*J Physiol* 603.9 (2025) pp 2487–2516



The Journal of Physiology

TOPICAL REVIEW

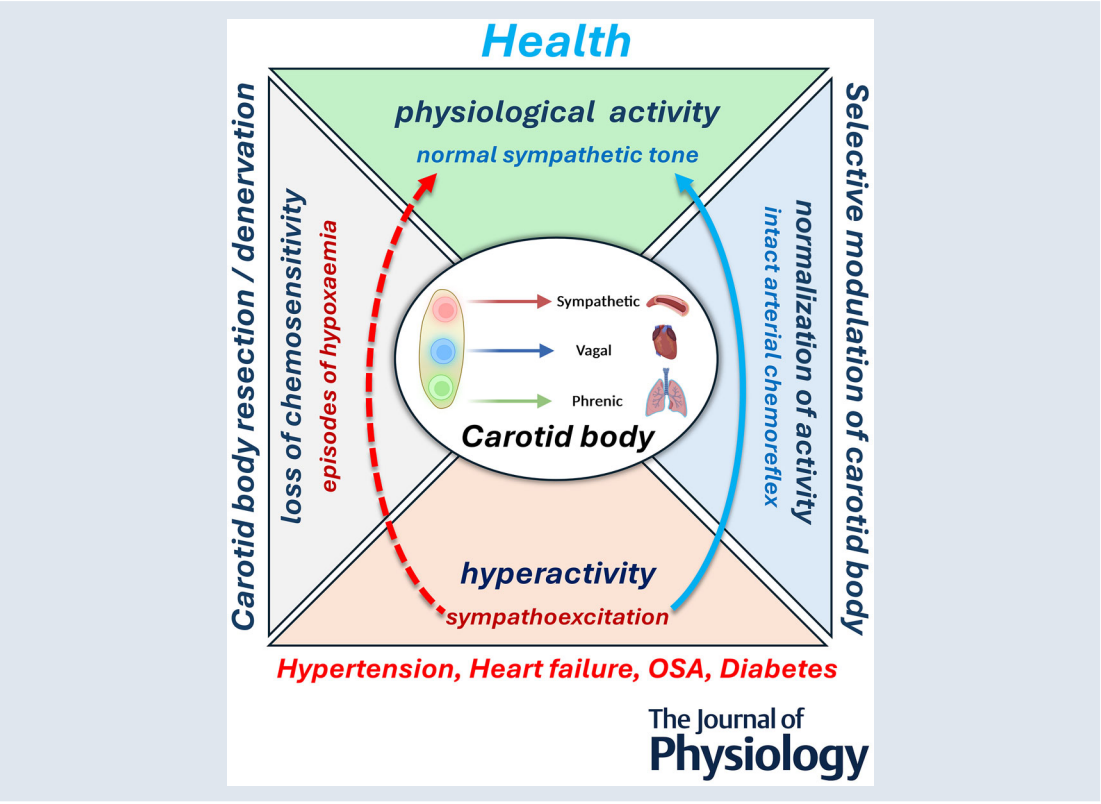
# Translating physiology of the arterial chemoreflex into novel therapeutic interventions targeting carotid bodies in cardiometabolic disorders

Tymoteusz Żera[1], Bartłomiej Paleczny[2], Maciej Siński[3], Sílvia V. Conde[4], Krzysztof Narkiewicz[5], Piotr Ponikowski[6], Julian F.R. Paton[7] and Piotr Niewiński[6]

[1]*Department of Experimental and Clinical Physiology, Medical University of Warsaw, Warsaw, Poland*
[2]*Department of Physiology and Pathophysiology, Wroclaw Medical University, Wroclaw, Poland*
[3]*Department of Internal Medicine, Hypertension and Vascular Diseases, Medical University of Warsaw, Warsaw, Poland*
[4]*iNOVA4Health, NOVA Medical School, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Lisbon, Portugal*
[5]*Department of Hypertension and Diabetology, Medical University of Gdańsk, Gdańsk, Poland*
[6]*Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland*
[7]*Manaaki Manawa – The Centre for Heart Research, Department of Physiology, Faculty of Medical & Health Sciences, University of Auckland, Auckland, New Zealand*

Handling Editors: Laura Bennet & Ken O'Halloran

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP285081#support-information-section).




J.F.R.P. is the senior author.



DOI: 10.1113/JP285081

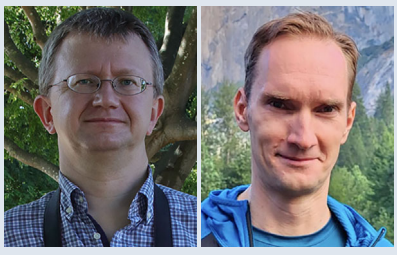
**Abstract figure legend** The carotid body develops aberrant high activity in chronic heart failure, resistant hypertension, obstructive sleep apnoea (OSA) and diabetes. Hyperactivity of the carotid body leads to both high tonicity and increased sensitivity of the arterial chemoreflex with resultant sympathoexcitation. This observation has led to several successful attempts at removing or denervating the carotid bodies to restore normal sympathetic activity in humans. However, such interventions are accompanied by loss of chemosensitivity resulting in episodes of hypoxia. The arterial chemoreflex comprises an integrative multi-system response. Accumulating evidence indicates that specific reflex components may be preferentially conveyed by functionally distinct transmitter systems. We discuss the exciting new discoveries of GLP-1 receptors, purinergic receptors, glutamate–GABA system, autonomic efferent innervation and regulation of blood flow in the CB and how they open new avenues for novel treatments modulating aberrant activity of the carotid body by selectively targeting specific receptors, mediators and neural pathways to correct distinct responses of the carotid body-evoked arterial chemoreflex, but sparing its physiological function.

**Abstract** This review resulted from a conference on the pathological role of arterial chemoreflex and carotid bodies in cardiometabolic diseases held at the 27th Congress of the Polish Cardiac Society in September 2023 in Poznan, Poland. It reflects the contribution of Polish researchers and their international collaborations, which have been fundamental in the development of the field. Aberrant activity of the carotid bodies leads to both high tonicity and increased sensitivity of the arterial chemoreflex with resultant sympathoexcitation in chronic heart failure, resistant hypertension and obstructive sleep apnoea. This observation has led to several successful attempts of removing or denervating the carotid bodies as a therapeutic option in humans. Regrettably, such interventions are accompanied by serious respiratory and acid–base balance side-effects. Rather than a single stereotyped reaction, arterial chemoreflex comprises an integrative multi-system response to a variety of stimulants and its specific reflex components may be individually conveyed at varying intensities. Recent research has revealed that carotid bodies express diverse receptors, synthesize a cocktail of mediators, and respond to a plethora of metabolic, hormonal and autonomic nervous stimuli. This state-of-the-art summary discusses exciting new discoveries regarding GLP-1 receptors, purinergic receptors, the glutamate–GABA system, efferent innervation and regulation of blood flow in the carotid body and how they open new avenues for novel pharmacological treatments selectively targeting specific receptors, mediators and neural pathways to correct distinct responses of the carotid body-evoked arterial chemoreflex in cardiometabolic diseases. The carotid body offers novel and advantageous therapeutic opportunities for future consideration by trialists.

(Received 15 October 2024; accepted after revision 10 March 2025; first published online 5 April 2025)
**Corresponding authors** Tymoteusz Żera: Department of Experimental and Clinical Physiology, Medical University of Warsaw, Poland; Piotr Niewiński: Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland. Email: piotr.niewinski@umw.edu.pl; tymoteusz.zera@wum.edu.pl

## Introduction

Since the early 1970s many academic and clinical researchers in Poland have focused on understanding the carotid body (CB) in health and disease (Kubin et al., 1985; Lipski et al., 1976, 1977; Majcherczyk & Willshaw, 1973; Majcherczyk et al., 1974; Pokorski & Lahiri, 1981, 1983; Przybylski, 1978, 1981; Przybylski et al., 1980; Trzebski



**Tymoteusz Żera** received his PhD from the Medical University of Warsaw, where he teaches medical physiology. He trained in internal medicine in the National Institute of Cardiology in Warsaw. His research interests encompass the physiology of the circulatory system and pathophysiology of cardiovascular diseases. His research focuses on hormonal and nervous regulation of the cardiovascular system in experimental models of hypertension and heart failure. He is a member of the Polish Physiological Society, the Polish Society of Cardiology and the European Society of Cardiology. **Piotr Niewiński** is a clinical scientist and active cardiologist specializing in heart failure and invasive cardiac electrophysiology. He received his PhD from Wroclaw Medical University in 2015 for his research has focused on the pathophysiology of peripheral chemoreceptors in systolic heart failure. His passion for translational research led to his involvement in a first-in-human trial of carotid body modulation. He is a member of the Polish Society of Cardiology and the European Society of Cardiology.

et al., 1982). Most notably, Professor Andrzej Trzebski pioneered contributions in the field and his discoveries have formed the basis on which numerous basic and clinical studies have been founded (Trzebski, 1992). This review has resulted from a conference to celebrate the contribution of Polish scientists on the pathological role of arterial chemoreflex and CBs in cardiometabolic diseases. It was held at the 27th Congress of the Polish Cardiac Society in September 2023 in Poznan, Poland. It reflects and summarizes the major contribution of Polish researchers and their international collaborations, which have been fundamental for the development of the CB research field.

The discovery that the CBs develop aberrant activity in chronic heart failure, type 2 diabetes, resistant hypertension and obstructive sleep apnoea (OSA) (Abdala et al., 2012; Chua, Clark et al., 1996; Narkiewicz et al., 1999; Ribeiro et al., 2013; Sun et al., 1999a; Trzebski et al., 1982) set up the challenge of how best to quench this activity for therapeutic benefit. This aberrant discharge contained both high background tonicity as well as increased reflex sensitivity (akin to allodynia in the pain field) of the arterial chemoreflex with resultant autonomic imbalance and gross sympathoexcitation (Felippe, Del Río et al., 2023). This observation first led to several surgical studies aimed at removing or denervating the CBs as a therapeutic option in both animals (Abdala et al., 2012; Del Río et al., 2013a, 2016; Fletcher, Lesske, Behm et al., 1992; Marcus et al., 2013; Paton, Sobotka et al., 2013; Ribeiro et al., 2013) and humans (Lobo, 2023; Narkiewicz et al., 2016; Niewinski, Janczak et al., 2013, 2014, 2017). Being outside the CNS, although connected to it, has distinct advantages for localized targeting. However, because the CB is a multi-modal organ controlling multiple autonomic, hormonal and behavioural functions such interventions are accompanied by serious adverse effects such as respiratory disturbances especially during sleep and acid–base balance deficits (Bardsley et al., 2023; Niewinski et al., 2021). Rather than a single stereotyped reaction, the arterial chemoreflex comprises an integrative multi-system response with specific reflex components being individually conveyed by functionally distinct transmitter systems. It is now appreciated that CBs express diverse receptors, synthesize multiple transmitters and modulators, and respond to a plethora of stimuli including blood gases, blood pH, the autonomic nervous system, blood-borne metabolites and hormones. We discuss the exciting new discoveries of GLP-1 receptors, purinergic receptors, glutamate–GABA system, autonomic efferent innervation and regulation of blood flow in the CB and how they open new avenues for novel treatments selectively targeting specific receptors, mediators and neural pathways to correct distinct responses of the CB-evoked arterial chemoreflex in cardiometabolic diseases.

