B* and *C*). Recently, Souza et al. (Souza et al., 2023) used short-term ablation of RTN CO_2-sensitive neurons which elicited a suppression of eupnoeic ventilation and retention of CO_2 in awake and sleeping rodents which was similar in magnitude to that shown in Fig. 2*C* with acute carotid chemoreceptor disfacilitation.

These CB tonic influences on cardiorespiratory control have been shown to be markedly upregulated in conditions of chronic hypoxia, chronic heart failure, renal disease, chronic obstructed pulmonary disease and hypertension – all of which elicit significant increases in CB tonic influences on sympathetic nerve activity, blood pressure and sleep disordered breathing (Dempsey, Powell et al., 2014; Marcus et al., 2014; Pijacka et al., 2016). Attempts to ameliorate the causes and consequences of CB plasticity and heightened tonic CB activity in these disease states are underway (Niewinski et al., 2017; Pijacka et al., 2016).

In summary, we propose that the interdependence of medullary and peripheral chemoreceptors contributes substantially in a hyperadditive manner to the ventilatory

responses to CO_2 – findings which speak against the common practice of using hyperoxic hypercapnia during rebreathe tests in order to 'isolate' the medullary chemoreceptor CO_2 response (Duffin, 2011; Read & Leigh, 1967). Further, the carotid chemoreceptors appear to contribute about 30–40% of the drive to air-breathing eupnoea in health – likely reflecting the CB tonic input to both the medullary pattern generator and to the CO_2-sensing medullary chemoreceptors. These chemoreceptor interdependencies plus the evidence for substantial extra-CB influences of even short durations of hypoxaemia and hyperoxia on ventilation suggest that attempts to quantify specific chemoreceptor sensitivity/tonicity in intact preparations should be limited to the carotid chemoreceptors and to the use of only transient (rather than steady state) alterations in arterial blood gases (see e.g. in Fig. 1*D*). (Also see Teppema & Dahan, 2010 for details concerning the complexities of testing chemosensitivity in intact humans). As outlined above (see *Alternative models*) our proposal requires further investigation of the nature of chemoreceptor interdependence using a variety of experimental models and innovative approaches.

Chemosensitivity/central respiratory drive as major players in obstructive sleep apnoea

Sleep apnoea (OSA) is a highly prevalent condition even in the general population, with consequences for cardiovascular and metabolic diseases and their exacerbation (Dempsey et al., 2010; Peppard et al., 2013; Young et al., 2008; (Fig. 3*A*). Physiologically it has been a challenge to decipher how the sleeping state permits – or even provokes – such abnormal behaviour as repeated apnoeas and airway obstructions by a respiratory control system that during wakefulness is so precise and mechanically efficient. OSA is commonly perceived and treated as a problem of sleep-induced upper airway collapse. Below, we argue that CO_2 and chemoreception and the central drive to breathe also play major roles in the pathogenesis of OSA.

Undoubtedly, an anatomically compromised, highly compliant and collapsible airway is required to elicit repeated airway narrowing or complete obstruction during sleep (Dempsey et al., 2010; Eckert & Malhotra, 2008). Indeed, the loss of the 'wakefulness drive' to breathe is associated with marked reductions in the hypoglossal nerve motor activity and EMG activity of major dilator muscles of the upper airway, leading to a narrowed and highly compliant and collapsible airway during sleep (Horner et al., 2002). However, loss of wakefulness also unmasks the critical dependence of central respiratory motor output on small changes in P_aCO_2 as shown by the occurrence of hypoventilation and central apnoeic episodes in response to transient ventilatory overshoots accompanied by hypocapnia (Dempsey, Xie et al., 2014) (Fig. 3*B*). Monitoring of respiratory-related EEG activity has revealed a 'cortical-sub-cortical cooperation' during transient ventilatory overshoots which would serve to preserve ventilation during wakefulness but would be lost or suppressed during NREM sleep (Dubois et al., 2016). Studies in the sleeping canine have shown that apnoeas following transient hyperventilation in sleep require: (1) intact carotid chemoreceptors (Nakayama et al., 2003); (2) intact vagally mediated lung stretch receptors (Chow et al., 1994); and (3) hypocapnia acting at both peripheral and central chemoreceptors (Smith et al., 2007). Further, OSA patients with high CO_2 sensitivity and control system 'loop gain' together with a collapsible upper airway, are especially prone to experiencing oscillatory changes in central respiratory motor output and repeated airway obstructions during sleep (Dempsey, Xie et al., 2014; Onal et al., 1985).