## Classic physiology of the arterial chemoreflex

**Arterial chemoreflex – oxygen sensing and acute/chronic adaptations to low oxygen.** The peripheral chemoreflex encompasses an intricate and highly contextual constellation of cardiorespiratory responses to a spectrum of blood-borne stimuli (Kumar & Bin-Jaliah, 2007), hypoxia being the most significant from the evolutionary perspective (Iturriaga et al., 2021; Marshall, 1994; Milsom & Burleson, 2007; Teppema & Dahan, 2010; Zera et al., 2019). Its paramount goal is to safeguard vital organs, particularly the brain and heart, from hypoxia by monitoring blood oxygen ($O_2$) levels and fine-tuning ventilation, cardiac function, vascular resistance, adrenomedullary output and blood pressure. Two topographically distinct sets of chemoreceptors, embedded in small, ellipsoidal structures known as *bodies*, have been featured in humans, the carotid and aortic bodies. The former are located strategically at the gateway to the brain, in the carotid bifurcation, whereas the latter populate the dorsal aspect of the ascending aorta (Iturriaga et al., 2021; Marshall, 1994; Milsom & Burleson, 2007; Paton, Ratcliffe et al., 2013; Teppema & Dahan, 2010; Zera et al., 2019). Such localities allow blood constituents to be sensed as arterial blood enters the cerebral and coronary circulations.

While our understanding comes primarily from CB studies, similar mechanisms probably operate in aortic bodies (Prabhakar, 2016a). Despite decades of research, the exact nature of the $O_2$ sensing mechanism in the carotid/aortic bodies remains elusive (Iturriaga et al., 2021; Ortega-Sáenz & López-Barneo, 2020; Prabhakar, 2016a). The widely accepted framework holds that glomus cells (type I cells) of the CB are the actual oxygen-sensitive units. Hypoxia is believed to close $K^+$ channels in the glomus cell's membrane, leading to depolarization, $Ca^{2+}$ influx via voltage-gated channels and $Ca^{2+}$-dependent neurotransmitter release onto the receptors on the afferents of the petrosal ganglion neurons synaptically opposed to the glomus cells. Acetylcholine and ATP are prime candidates for excitatory neurotransmitters, although multiple other molecules [including dopamine, histamine, nitric oxide (NO) and endothelin-1] appear to modulate $O_2$ sensing. The conundrum here is the nature of 'the oxygen sensor' in type I cells. Simplistic concepts, positioning the *acute* oxygen sensor either within the membrane ($O_2$-dependent $K^+$ channels) or in the mitochondrial oxidative phosphorylation machinery, have been refuted (for reviews see: Iturriaga et al., 2021; López-Barneo et al., 2016; Ortega-Sáenz & López-Barneo, 2020; Rakoczy & Wyatt, 2018), and a hybrid model was proposed, claiming that hypoxia impacts production of certain molecules within the mitochondria (i.e. ATP, NADPH, reactive oxygen species), and in turn alters the membrane $K^+$ currents, leading to depolarization,

$Ca^{2+}$ entry and transmitter release (Iturriaga et al., 2021; Ortega-Sáenz & López-Barneo, 2020). Other mechanisms include: (i) hypoxia-induced inhibition of carbon monoxide (CO) production, which, in turn, enhances hydrogen sulphide ($H_2S$) production, and results in $K^+$ channel inhibition (Peng et al., 2010, 2017), and (ii) accumulation of lactate under low-oxygen conditions, with subsequent activation of the olfactory receptor – Olfr78 (Chang et al., 2015; Chen et al., 2018). Furthermore, the CB appears to contain glomus cells of distinct phenotypes varying in receptors and enzymes expressed, which determine their differential responsiveness to stimuli (see for a review: Zera et al., 2019).

The CB displays remarkable functional and structural plasticity when subjected to chronic hypoxia (Iturriaga et al., 2021; Ortega-Sáenz & López-Barneo, 2020; Prabhakar et al., 2022). Short-term chronic hypoxia (hours to days, i.e. sojourn at high altitude) enhances ventilation in a biphasic manner, with an initial increase (5–7 min) followed by stabilization at the slightly higher level. Ventilatory adaptation is accompanied by sympathetic activation, and resultant blood pressure elevation, offset within the first hours by local vasodilatory effects of hypoxia. A spectrum of modifications of the CBs at cellular and whole-organ levels have been proposed as potential contributors, including increased $Na^+$ and/or $Ca^{2+}$ channel density, lowered $K^+$ current amplitude, upregulation of the dopaminergic system, cholinergic system, local angiotensin generating-system, endothelin-1 and endothelin A receptors, and increased proinflammatory cytokines. Furthermore, data from animal models suggest that Olfr78 is essential for cardio-respiratory adaptation to hypoxia (Wang et al., 2021). Hypoxia-induced proliferation and differentiation of multipotent adult neural crest-derived stem cells (arising from sustentacular type II cells) into new glomus cells, endothelial cells and smooth muscle cells may underlie long-recognized CB enlargement under chronic hypoxia, resulting in an increased afferent input to the brainstem (López-Barneo et al., 2016; Ortega-Sáenz & López-Barneo, 2020). Hypoxia-inducible factors (HIFs), HIF-1 and HIF-2, are likely to mediate these adaptations, possibly by enhancing expression of endothelin-1 and promoting hyperplasia and neovascularization (Cheng et al., 2020; Lam et al., 2006; López-Barneo, 2022; Prabhakar et al., 2022; Prange-Barczynska et al., 2024).

Contrary to short-term exposures, long-term chronic hypoxia, as experienced by high-altitude natives, results in decreased baseline ventilation and blunted hypoxic ventilatory responsiveness ('hypoxic desensitization'), which is accompanied by lowered blood pressure. Increased intra-CB dopaminergic transmission, elevated production of gaseous messengers (NO and CO) and neovascularization have been suggested as underling mechanisms (Ortega-Sáenz & López-Barneo, 2020; Prabhakar et al., 2022).

**Arterial chemoreflex – sympathoexcitation, phrenic activity/hyperventilation, brady/tachycardia.** The net effect of arterial chemoreceptor stimulation with the acute hypoxia test in humans includes increased rate and depth of breathing, peripheral sympathoexcitation, tachycardia and blood pressure elevation (Gonzalez et al., 1994; Iturriaga et al., 2021; Marshall, 1994; Saito et al., 1988; Teppema & Dahan, 2010; Zera et al., 2019). Notably, the contribution of carotid and aortic subsets of chemoreceptors seems to be different in magnitude or even antagonistic, and modified by other reflex mechanisms (Comroe & Mortimer, 1964; Iturriaga et al., 2021; Marshall, 1994; Prabhakar & Peng, 2004). Heart rate acceleration is typically observed in human studies employing hypoxic or hypercapnic provocations, but direct stimulation of the CB with adenosine administrated into the carotid artery induced bradycardia, not tachycardia (Tubek et al., 2016), thereby confirming the cardioinhibitory effects of the CB activation found in animal models (Comroe & Mortimer, 1964). No change in hypoxia-induced tachycardia after volitional restriction of the hypoxic ventilatory response (HVR) in healthy subjects (Paleczny et al., 2019; Siebenmann et al., 2019) indicates that the tachycardic response, contrary to animal models (de Daly & Scott, 1958; Karim et al., 1980; Kato et al., 1988; Scott, 1966), is not secondary to enhanced ventilation and concomitant activation of pulmonary stretch receptors, but probably represents the original aortic body response. Eventually, the effect of acute hypoxia on peripheral vascular resistance reflects opposing actions of local hypoxic vasodilatation and sympathetically mediated vasoconstriction (Marshall, 1994; Weisbrod et al., 2001). The former predominates in healthy subjects, leading to a decrease in vascular resistance, whereas the exaggerated sympathetic response (along with impaired endothelial function) observed in heart failure outbalances the local effects of hypoxia, thereby producing an increase in the resistance (di Vanna et al., 2007; Nazaré Nunes Alves et al., 2012). A recent study by Tubek et al. (2021) in heart failure patients employing acute hyperoxia exposure corroborates these conclusions.

The CB-evoked reflex comprises a variety of responses that allow for integrated multi-system adaptations to low oxygen levels and disturbances in body homeostasis. These include endocrine responses marked by vasopressin release (Share & Levy, 1966; Wilson et al., 1987), release of catecholamines from the adrenal medulla (Critchley et al., 1980, 1982), basal and exercise-dependent glucagon liberation (Koyama et al., 2001), and secretion of ACTH and cortisol (Marotta, 1972; Raff et al., 1984)

as anti-inflammatory responses. Furthermore, the CB-evoked reflex triggers haematological, circulatory and renal reactions manifested by an increase in haematocrit (Raff et al., 1984), contraction of spleen capsule, mobilization of blood volume, vasoconstriction and venoconstriction (Emans et al., 2024; Hoka et al., 1989; Kahler et al., 1962; Pelletier & Shepherd, 1972), increase in cerebral blood flow (Ponte & Purves, 1974), increase in coronary blood flow and cardiac contractility (Hoka et al., 1989; Ito & Feigl, 1985; Kahler et al., 1962; Pachen et al., 2021), and reduced renal blood flow and sodium excretion (Karim et al., 1987). Finally, it also encompasses alterations in gastrointestinal motility and secretion (Kimura et al., 1993; Sinski et al., 2002), emetic response (Uchino et al., 2006), inhibition of sympathetic nerves to the brown adipose tissue (Madden & Morrison, 2005), bronchoconstriction (Denjean et al., 1991; Jendzjowsky et al., 2018; Moraes et al., 2021), sensation of breathlessness (Davidson et al., 1974), and behavioural responses with arousal and fight or flight reaction (Bizzi et al., 1961; Hilton & Marshall, 1982; Marshall, 1994).

**Arterial chemoreflex – integrative multi-system response.** The polymodal sensing properties of CBs reject the notion that glomus cells are homogenously responding to various modalities and intensities of stimuli to uniformly elicit all components of the chemoreflex. Rather, there are glomus cells or glomus cell clusters that show selectivity/preference for specific stimuli allowing for varied magnitude of responses and preferential engagement of some, but not all, components of the arterial chemoreflex (Gold et al., 2022; Zera et al., 2019). Functional studies indicate that glomus cells form distinct populations responsive only to hypoxia, acidity, or to both hypoxia and acidity (Lu et al., 2013). Furthermore, chemosensitive glomus cells and their clusters have unique neurochemical phenotypes in relation to expressed enzymes, receptors, transmembrane transporters and transmitters. These glomus cells and their clusters form synaptic connections of various morphologies with afferent myelinated and non-myelinated fibres (for a detailed review see Zera et al., 2019). The CB afferents also exhibit distinct morphological (McDonald & Mitchell, 1975) and electrophysiological properties (Fidone, & Sato, 1969), and different sensitivities to oxygen levels (Biscoe et al., 1970; Niu et al., 1990; Vidruk et al., 2001). The afferent fibres from the CB project to distinct regions of the nucleus of the solitary tract (NTS) in the medulla oblongata (Claps & Torrealba, 1988; Donoghue et al., 1984; Erickson & Millhorn, 1994; Finley & Katz, 1992; Paton et al., 2001) as well as to extra-NTS regions, including the area postrema, dorsal vagal motoneurons and the nucleus ambiguus, at least in the rat (Erickson & Millhorn, 1994; Finley & Katz, 1992; Paton et al., 2001). Furthermore, at least a subpopulation of second-order NTS neurons is solely chemoreceptive and distinct from baroreceptive ones (Accorsi-Mendonca et al., 2011; Paton et al., 2001) and directly projects to the rostral ventrolateral medulla (RVLM) (Accorsi-Mendonca et al., 2011; Kline et al., 2010) or to the retrotrapezoid nucleus (RTN) containing central chemoreceptors (Takakura et al., 2006). Based on these premises, we proposed the ribbon cable hypothesis that illustrates how glomus cells and their afferents characterized by distinct functional and phenotypic properties may form distinct/separate/individual pathways connecting the CB with the brainstem allowing for selective or preferential engagement of various effectors of the arterial chemoreflex (Gold et al., 2022) (Fig. 1; Zera et al., 2019). One of the striking examples of distinct CB connectivity is arterial chemoreflex-evoked concomitant sympathoexcitation to the cardiovascular system and inhibition of sympathetic nerves to the brown adipose tissue (Madden & Morrison, 2005). Such organization of the arterial chemoreflex would also explain selective augmentation of sympathetic outflow seen in hypertension (McBryde et al., 2017; Paton, Sobotka et al., 2013; Pijacka et al., 2016; Sinski et al., 2012), and highly selective silencing of sympathetics without significant effect on the respiration by pharmacological inhibition of P2X3 receptors in the CB in a spontaneously hypertensive rat model of essential hypertension (Pijacka et al., 2016). Collectively, available evidence supports the notion that the intricate connectivity of CBs to the brain consists of separate pathways allowing, at least in part, for selective activation/modulation of the reflex responses. Carefully designed experiments *in situ* and *in vivo* should test if stimulation of a given cluster or phenotypically distinct glomus cell population is relayed throughout separate neural networks allowing for control of distinct effector responses of the arterial chemoreflex.

The vasculature of CBs also shows heterogeneity manifested by arterial–venous polarity within the CB, presence of microcirculation consisting of large-diameter capillaries encompassing glomus cells and smaller-diameter capillaries with surrounding pericytes bypassing glomus cells, and arterio-venous anastomoses, together allowing for a reduction of CB blood flow or redistribution of the flow through various lobules or glomus cell clusters of the CB (Brognara et al., 2021; Gold et al., 2022). The functional consequences of these circulatory features are yet to be revealed.

**Chemoreflex sensitivity and tonicity under pathologic conditions.** Since CBs are highly sensitive to oxygen delivery, arterial $O_2$ and carbon dioxide ($CO_2$) levels, low blood pH and reduced blood flow, all clinical states that alter gas exchange or peripheral blood flow

will influence peripheral chemoreceptor sensitivity. CB chemoreceptors have a significant physiological activity in normoxia called tonic activity (Binet & Dejours, 1962). Various studies have documented augmented tonic chemoreflex activation, or hypertonicity of the reflex (Felippe, Del Río et al., 2023), contributing to resting sympathetic nerve activation under pathological conditions in either a normoxic state, such as patients presenting with sleep apnoea investigated during wakefulness (Narkiewicz et al., 1998) or hypoxaemic as a result of chronic obstructive lung disease (Heindl et al., 2001) or pulmonary arterial hypertension (Velez-Roa et al., 2004). In hypertensive patients, the CBs exhibit hypertonicity, and their deactivation elicits reductions in blood pressure, peripheral resistance and sympathetic activity (Izdebska et al., 1996, 1998; Sinski et al., 2012, 2014; Tafil-Klawe et al., 1985). Even in healthy subjects, a reduction of chemoreceptor tonic activity using hyperoxic gas mixtures diminishes sympathetic outflow measured by microneurographic methods (Seals et al., 1991). In contrast to hypertonicity, the sensitivity of peripheral chemoreceptors describes changes in ventilation following a specific stimulus at a given intensity. Increased sensitivity, or hyperreflexia of the chemoreflex, resulting in increased amplitude of a motor response may occur in clinical conditions and may vary between diseases as well as between individuals with cardiovascular diseases (Felippe, Del Río et al., 2023). Peripheral chemoreceptor-mediated ventilatory hyperreflexia is a common feature in chronic heart failure (Ponikowski et al., 2001; Toledo et al., 2017), and patients with a high sensitivity of the chemoreflex are among those who benefit most from therapy focused on CBs (Niewinski, Engelman et al., 2013, 2017). Young hypertensives as well as borderline subjects present with hyperreflexia (Somers et al., 1988; Trzebski et al., 1982), which suggests a role of arterial chemoreceptors in the development of hypertension (Paton et al., 2013; Przybylski, 1981; Trzebski, 1992). Data from animal studies in spontaneously hypertensive rats support that in resistant hypertension increased chemosensitivity is also present (Fukuda et al., 1987; Pijacka et al., 2016). In OSA syndrome it is well documented that the response to hypoxia is potentiated due to increased chemoreceptor sensitivity (Narkiewicz & Somers, 1997; Narkiewicz et al., 1999; Prabhakar, 2016b). In most experimental models of hypertension and heart failure hypertonicity and hyperreflexia are found concomitantly (Felippe, Del Río et al., 2023). In summary, hyperactivity of the CB and arterial chemoreflex comprises two phenomena: hypertonicity and hyperreflexia. They are

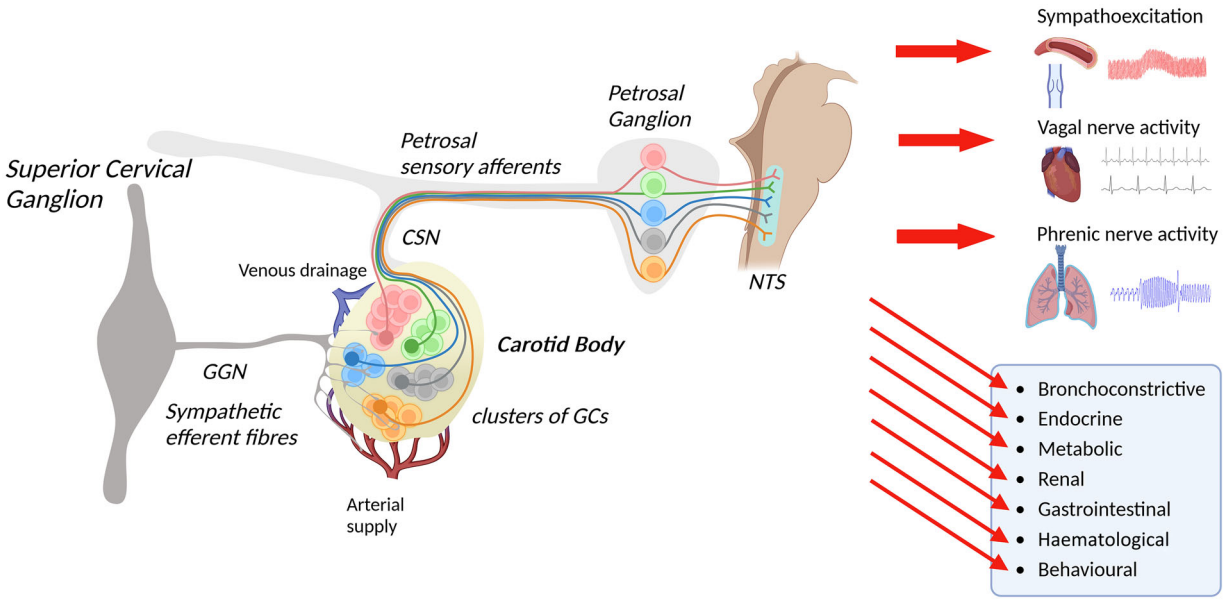



**Figure 1. The ribbon cable hypothesis of carotid body connectivity**
The CB contains clusters of chemosensitive glomus cells (type I) that show varied sensitivities to distinct and specific stimuli (e.g. oxygen partial pressures, acidity) and have unique neurochemical phenotypes (expressed enzymes, receptors, transmembrane transporters and transmitters). Histological and functional evidence indicates that different glomus cells and their clusters may be connected to defined physiological outputs and reflex arcs. Distinct/separate/individual pathways connecting the CB with the NTS and other centres of the brainstem would allow for selective or preferential engagement of various effectors of the arterial chemoreflex (Zera et al., 2019). Glomus cells and the CB vasculature receive efferent postganglionic sympathetic fibres from the superior cervical ganglion (SCG) via the ganglioglomerular nerve (GGN) that may modulate CB activity directly by acting on the glomus cells or by affecting CB blood flow (Brognara et al., 2021; Gold et al., 2022). Created with Biorender.com. [Colour figure can be viewed at wileyonlinelibrary.com]

respectively manifested by enhanced resting activity and augmented response to stimuli of the carotid sinus nerve (Fig. 2), which in turn leads to higher resting sympathetic activity (hypertonicity) and greater CB-evoked ventilatory and sympathetic responses to hypoxia (hyperreflexia) (Fig. 3). It is not fully established if all reflex responses such as ventilation, sympathetic activity or heart rate are equally affected. Whether hyperreflexia can coexist with normal tonicity and vice versa, hypertonicity is present with normal sensitivity or reflexia, remains open (Paton, Ratcliffe et al., 2013). The answer to that question might impact therapeutic approaches to modulating CBs. Nevertheless, the presence of aberrant CB tonicity and hyperreflexia makes this organ a target for modulation through quenching of its afferent output.

**Historical perspective – CB removal as a way to modulate the peripheral chemoreflex.** The idea of unilateral CB resection for the treatment of conditions other than CB tumours (Farrar et al., 1956) was introduced by Nakayama (1961). Over the next decades this unilateral procedure and its bilateral extension were performed