Thus, several types of experiments have shown significant effects of altering the drive to breathe on airway calibre during sleep: (1) using hypoxic exposure to create an unstable respiratory output during sleep elicited high airway resistance and even complete airway closure at the nadir of the oscillating drive to breathe (Hudgel et al., 1987; Warner et al., 1987); (2) spontaneous central apnoeas during sleep elicited narrowing/closure of the pharyngeal airway (Badr et al., 1995) (see Fig. 3*C*); and (3) reducing the loop gain (via hyperoxic inhalation) or both reducing loop gain and recruiting inspiratory drive and upper airway muscle dilators (via CO_2 inhalation or acetazolamide administration) stabilized central respiratory motor output and significantly reduced airway obstruction in significant numbers of OSA patients (Bordier et al., 2016; Edwards et al., 2013; Sands et al., 2018; Wellman et al., 2008; Xie et al., 2013).

The above-cited argument for a role of a reduced central drive to breathe in airway obstruction has been made based on findings from several observational studies using relatively small numbers of subjects. Recently, however, this hypothesis has been more comprehensively tested in 50 moderate-to-severe OSA patients examining almost 5000 obstructive events. The investigators used a high-resolution oesophageal/gastric EMG electrode to quantify the 'neural drive' to inspiration along with measurements of genioglossus EMG (EMG_{gg}) activity as a measure of central neural drive to a major upper airway muscle dilator (Gell et al., 2022). Two types of obstructive events were identified which revealed precipitating causes (see Fig. 3*D*).

- In 40% of the patients a gradually reduced flow rate leading to airway obstruction was accompanied by reduced EMG_{gg} but no change in EMG_{di}. EMG_{di} rose only during the very latter stages of the obstructive apnoea (likely in response to increased chemoreceptor