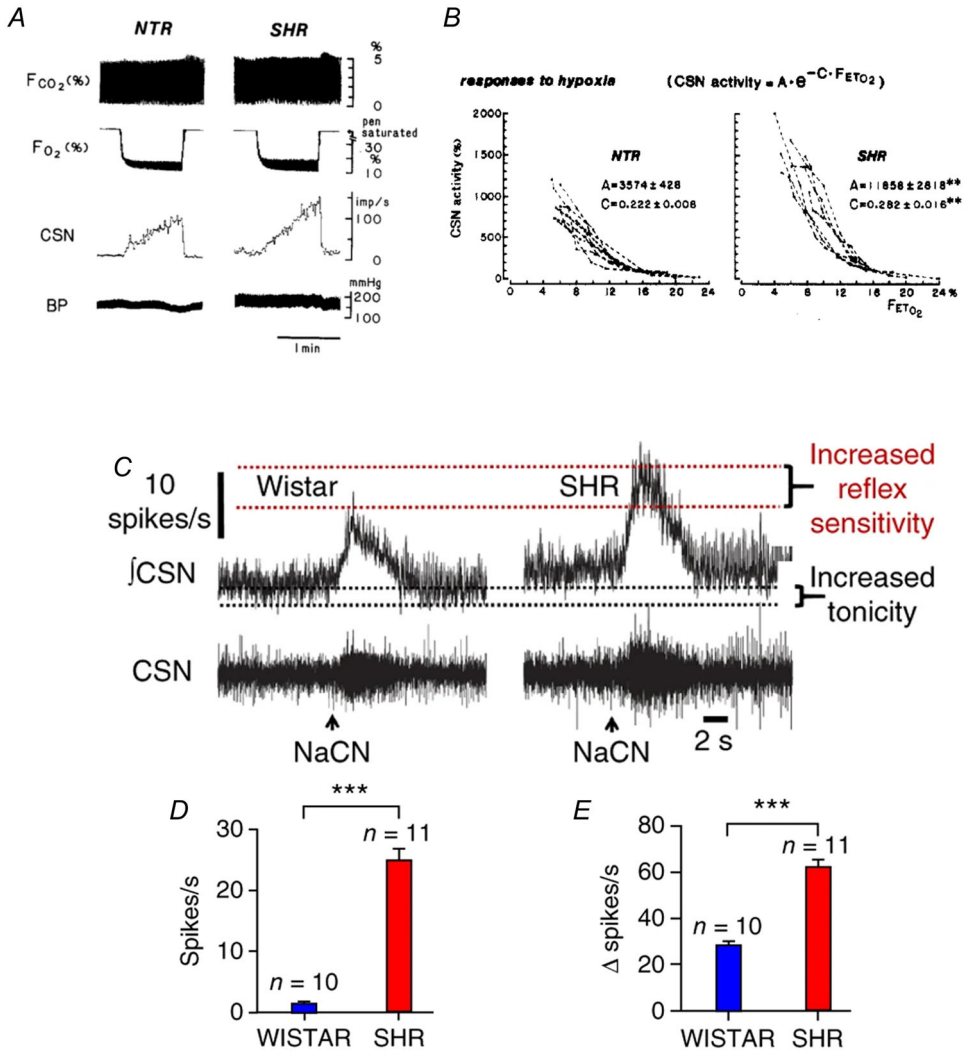



**Figure 2. Hyperactivity of the CB and arterial chemoreflex comprises hypertonicity and hyperreflexia**
Carotid sinus nerve (CSN) activity in the normotensive rat (NTR) and spontaneously hypertensive rat (SHR) in response to decreased levels of oxygen in respiratory gas mixture [$F_{O_2}$ (%)] shows a greater response in SHR (hyperactivity) – note that $CO_2$ [$F_{CO_2}$ (%)] and blood pressure (BP) are kept constant (*A*); response of the CSN activity to varied levels of oxygen [$F_{ETO_2}$ (%)] shows a steeper slope (hyperreflexia) and right-shift of the relationship to higher concentrations of $O_2$ (hypertonicity) (*B*) (Fukuda et al., 1987). Recordings of CSN activity in SHR and normotensive Wistar rats at rest and in response to pharmacological CB-evoked chemoreflex with cyanide show increased tonicity and hyperreflexia (increased reflex sensitivity) in hypertensive rats (*C*); quantitative evaluation of hypertonicity (*D*) and hyperreflexia (*E*) in SHR rats (red bars) (Pijacka et al., 2016). Reproduced with permission from Fukuda et al. (1987) and Pijacka et al. (2016). [Colour figure can be viewed at wileyonlinelibrary.com]

mostly for drug-resistant asthma. However, the efficacy of the Nakayama procedure had quickly become a matter of fierce controversy (Winter, 1973). While the initial reports showed symptomatic improvements in the majority of patients (Overholt, 1962), further studies employing sham-procedures and lung function testing delivered less promising results (O'Rourke & O'Rourke, 1964). Eventually, the procedure in asthma patients was disapproved by the Executive Committee of the American Academy of Allergy and Immunology (Anderson et al., 1986). Those findings together with the development of pharmacological therapeutics (e.g. $\beta$2-receptor agonists) for the management of asthma led to the abandonment of CB ablation in humans for years to come.

Retrospective appraisal of CB-modulating strategies since the 1960s provided an opportunity to look for important clues for informing future endeavours. First, the inconsistent degree of clinical improvement following unilateral CB resection reported in historical asthma trials (Winter, 1973) speaks for an unpredictable contribution of a single CB to the magnitude of reflex response seen in a given individual. This was confirmed after unilateral CB resection in heart failure patients in whom the resection led to varying changes in HVR with a tendency to

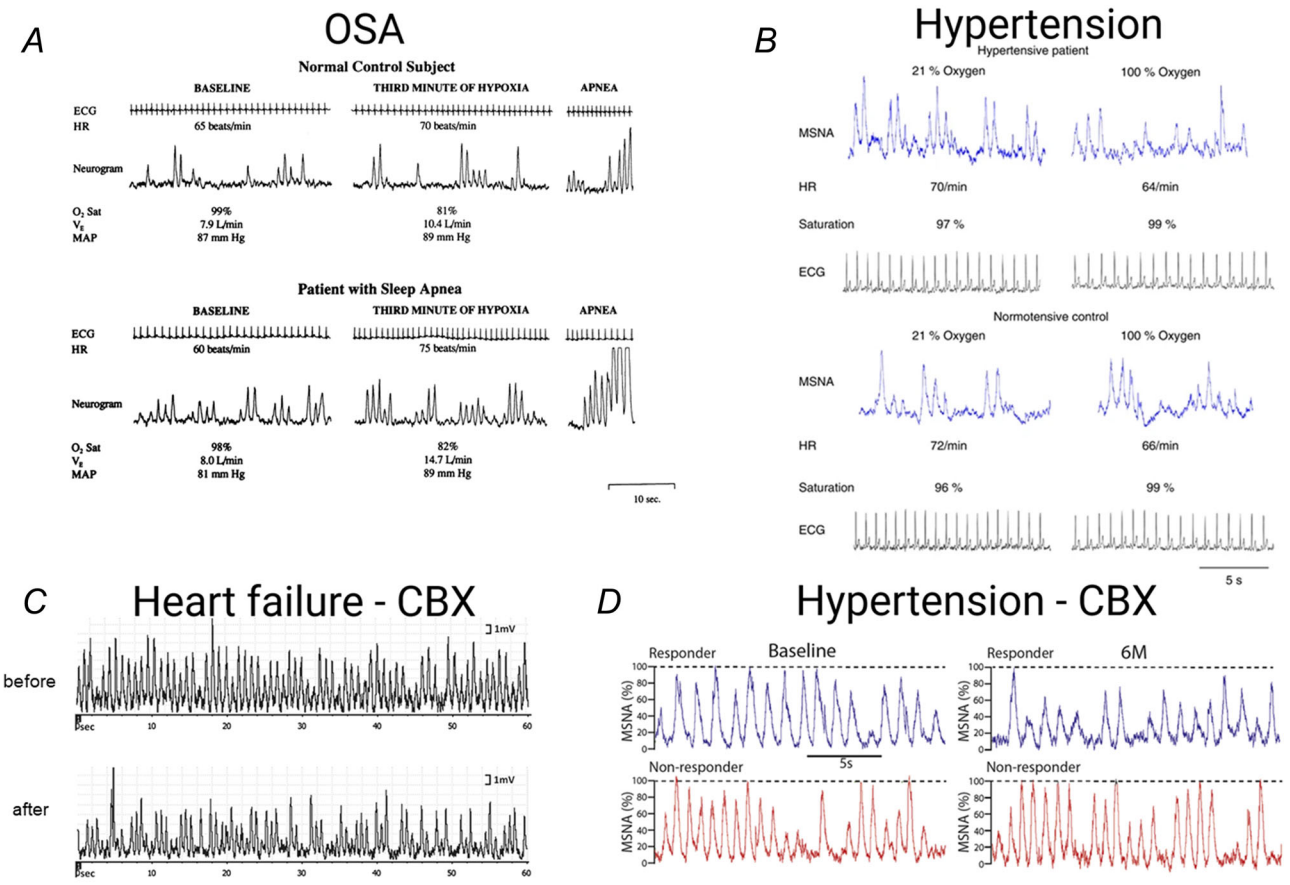



**Figure 3. Hyperactivity of the arterial chemoreflex in obstructive sleep apnoea, hypertension and heart failure**
Electrocardiogram (ECG) and sympathetic nerve activity (SNA) in a patient with obstructive sleep apnoea (OSA; top) and a normal subject (bottom) recorded in resting conditions and in the third minute of hypoxia. During hypoxia, increase in minute ventilation and heart rate were higher in patients with obstructive sleep apnoea compared to the control group; increased sympathetic activity was particularly evident during the apnoea, indicative of hyperreflexia (*A*) (Narkiewicz et al., 1999). ECG and muscle SNA (MSNA) in a hypertensive patient (top) and normotensive subject (bottom) exposed to room oxygen and during hyperoxia to silence arterial chemoreceptors; hyperoxia-induced reduction of MSNA was greater in the hypertensive patient, indicative of hypertonicity (*B*) (Sinski et al., 2012). Bilateral CB ablation (CBX) in a heart failure patient reduced SNA (*C*) (Niewinski et al., 2017). Unilateral CBX in resistant hypertensive patients decreased SNA at 6 months (6M) from baseline in responders (blue), and had no effect on non-responders (red) (*D*) (Narkiewicz et al., 2016). These CBX trials show tonic CB-evoked sympathoexcitation in heart failure and hypertension in humans. Reproduced with permission from Narkiewicz et al. (1999), Sinski et al. (2012), Niewinski et al. (2017) and under CC-BY licence from Narkiewicz et al. (2016). [Colour figure can be viewed at wileyonlinelibrary.com]

compensation in some (Niewinski et al., 2017). Second, the discrepancy between unchanged lung function tests and often striking clinical benefit might be explained by a diminished HVR and thus lessened hyperventilation during asthmatic attacks without significant changes regarding lung tissue or a tendency for bronchospasm. Such a phenomenon was not uniformly seen in asthmatic patients undergoing CB resection possibly because only a proportion of patients develop a significant CB hyperreflexia expressed as an exaggerated HVR (Narkiewicz et al., 2016; Niewinski, 2014). To summarize, unilateral CB ablation is characterized by rather unpredictable clinical benefits in terms of both acute and long-term efficacy. By contrast, bilateral CB ablation results in loss or profound impairment of hypoxic chemosensitivity (Lugliani et al., 1971; Wade et al., 1970), found even two decades after the surgery in patients from Nakayama's cohort (Honda et al., 1979). The loss of hypoxic chemosensitivity comes at the risk of nocturnal oxygen desaturation, which was not reported in historical data (possibly due to the lack of an adequate armamentarium), but is evident in contemporary studies (Niewinski et al., 2017, 2021).

## Pathological arterial chemoreflex – review of human and animal studies

**Heart failure.** The observation that ejection fraction of the left ventricle is a poor predictor of exercise tolerance in heart failure (Mancini et al., 1991) suggests that other mechanisms beyond cardiac haemodynamics might contribute to the progression of the disease. The interest in arterial chemoreceptors as potential players in the development of heart failure surfaced in the late 1990s when their hyperactivity was linked to autonomic and respiratory dysfunction in heart failure in animal models (Sun et al., 1999a, 1999b) and in patients (Chua, Ponikowski et al., 1996; Ponikowski et al., 1997, 1999). This was followed by a seminal publication documenting a clear relationship between heightened HVR and impaired long-term survival in heart failure patients (Ponikowski et al., 2001). While the causality of the association was not evident at that time, numerous studies have consistently showed that high HVR often coexists with: poor exercise tolerance, sympathetic overactivity and ventilatory instability in the heart failure population, which has been recently confirmed in patients on current pharmacotherapy (Giannoni et al., 2008, 2022; Ponikowski et al., 1998, 1999). Furthermore, augmentation of HVR is present in ∼40% of heart failure patients (Niewinski, 2014) but only in 8% of healthy subjects (Tubek et al., 2018).

The pathophysiological link between hyperactivity of the peripheral chemoreceptors comprising both hyperreflexia and hypertonicity, and heart failure was elegantly demonstrated by Ding et al. (2011) who showed that impaired blood flow through the CB (caused by reduced cardiac output) constitutes a key stimulus in a rabbit heart failure model. The hypersensitization of CB in heart failure is mediated, in part, by downregulation of Krüppel-like Factor 2 (KLF2, a shear stress-sensitive transcription factor). Interestingly, *in vivo* adenoviral transfection of KLF2 to the CB in heart failure rabbits reduced: HVR, apnoea–hypopnoea index, sympathetic tone and cardiac arrhythmia incidence (Marcus et al., 2018). Alternatively (or complementarily), stimulation of sympathetic nerves to the CB might tonically activate and sensitize peripheral chemoreceptors as was described in hypertensive rats (Felippe, Zera et al., 2023).

Two important animal studies supported the notion that arterial chemoreceptors have a *causative* role in heart failure progression beyond being a biomarker of advanced disease. In a rat model of heart failure induced by coronary ligation, survival of animals undergoing bilateral CB ablation improved (85% without CBs *vs*. 45% with intact CBs) (Del Río et al., 2013a) and was accompanied by a 40% reduction in central pre-sympathetic neuronal activation and reduced deterioration of left ventricle ejection fraction and corrected sympatho-respiratory coupling (Marcus, Del Río, Schultz, Xia et al., 2014).

In humans with heart failure the initial experimental studies employed acute, reversible inhibition of arterial chemoreceptors to document their direct involvement in exercise intolerance. Blockade of chemoreceptors was achieved with: hyperoxia (Chua, Ponikowski et al., 1996), low-dose dopamine (Janssen et al., 2009) or opiates (Chua et al., 1997). While none of these methods is selective to peripheral chemoreceptors, the results were quite comparable regarding improvements seen in various parameters derived from a cardiometabolic stress test. Until recently, all studies have been performed in heart failure with reduced ejection fraction of the left ventricle. However, a recent trial also studied heart failure patients with preserved systolic function, where an improvement in ventilatory response to exercise (decrease in slope relating minute ventilation to $CO_2$ production; $V_E/V_{CO_2}$ slope) was found following low-dose dopamine infusion compared to placebo (Kulej-Lyko et al., 2022).

To date, only one chronic trial of peripheral chemoreceptor modulation in heart failure has been carried out. In a small group of heart failure patients ($n = 10$) with an augmented HVR, surgical CB resection decreased global sympathetic activity at 2 months following the procedure (Niewinski et al., 2017) (Fig. 3). Bilateral resections resulted in more pronounced reduction in muscle sympathetic nerve activity (MSNA) compared to a unilateral procedure (5.5% *vs*. 13.3%). In line with previous acute experiments an improvement in $V_E/\dot{V}_{CO_2}$ slope was found following CB removal. On the other hand, CB resection (unilateral or bilateral) had no influence on left

ventricle systolic function or level of natriuretic peptides (NT-proBNP, a biomarker of heart failure). At the same time there was a worsening of oxygen desaturation at night seen in 4 out of 10 CB-resected individuals (mostly from the bilateral group) (Niewinski et al., 2017).

**Hypertension and sleep apnoea.** Hypertension and OSA often coexist and interact, sharing multiple pathophysiological mechanisms and consequences (Wolk et al., 2003). OSA may contribute to some of the pathological processes traditionally ascribed to hypertension alone. There is growing evidence that increased hyperactivity of peripheral chemoreceptors may be a common pathophysiological mechanism linking hypertension and OSA.

Early animal studies have shown that the magnitude of peripheral chemoreceptor responses is increased in spontaneously hypertensive rats (Fukuda et al., 1987; Przybylski, 1978). Follow-up studies in humans showed that both ventilatory and blood pressure responses to hypoxia are potentiated in mild hypertension (Trzebski et al., 1982). Studies using microneurography have confirmed an exaggerated peripheral chemoreflex-mediated sympathoexcitation in borderline hypertension (Somers et al., 1988). The sympathetic response to hypoxia during free breathing was twofold greater in mild hypertensives than in closely matched controls. Importantly, deactivation of peripheral chemoreceptors using short-term hyperoxia resulted in reductions in both skeletal muscle sympathetic nerve activity and blood pressure in human hypertension, indicating hypertonicity in addition to hyperreflexia (Sinski et al., 2012, 2014) (Fig. 3). Furthermore, increased combined volume of the left and right CB measured by computed tomography angiography was found to be positively correlated with higher blood pressure, greater systolic blood pressure variability and lower heart rate variability in hypertensive patients (Jaźwiec et al., 2015, 2016), providing morphological evidence for an association between CBs and autonomic disturbances in hypertension.

The chronic intermittent hypoxia (CIH) paradigm developed by Fletcher, Lesske, Qian et al. (1992) has served as an experimental model of OSA reflecting recurrent episodes of acute hypoxia experienced by sleep apnoea patients. Despite its limitations due to the lack of respiratory effort and hypercapnia upon upper airway obstruction and absence of disturbed respiratory pattern seen clinically (Paton, 2016; Sforza & Roche, 2016), the CIH model has provided important insights into the pathophysiological role of CBs in driving sympathoexcitation and eventually hypertension. Development of hypertension in this model critically depends on intact CBs, as their denervation before CIH exposure (Fletcher, Lesske, Behm et al., 1992) or bilateral CB ablation after establishing high blood pressure induced by CIH (Del Río et al., 2016) prevented or reversed hypertension, respectively. Similarly in spontaneously hypertensive rats, development of arterial hypertension is preceded by an enhanced peripheral chemoreflex and augmentation of sympathetic activity (Iturriaga et al., 2010), and CIH-exposed animals showed increased hyperreflexia manifested by increased activity of chemosensitive fibres of the carotid sinus nerve, augmented HVR and enhanced sympathetic activity upon peripheral chemoreflex activation (Del Río et al., 2016; Greenberg et al., 1999; Peng et al., 2003; Rey et al., 2004, 2008). An enhanced peripheral chemoreflex marked by increased HVR and augmented MSNA was also found in men exposed to intermittent hypoxia for 10 days, which closely resembles findings in patients with OSA (Lusina et al., 2006).

Normotensive patients with OSA have an enhanced peripheral chemoreflex-evoked HVR (Narkiewicz et al., 1999), much as is seen in some patients with hypertension (Narkiewicz et al., 2016). During hypoxia, the increase in minute ventilation in patients with OSA is greater than in the control group (Fig. 3). Increased minute ventilation and enhanced pulmonary receptor afferent feedback attenuate adrenergic activity, thus masking the primary effect of peripheral chemoreceptor stimulation on the autonomic system. Increased sympathetic activity could be seen at the end of the period of hypoxia during an apnoeic spell (Fig. 3), clearly indicating increased sensitivity of peripheral chemoreceptors (hyperreflexia) to hypoxia in normotensive patients with OSA. Hypertonicity of the peripheral chemoreflex may be responsible for increased adrenergic activity during awake periods as ventilation with 100% oxygen (to suppress peripheral chemoreceptor activity) leads to decreased sympathetic activity as assessed using microneurography in normotensive patients with OSA (Narkiewicz et al., 1998). Hypertensive OSA patients demonstrate enhanced arterial chemoreflex activity as compared with normotensive OSA subjects (García-Río et al., 2000; Tafil-Klawe et al., 1991). Whether hypertension and OSA have additive or synergistic effects on arterial chemoreceptors in humans is unknown.

**Insulin resistance, diabetes mellitus and metabolic syndrome.** Alterations in arterial chemoreflex are associated with metabolic dysfunction in both animals and humans. Prediabetic patients exhibited higher CB activity, as assessed by their ventilatory response to a Dejour test (normoxia–hyperoxia–hypoxia), which correlated with fasting insulin levels and insulin resistance (Cunha-Guimaraes et al., 2020). Additionally, individuals with type 2 diabetes demonstrated an exaggerated peri-

pheral chemoreflex sensitivity, measured by the HVR (Limberg et al., 2024; Lis et al., 2022); the magnitude of the HVR was associated with disease severity and higher fasting insulin levels (Lis et al., 2022) and with glycaemic control (Limberg et al., 2024). Despite enhanced HVR, diabetic patients show impaired respiratory modulation of MSNA that contributes to higher blood pressure (Plunkett et al., 2024). The findings in humans align with prior data obtained from animal studies. For example, rodent models exposed to hypercaloric diets, representing prediabetes, early type 2 diabetes and metabolic syndrome, consistently demonstrate heightened ventilatory responses to ischaemic and hypoxic hypoxia (Melo et al., 2022; Ribeiro et al., 2013) and increased levels of carotid sinus nerve activity (Cracchiolo et al., 2019; Ribeiro et al., 2018), indicative of a pronounced hyperactivity of the arterial chemoreflex. This dysfunction was substantiated by an increase in CB weight, in the percentage of CB chemoreceptor cells, tyrosine hydroxylase activity, and the release of both catecholamines and adenosine from the CB evoked by hypoxia (Cracchiolo et al., 2019; dos Santos et al., 2018; Melo et al., 2022; Ribeiro et al., 2013). The observed rise in CB weight and the percentage of type I cells in animals with metabolic diseases correlates with a 20–25% increase in the size of the CB found in human patients with diabetes mellitus (Cramer et al., 2014). In contrast, Pokorski et al. (2015) discovered a dampened HVR in a rodent model of diabetes mellitus type 1 induced by streptozotocin (Pokorski et al., 2015), which was linked to significant changes in CB cell proliferation and structure. A lack of insulin and its stimulatory effect towards the CB due to streptozotocin-induced death of pancreatic beta cells may be a contributing factor to the contrasting effects on HVR reported by Pokorski. That aside, it is evident that metabolic disorders with insulin resistance promote CB dysfunction, manifested by hyperactivity of the arterial chemoreflex.

**Identifying 'responder' patients for CB interventions.** Given the central role of the peripheral chemoreflex in respiratory control, and the technical ease of respiratory airflow/minute ventilation measurement, it emerged as the natural choice to identify patients with heightened chemosensitivity manifested as hyperreflexia based exclusively on the ventilatory component of the reflex. Ponikowski et al. (1997, 2001) used the cut-off value of HVR, as assessed with transient hypoxia, corresponding to mean ± 2 SD of the value reported in age-matched healthy controls. This approach has been adopted in subsequent studies employing either transient hypoxia (Niewinski, Engelman et al., 2013, 2017) or a hypoxic isocapnic rebreathing test (Giannoni et al., 2008, 2009), including the first (and only so far) completed clinical trial on CB resection for heart failure therapy (Niewinski, Janczak et al., 2013, 2017). It should be emphasized that evaluation of peripheral chemoreflex activity solely by the ventilatory component may not be explicitly translated into corresponding sympathetic responses (Keir et al., 2020). Thus, selection based on HVR criteria in clinical trials may be suboptimal for identifying patients who will benefit most from treatments targeting CBs aimed at reducing sympathetic outflow, as discussed later.