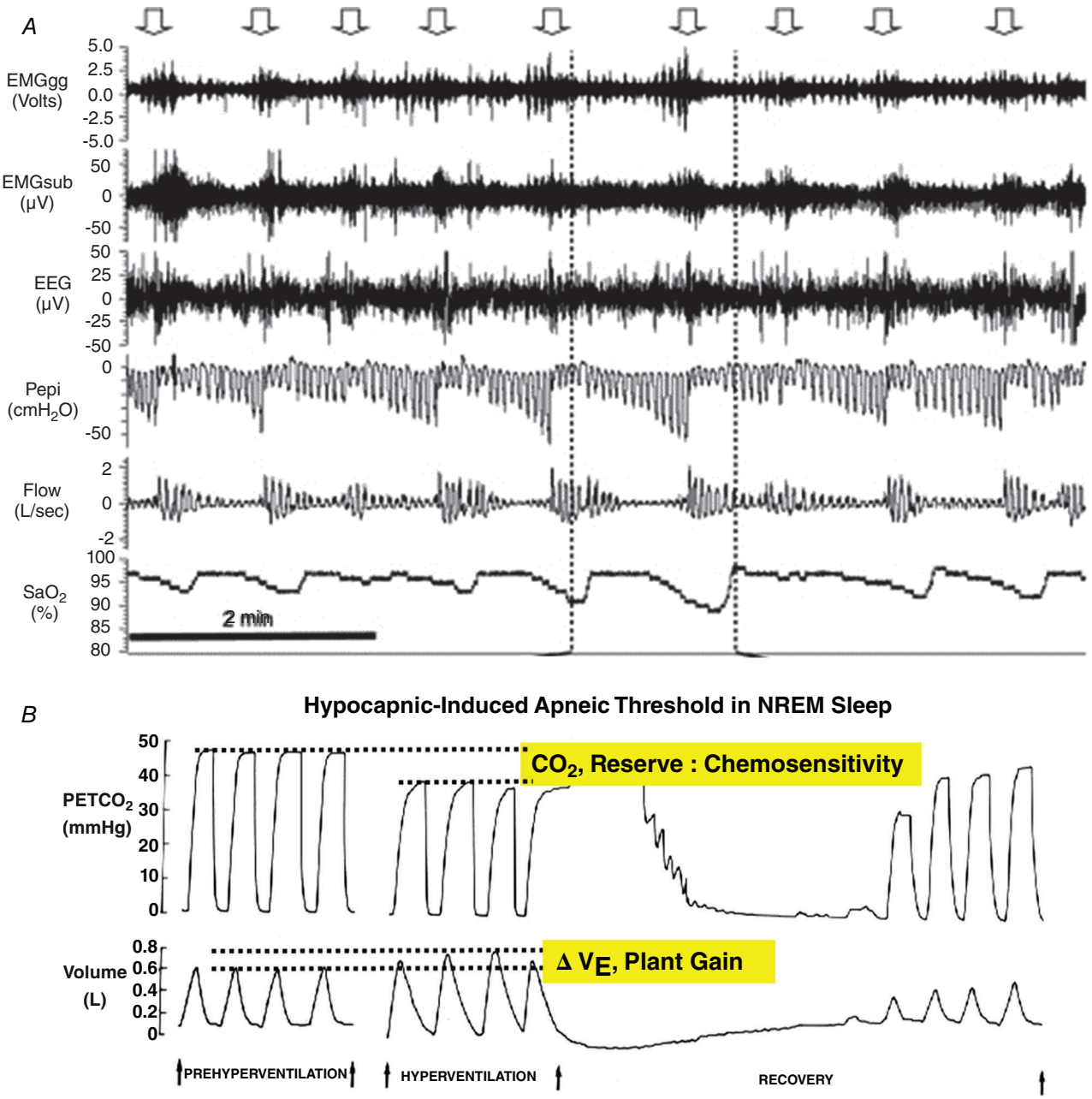

Figure 3. Contributions of chemoreception/central drive to breathe to obstructive sleep apnoea (OSA)
A, polysomnographic tracings of severe obstructive sleep apnoea (OSA). Note: (1) the reduction in upper airway dilator genioglossus EMG (EMG_{gg}) accompanying each obstruction; (2) the repeated O_2 desaturations resulting from severely impaired (hypopnea) or absent (apnoea) airflow despite continued breathing effort, as indicated by increasing amplitude in epiglottic pressure(P_{epi}); and (3) the cyclical breathing pattern that ensues as the patient oscillates between sleep and transient arousals (downward pointing arrows). Reproduced with permission (Eckert & Malhotra, 2008). *B*, sleep unmasks a sensitive, hypocapnic-induced apnoeic threshold, as elicited here by a mechanical ventilator-induced transient hyperventilation followed by apnoea. The tendency toward breathing instability is determined by the components of 'loop gain' (Khoo, 2000): (1) 'controller gain' or CO_2 chemosensitivity represented here as the difference between eupnoeic and apnoeic threshold P_aCO_2 or 'CO_2 reserve'; and (2) the increase in $\dot{V}_E$ above eupnoea required to produce the amount of hypocapnia needed to reach the apnoeic threshold, i.e. 'plant gain' (Dempsey, 2019). The two references cited contain detailed descriptions of the components of loop gain and experiments which demonstrate their influence on breathing stability during sleep in health and disease. Figure modified and reproduced from Skatrud & Dempsey (1983). *C*, central apnoea during NREM sleep precipitating upper airway closure. The images of the pharyngeal airway cross-section were obtained via fiberoptic nasopharyngoscopy in sleeping humans. Continuous measures of airflow and oesophageal pressure are also shown. The cessation of airflow and pressure swings indicates the onset of a central apnoea at which time

stimulation) with the obstruction terminating in a transient arousal from sleep. These findings fit the 'classic' conventional view of OSA pathogenesis as sleep -induced airway obstruction.

- In 60% of patients the reduction in airflow leading to an obstructive apnoeic event coincided with a corresponding gradual reduction in EMG_{di} (and EMG_{gg}), culminating in airway obstruction. Both