Notably, however, it remains unknown which aspect of peripheral chemoreflex malfunction – CB hypertonicity and/or CB hyperreflexia – contributes most to the adverse outcome in cardiovascular disorders, precluding any firm conclusions regarding the optimal strategy for identifying 'responders' to CB modulation therapies (Paton, Ratcliffe et al., 2013). A transient hypoxia test with the aforementioned cut-off value (Niewinski, Engelman et al., 2013, 2017; Ponikowski et al., 1997, 2001) demonstrated reasonable efficacy in predicting responders in a small group of heart failure patients subjected to uni- or bilateral CB resection (Niewinski et al., 2017). Data collected in drug-resistant hypertensive patients subjected to unilateral CB resection also partially support the applicability of transient hypoxia in this context (Narkiewicz et al., 2016). Although no chemosensitivity-based pre-selection of patients was performed in this study, *post hoc* analysis revealed higher HVR in 'responders' (≥10 mmHg reduction in ABP at 3 months of follow-up). Of note, however, the fraction of 'non-responders' was relatively high (6 out of 14 patients, 43%). Thus, although not perfect, CB modulation therapy does permit non-invasive testing for screening prior to enrolment of patients into studies.

Currently, there are no widely accepted 'gold standard' methods for both CB tonicity and peripheral chemosensitivity being performed *a priori* to a clinical study. Regarding the latter, a transient hypoxia test for measurement of the HVR is believed to reflect a 'pure' peripheral chemoreflex response, not confounded by cardiovascular or cerebrovascular phenomena that occur during longer hypoxic exposures (Edelman et al., 1973; Pfoh et al., 2016). It has been suggested, however, that transient hypoxia may underestimate peripheral chemosensitivity due to the opposing effects of concomitant hypocapnia (Keir et al., 2020). Alternatively, the modified rebreathing method provides an opportunity for reproducible assessments of the ventilatory recruitment threshold to $CO_2$ and responses to hyper- and hypoxia (Duffin, 2011). Note that the sympathetic responses following peripheral chemoreceptor stimulation cannot be predicted from the HVR in young healthy men (Keir et al., 2019) nor middle-aged patients with OSA (Prasad et al., 2020). Since the pathological repercussions of CB hyperactivity are probably conveyed by the sympathetic nervous system, and not ventilatory component of the

reflex (Toledo et al., 2017), there is a need for a more complex evaluation of arterial chemoreflex for identifying 'responders' to CB modulation that would encompass not only the ventilatory response, but also the sympathetic component (Keir et al., 2020).

Alternatively, reflex bradycardia (Hennersdorf et al., 2001) or a reflex decrease in MSNA (Despas et al., 2012) during hyperoxia was used to identify heart failure patients with elevated peripheral chemoreceptor hypertonicity. However, in contrast to HVR, the literature on the clinical relevance of heart rate- or MSNA-based assessment of chemoreceptor function during either hyperoxia or hypoxia is scarce. Eventually, novel methods, such as functional magnetic resonance imaging of subcortical centres during acute hypoxia (Gerlach et al., 2021), or direct stimulation of the CB with adenosine injected into the carotid artery (Tubek et al., 2016) may be useful in the discussed context, although while the additional cost and invasiveness are acknowledged respectfully, clinical data are lacking. Figure 4 summarizes available methods for evaluation of the peripheral chemoreflex in humans.

**Side-effects of chronic CB removal and lack of arterial chemoreflex.** When considering any modulation therapy for the CB there are potential side-effects related mostly to a diminished HVR. A major role for arterial chemoreceptors is the homeostatic control of arterial blood oxygen tension. Low partial pressure of oxygen in arterial blood could be a result of either: (1) low oxygen availability in the environment, (2) thickening of the respiratory gas exchange membrane or (3) low minute ventilation. A typical example of the first would be exposure to high altitude or during a long-haul flight. Such a scenario was simulated in a study performed in a small sample of heart failure patients 5 years following bilateral CB resection (Niewinski et al., 2021). Brief exposure to mild hypoxia (5 min of 15% $O_2$; equivalent of 2700 m above sea level) resulted in oxygen desaturation to 82.5 ± 1.2%, while in subjects with intact peripheral chemoreceptors it was 92.6 ± 2.6%. An ∼10% lower minimal $S_{pO_2}$ is of clinical significance especially in subjects with cardiac comorbidities. Furthermore, under mild hypoxic conditions (15% $O_2$) the oxygenation pattern observed in bilateral CB-resected individuals displayed a pronounced short-term variability not present in controls. It speaks for the need of CB functionality for breath-by-breath $S_{pO_2}$ stabilization (Niewinski et al., 2021).

Repetitive episodes of low minute ventilation and/or apnoea are a hallmark of sleep disordered breathing. In animal models of heart failure, bilateral CB ablation results in normalization of disturbed breathing architecture (Del Río et al., 2013; Marcus et al., 2013). This can be explained by attenuation of the controller gain which in the state

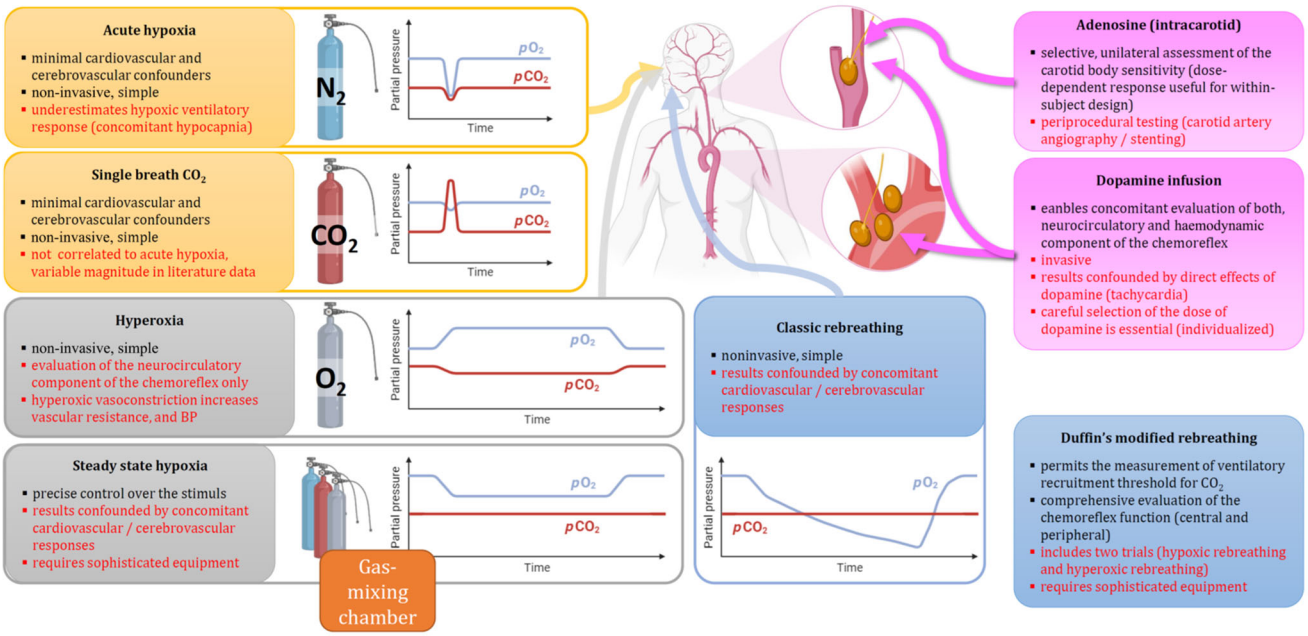



**Figure 4. Evaluation of arterial chemoreflex in humans**
Activation of the chemoreflex includes (counterclockwise): (1) acute exposure to pure nitrogen ($N_2$) leading to a decrease in arterial $O_2$ and hypocapnia; (2) single breath $CO_2$ producing hypercapnia and transient hypoxia; (3) exposure to hyperoxia leading to an increase in arterial $O_2$ and decrease in $CO_2$; (4) steady-state hypoxia with clamped $CO_2$ levels allowing for precise control over stimulus; (5) classic rebreathing; and (6) Duffin's modified rebreathing method. The advantages and disadvantages of each method are in black and red font, respectively. Created with Biorender.com. [Colour figure can be viewed at wileyonlinelibrary.com]

of heart failure is fuelled by overactive CBs leading to central sleep apnoea (Marcus, Del Río, & Schultz, 2014). On the other hand, heart failure patients are often characterized by a mixed pattern of both central and obstructive sleep apnoea (Dharia & Brown, 2017). When CBs providing the rapid response to changes in $P_{aO_2}/P_{aCO_2}$ are absent, the ventilatory reactivity during obstructive episodes relies solely on the central and slower-acting chemoreceptors. This in turn leads to prolonged apnoeas and pronounced desaturations after bilateral CB ablation (Niewinski et al., 2017). Thus, when considering any CB modulating therapy, particular attention should be given to sparing the ventilatory response to hypoxia – particularly in subjects with obstructive phenotype of sleep disordered breathing, which (in contrast to the central phenotype) is unlikely to be favourably affected by modulation of peripheral chemosensitivity. All told, we do not advocate resection or ablation of the CBs for treatment of cardiovascular, metabolic or respiratory disease.

## New paths – recent advances in CB function and its hyperactivity

Advances in peripheral chemoreflex research are revealing novel ways to consider its organization in terms of afferent connectivity and involvement of various mediators. This is opening novel potential approaches for modulating specific components of the arterial chemoreflex, instead of partial or complete removal of the CBs.

**Arterial chemoreceptors – beyond oxygen sensing.** CB sensitivity extends beyond its classical role as an $O_2$ sensor. It is now widely recognized that the CB is a polymodal sensor. CB sensing of $CO_2$, pH, temperature and osmolality were described several decades ago (Gallego & Belmonte, 1979; Gonzalez et al., 1994; Molnár et al., 2003). New sensing abilities have emerged including a crucial role in counterregulatory responses to hypoglycaemia and in glucoregulation (Alvarez-Buylla & de Alvarez-Buylla, 1988; Conde et al., 2018; Wehrwein et al., 2010). In contrast, the initial direct glucose-sensing properties of the CB proposed by Pardal & López-Barneo (2002), and others (García-Fernández et al., 2007; Zhang et al., 2007), have faced opposition. Several groups (Bin-Jaliah et al., 2004; Conde et al., 2007; Gallego-Martin et al., 2012) have attributed its 'sensing' of glucose to a direct effect exerted by insulin (Baby et al., 2023; Conde et al., 2014, 2018; Ribeiro et al., 2013) or adrenaline (Thompson et al., 2016).

Apart from insulin and adrenaline, several studies described sensitivity to leptin (Caballero-Eraso et al., 2019; Ribeiro et al., 2018), glucagon-like peptide 1 (GLP1) (Melo et al., 2022; Pauza et al., 2022), angiotensin II (Fung, 2016), endothelin-1 (Li et al., 2019), and to pro-inflammatory cytokines such as as TNF-$\alpha$, IL1$\beta$ and IL6 (for reviews see Conde et al., 2020; Sacramento et al., 2020). Furthermore, recent transcriptomic analysis of the CB (Pauza et al., 2022, 2023) showed that the organ exhibits receptors for a multitude of other hormones and neuropeptides, including the MC4R receptors, whose ligands are $\alpha$-melanocyte-stimulating hormone ($\alpha$-MSH) or $\beta$-MSH, the NPY4R for neuropeptide Y (NPY) and Gal3R for galanin. Future research needs to validate these new stimuli by testing whether the CB responds to them and if they have a physiological function.

Chemosensitive cells of the CB abundantly express olfactory receptor Olfr78 that binds lactate and short-chain fatty acids (Chang et al., 2015). Initial results in Olfr78 knock-out mice indicated that lack of the receptor leads to loss of normal hypoxia sensing and diminished HVR (Chang et al., 2015; Peng et al., 2020). In addition, Olfr78 was suggested to mediate sympathoexcitation and hypertension in a chronic intermittent hypoxia model (Peng et al., 2021). However, further studies in Olfr78 knock-out mice did not confirm the role of this receptor in the CB for sensing hypoxia (Chang et al., 2018; Colinas et al., 2024; Torres-Torrelo et al., 2018), which is in line with earlier findings by Spiller et al. (2021) indicating an absence of cellular and physiological responses to lactate at physiological and supraphysiological concentrations in normotensive rats. These contradictive reports require further investigations, especially given the important role of lactate as an energy substrate for cardiomyocytes and neurons, as well as a marker of anaerobic metabolism.

**Modulation of CB sensitivity and tonicity.** Modulation of CB activity may affect its tonicity and/or sensitivity and hence the amplitude of the chemoreflex response (Felippe, Del Río et al., 2023). The challenge in the research field is whether modulation of CB activity may be guided towards a specific sensing modality to modulate a selective motor response of the arterial chemoreflex that provides therapeutic advantage.

Sensitization of the CBs involves changes in excitability of both the glomus cells and their afferents, which may be accomplished by release of classic, gaseous and peptidergic neurotransmitters within the CB, changes in the expression of receptors and enzymes, access of hormones and mediators present in the bloodstream to the CB, reduction or redistribution of the blood flow within the CB, activity of efferent innervation to the organ, and histological remodelling of the CB, as recently summarized by Felippe, Del Río et al. (2023).

Several mediators, enzymes and receptors have been identified to increase CB activity in hypertension, heart failure and CIH/OSA, including reduced expression of NO synthase isoforms and NO production (Atanasova et al., 2020, 2023; Ding et al., 2011), increased generation

of reactive oxygen species and oxidative stress (Iturriaga, 2018; Nanduri et al., 2018; Pawar et al., 2009; Peng & Prabhakar, 2004; Peng et al., 2003; Schultz et al., 2013), increased local synthesis of angiotensin II and increased expression of angiotensin receptors (Allen, 1998; Li et al., 2006; Pauza et al., 2022; Peng et al., 2011; Schultz et al., 2013), leptin (Shin et al., 2019), endothelin-1 (Li et al., 2019; Pawar et al., 2009), proinflammatory cytokines and inflammation (Del Río et al., 2012; Iturriaga, 2023; Katayama et al., 2022; Lataro et al., 2024), cystathionine-gamma-lyase (CSE) and hydrogen sulphide ($H_2S$) production (Del Río et al., 2013b; Schultz et al., 2013), KLF2 (Marcus et al., 2018), ATP and P2X3 receptors (Pijacka et al., 2016), and GLP-1 and GLP-1 receptor (GLP1R) (Pauza et al., 2022). In addition, the excitatory neurotransmitter glutamate, NMDA and metabotropic glutaminergic receptors (mGlur) as well as the inhibitory $\gamma$GABA and $GABA_A$ and $GABA_B$ receptors are expressed in the glomus cells, sustentacular cells and afferents of the petrosal neurons (Gold et al., 2022; Liu, Ji et al., 2009). It is likely that they are involved in modulating excitability within the CB, which may change under pathophysiological conditions, which needs verifying experimentally.

The increased sensory output from the CB leading to hypertonicity and hyperreflexia may be also accomplished by reduction of the CB blood flow resulting in local 'stagnant' hypoxia, as is well defined in heart failure (Ding et al., 2011; Schultz et al., 2013, 2015). The reduction of blood flow in CBs with consequent chemoreceptor activation as a cause of arterial hypertension was postulated by Przybylski (1981) after he found increased sensitivity of the reflex in young spontaneously hypertensive rats manifested by alveolar hyperventilation (Przybylski, 1978). Available evidence summarized by Brognara et al. (2021) points to adrenergic receptors, NPY, nicotinic and muscarinic receptors, and NO as potential modulators of CB blood flow and sensitivity.

A reduction in CB blood flow may result from: (1) decreased cardiac output, (2) increased pre- and intra-CB vascular resistance, and (3) redistribution of the flow away from the glomus cells within the CB. The autonomic efferent innervation may alter global blood flow or redistribute blood flow within the CB as stimulation of the preganglionic sympathetic neurons innervating the CB and stimulation of the carotid sinus nerve (which contains parasympathetic pre-ganglionic fibres) reduced and increased blood flow, respectively, under physiological conditions (Acker & O'Regan, 1981). Recently, stimulation of the sympathetic innervation from the superior cervical ganglion enhanced CB sensitivity via $alpha_1$-adrenergic receptors and confirmed that the sympathetic innervation of the CB maintains both hypertonicity and hyperreflexia in spontaneously hypertensive rats (Felippe, Zera et al., 2023).

Vasoactive factors and hormones such as angiotensin II, NPY, endothelin-1, vasopressin, natriuretic peptides or gastrointestinal hormones (e.g. GLP1) that are released into the circulation under physiological (e.g. exercise, digestion, changes in plasma osmolarity) and pathological conditions (e.g. hypo- and hypernatraemia, hypovolaemia, hypotension, hypoxia, hypertension and heart failure) may bind to their receptors located in the CB vasculature to participate in regulation of CB sensitivity by affecting local blood flow and, in turn, the activity of glomus cells (He et al., 2000; Kim et al., 2018; Li et al., 2019; Liu, Ji et al., 2009; Potter & McCloskey, 1987; Proczka et al., 2021; Wang et al., 1991; Zera et al., 2018).

In the ribbon-cable hypothesis (Zera et al., 2019), we hypothesized that sensitization of the CB may be restricted to specific motor outputs, which could explain selective sympathoexcitatory response in heart failure or neurogenic hypertension under normoxic conditions, and predominantly enhanced respiratory response in idiopathic hyperventilation (Jack et al., 2004) or long-COVID patients (El-Medany et al., 2024). There is compelling evidence for purinergic P2X3 receptor and GLP1 via GLP1R in the CB for preferential modulation of the CB-driven sympathetic activity with insignificant effect on respiration, which is discussed next.

Selective augmentation of CB-evoked sympathoexcitation has been shown for purinergic P2X3 receptors in both spontaneously hypertensive rats (Pijacka et al., 2016) and in rats with heart failure (Lataro et al., 2023) (Fig. 5). ATP is one of the key excitatory transmitters released in the CB upon hypoxia (Buttigieg & Nurse, 2004; Conde et al., 2012) and binds to purinergic P2X2/P2X3 receptors expressed on the sensory afferents projecting to the petrosal ganglion (Campanucci et al., 2006; Prasad et al., 2001; Zhang et al., 2000). The P2X receptors form homo- and heterotrimeric structures resulting in an array of P2X3, P2X2 and P2X2/3 receptors characterized by a varied degree of fast and slow responses and affinity for ATP, with P2X3 being fast deactivating and more sensitive to ATP (Bardsley et al., 2021; Gever et al., 2006; Lewis et al., 1995; Liu et al., 2001). Upregulated expression of P2X3 has been found in the petrosal chemosensitive afferents supplying the CB in spontaneously hypertensive rats (Pijacka et al., 2016). In these rats, pharmacological inhibition of P2X3 and P2X2/3 receptors was shown to selectively attenuate the sympathetic component of the CB-driven hypertonicity and hyperreflexia and reduce arterial blood pressure, but without a significant respiratory effect (Pijacka et al., 2016). This was later confirmed with downregulation of P2X3 receptors in the CB in a hypertensive canine model (Xue et al., 2021). Recently, expression of P2X3 receptors in petrosal afferents in the CB was shown to be increased in heart failure rats and administration of a P2X3 and P2X2/3 antagonist attenuated sympathetic hyper-

activity and improved cardiac function and biomarkers of cardiac failure (Lataro et al., 2023). Importantly, P2X3 and P2X2/3 receptor inhibition also abolished spontaneous CB discharge causing sympathetic activity surges and CB-induced apnoea, distinct from central sleep apnoea and OSA (Lataro et al., 2023). It remains to be experimentally determined if CB hypertonicity and hyperreflexia of the sympathetic component depend only on upregulation of the P2X3 and P2X2/3 receptors, and/or whether increased extracellular levels of ATP are also present in the CB (Bardsley et al., 2021). These promising findings await further clinical verification in hypertensive and heart failure patients.

GLP1 is one of the key incretin hormones released from the intestinal wall in response to nutrients and primarily participates in boosting insulin release from the pancreatic beta cells and inhibition of food intake post-prandially (Drucker & Holst, 2023). Recently, GLP1 receptors (GLP1R) were found in the CB and their expression was downregulated in the chemosensitive glomus cells and lost in the CB vasculature of spontaneously hypertensive rats (Pauza et al., 2022, 2023). Local into the CB and systemic administrations of exendin-4, a GLP1R agonist, decreased CB-evoked sympathoexcitation and blood pressure rises in response to pharmacological activation of the CB. This effect was found in both normotensive and hypertensive rats, despite lower expression of GLP1R in the latter (Pauza et al., 2022) (Fig. 6). Since the CB vasculature of hypertensive rats is devoid of the receptor, and presumably GLP1R-dependent vasodilatation, it may act directly to curb glomus cell excitability and reduce the arterial chemoreflex sympathoexcitatory response in hypertension.