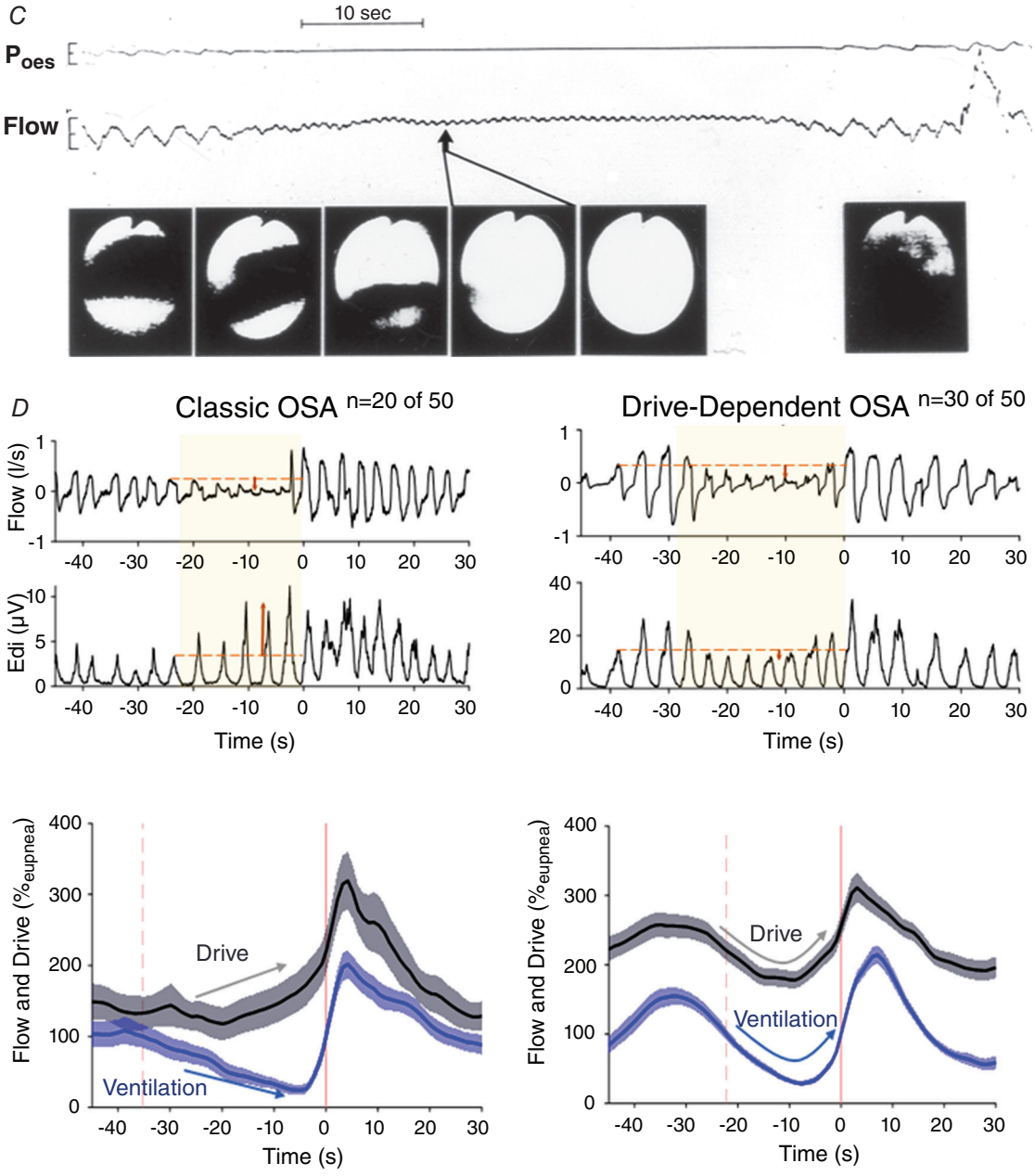

Figure 3. Continued

the airway is open. A few seconds later the airway closes and remains closed until inspiratory efforts begin and arousal occurs at end apnoea. Reproduced with permission (Badr et al., 1995). *D*, measurements of airflow and integrated diaphragm EMG (EMG_{di}) immediately prior to and during an obstructed apnoea. The top two panels show individual traces and the bottom two panels show ensemble averages in two groups of OSA patients. (1) On the left side is a 'classic' OSA patient in whom the reduction in airflow leading to airway obstruction is not attended by a coincident decline in the drive to breathe, i.e. EMG_{di}; and (2) on the right side are OSA patients in whom declines in EMG_{di} and airflow coincide, preceding the obstruction. Modified and reproduced with permission from Gell et al. (2022).

EMG_{gg} and EMG_{di} then rose during the latter portions of the apnoea, ending with an arousal.

In summary, the role of a highly state-dependent, CO_2-sensitive drive to breathe coinciding with that of upper airway dilator muscle neural modulation, results in repeated airway obstruction in those patients with pharyngeal airways susceptible to closure. Importantly, this scenario in which a declining central drive to breathe precipitates airway obstruction appears to be highly prevalent in OSA patients. These findings suggest that interventions which elevate and stabilize the drive to breathe may be of value in alleviating airway obstruction in a majority of OSA patients. Given the reported effects of sex and age on OSA prevalence and its pathogenesis (Huang et al., 2018), it is important that future studies address the role of these risk factors as determinants of the relative importance of a declining/oscillating neural drive to breathe in OSA.

Conclusion

This brief review has focused on the complexities and the clinical importance of chemoreception. Oxygen sensing occurs at multiple sites outside of the carotid chemoreceptor eliciting substantial effects on cardio-respiratory control. CO_2 and O_2 sensing in and outside of the central nervous system function in a highly interdependent fashion in their influence on cardiorespiratory function, including the normal eupnoeic drive to breathe. Removal of the wakefulness stimulus during NREM sleep unmasks a highly sensitive influence of transient alterations in P_aCO_2 on the drive to breathe and also on upper airway calibre, often resulting in repeated airway obstructions. Collectively, excessive chemoreceptor sensitivity and especially elevated tonic chemoreceptor activity appear to contribute significantly to the pathogenesis and exacerbation of several chronic diseases.

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Additional information

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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