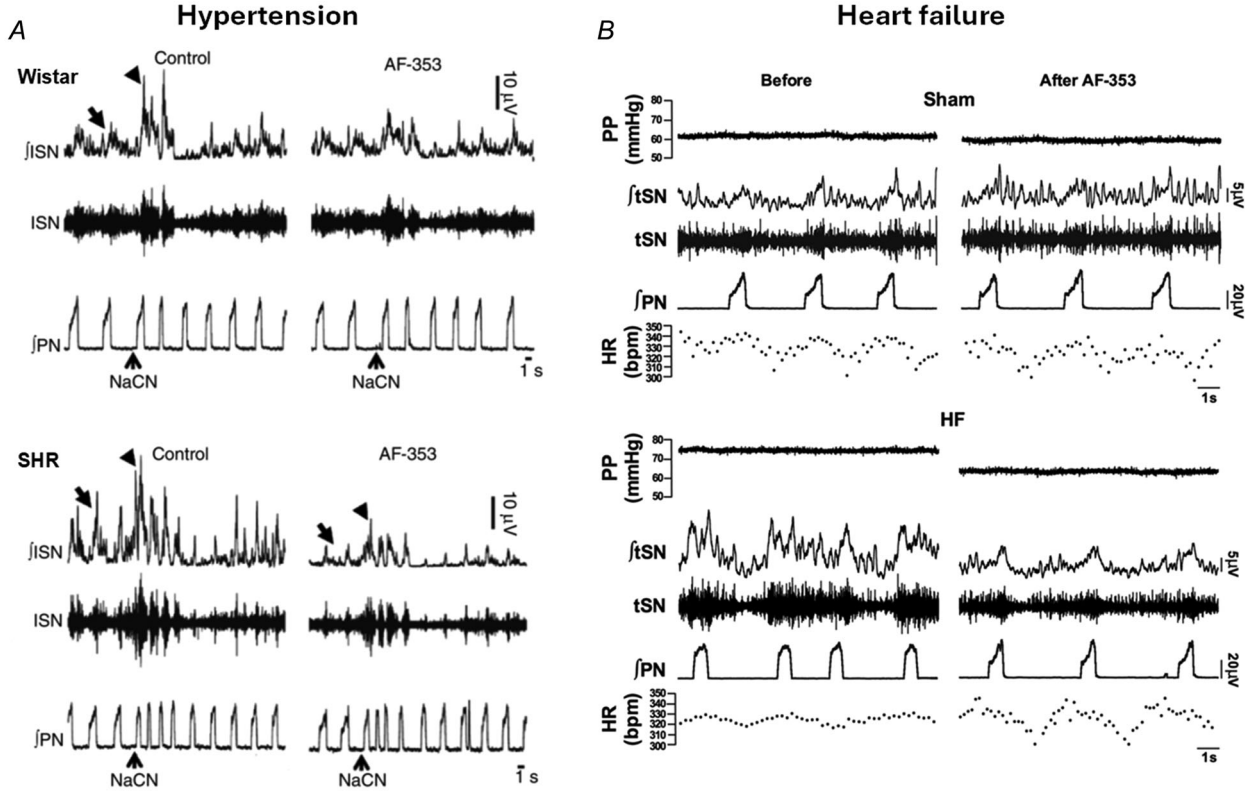



**Figure 5. Preferential involvement of purinergic P2X receptors in CB-evoked sympathoexciation in hypertension and heart failure**
The P2X3 and P2X2/3 antagonist (AF-353) applied bilaterally to both carotid bodies normalizes the ongoing basal thoracic chain sympathetic activity (arrow) in spontaneously hypertensive rats (SHR) to the levels of normotensive Wistar rats and attenuates the sympathetic nerve reflex response (arrowhead) to pharmacologically evoked arterial chemoreflex with sodium cyanide (NaCN) without affecting phrenic nerve activity (PN) (*A*) (Pijacka et al., 2016). Administration of the P2X3 and P2X2/3 antagonist (AF-353) to the CBs attenuated sympathetic hyperactivity and abolished spontaneous CB discharge causing sympathetic activity surges and CB-induced apnoea (*B*) (Lataro et al., 2023). Abbreviations: thoracic chain sympathetic activity (raw – tSN; integrated – ∫tSN) and phrenic activity (raw – PN; integrated – ∫PN) and heart rate (HR). Reproduced with permission from Pijacka et al. (2016) and under CC-BY licence from Lataro et al. (2023).

## Perspective for new treatments modulating CB-evoked arterial chemoreflex

Ideally, one would like to treat distinct chemoreflex pathways but spare those that play a protective role. Since there are numerous sensory modalities converging in the CB, modulation of its activity may hold potential for 'one stop shop' treatment of cardiovascular, respiratory and metabolic comorbidities.

**Systemic pharmacological treatment strategies controlling distinct chemoreflex pathways.** The standard pharmacotherapy used to treat sympathetically mediated diseases can also affect CB function. When $\beta$-blockers such as carvedilol and nebivolol are used to treat heart failure, they were also found to decrease CB hyperreflexia in humans (Contini et al., 2013) – an effect possibly mediated by the blockade of $\beta_1$, $\beta_2$ and $\alpha_1$ receptors and (in the case of nebivolol) by increased NO synthesis. Of the drugs interfering with the renin–angiotensin system, only the AT-1 receptor antagonist was reported to attenuate HVR in a rabbit model of heart failure (Li et al., 2006). Digoxin, often employed for heart rate control in heart failure, increases the acute reactivity of CBs (Janssen et al., 2010). Interestingly, the use of digoxin has been linked to worse outcomes in some heart failure patients (Gazzaniga et al., 2023). Simvastatin, which promotes an upregulation of KLF2 and normalization of CB sensitivity, improved respiratory pattern, reduced cardiac arrhythmia and ameliorated HVR in a rat model of heart failure (Haack et al., 2014), which is consistent with protective effects of overexpressing KLF2 in the CB of rabbits with heart failure (Marcus et al., 2018).

A sensitization of peripheral chemoreceptors has been reported following the use of ticagrelor – an anti-platelet agent (reversible P2Y12 receptor antagonist) widely prescribed after acute coronary syndromes (Tubek et al., 2023). A common side-effect of ticagrelor is dyspnoea and this is seen in ∼10% of patients (Bergmeijer et al., 2017). In a recent study, ticagrelor-related dyspnoea was found only in those patients who showed a high augmentation of their HVR (Tubek et al., 2023). These findings provide another piece of evidence linking overactive CBs to respiratory symptoms regardless of the presence of heart failure. Moreover, given the multiple pharmacological treatments for heart failure, it may be difficult to predict what the net effect will be on CB activity given the opposing effects of several medications.

Based on preclinical studies in rat models of hypertension and heart failure (Lataro et al., 2023; Pijacka et al., 2016), inhibition of purinergic P2X3 and P2X2/3 receptors in the CB provides a new potential target that calls for translation into clinical trials. First, the P2X3 and P2X2/3 receptor antagonist – gefapixant – was tested and registered for treating persistent cough in humans (McGarvey et al., 2022; Nussbaum et al., 2024). The advantages of using this antagonist *versus* CB ablation include: (1) re-setting the sensitivity instead of removing the sensor, thereby allowing the CB to maintain its physiological, protective functions; (2) lowering sympathetic tone making it a novel target for modulation in hypertension and heart failure; and

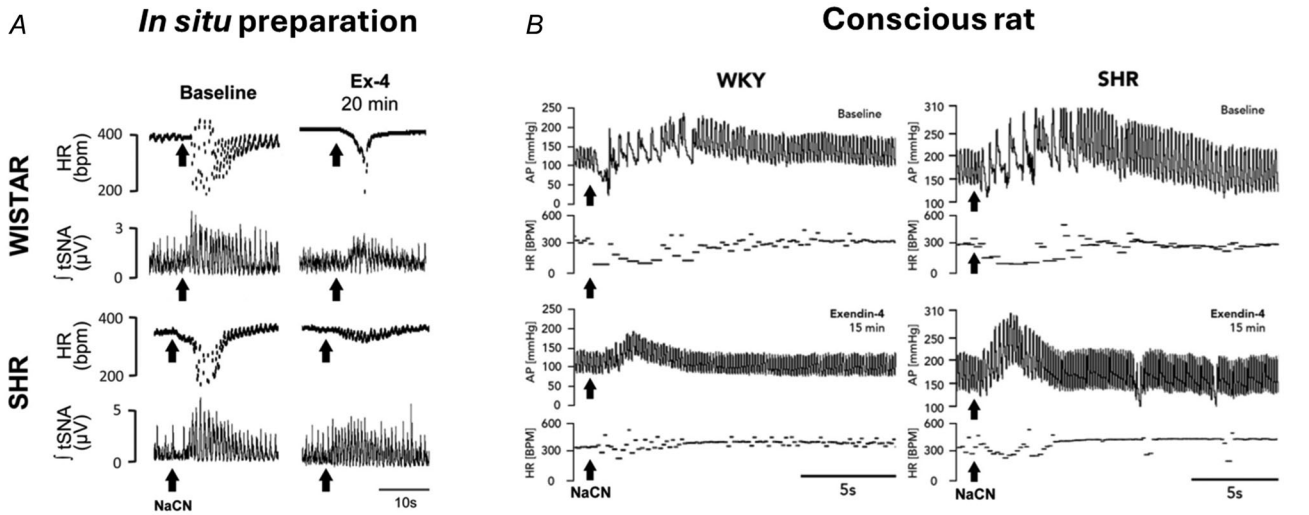



**Figure 6. Incretins and CB-evoked sympathoexcitation**
Administration of exendin-4, a GLP1R agonist, locally into the CB in the *in situ* working heart–brainstem preparation (*A*) or systemically *in vivo* in conscious rats (*B*) decreased CB-evoked sympathoexcitation and blood pressure rises, respectively, in response to pharmacological activation of the CB with sodium cyanide (NaCN) in both normotensive Wistar-Kyoto (WKY) and spontaneously hypertensive (SHR) rats (Pauza et al., 2022). Abbreviations: sympathetic nerve activity (raw – tSNA; integrated – ∫tSNA); heart rate (HR); arterial pressure (AP). Reproduced under CC-BY licence from Pauza et al. (2022).

(3) sparing the ventilatory chemoreflex response while attenuating sympathetic activity thereby reducing the risk of worsening of sleep apnoea. Recently, results of a small clinical trial showed no improvement in OSA severity with P2X3 receptor antagonist gefapixant treatment (Robbins et al., 2024); the latter is consistent with the preferential effects on sympathetic control discussed above. However, there are no data on the effect of P2X3 and P2X2/3 receptor antagonists given systematically on haemodynamics or CB function in human patients with hypertension or heart failure.

Several other compounds not routinely used for the treatment of heart failure, hypertension or diabetes have been found to exert an inhibitory influence over the peripheral chemoreflex. These include: caffeine (Sacramento et al., 2015), ibuprofen (Liu, He et al., 2009) and dietary nitrates (beetroot powder) (Bock et al., 2018). Possibly combining some of the above-mentioned molecules in one formulation such as a polypill might offer a more clinically effective blockade of CBs due to their complementary mechanisms of action.

Alternative approaches to target CB-evoked arterial chemoreflex in the context of cardiometabolic diseases may also involve the modulation of insulin, leptin and/or adiponectin receptors. While some information exists on the mechanisms through which insulin and leptin promote CB activation (Caballero-Eraso et al., 2019; Gauda et al., 2020; Ribeiro et al., 2018), there is a dearth of knowledge regarding the presence of adiponectin receptors and the role of adiponectin in the CB.

Insulin and leptin stimulate CB activity (Caballero-Eraso et al., 2019; Ribeiro et al., 2013, 2018). Furthermore, leptin's impact on the CB, especially in obesity-associated hypertension, is mediated through the transient receptor potential melastatin 7 (TRPM7) (Shin et al., 2019), suggesting the potential use of channel blockers to regulate CB activity in pathological conditions. However, the quest for therapeutic strategies by modulating insulin and leptin receptors on the CB must address the dual challenge of specificity/selectivity (tissue and receptor selectivity to minimize off-target adverse effects) and resistance for these mediators, recognizing the potential for groundbreaking advancements in the regulation of CB-evoked arterial chemoreflex in cardiometabolic diseases.

Exendin-4, a GLP1R agonist, selectively inhibited CB-triggered sympathetic activity without effects on phrenic nerve activity (Pauza et al., 2022). This points to the potential of pharmacological modulation of the CB in cardiovascular and metabolic diseases by GLP1R. Recently, semaglutide and other GLP1R agonists have been shown in large clinical trials to confer cardiovascular benefits in addition to body weight reduction and improved control of glycaemia (Honigberg et al., 2020; Lincoff et al., 2023). However, a small study showed that systemic acute administration of a GLP1R agonist increases MSNA in healthy human subjects (Bharucha et al., 2008). Given the clinical improvement, long-term sympathoexcitation in the course of GLP1R agonist treatment seems unlikely in cardiovascular, diabetic and obese patients. Future studies in humans should specifically aim at the effects of GLP1R agonists on HVR, chemoreflex and basal sympathetic activity in cardiometabolic diseases.

**CB-targeted interventions.** We discuss the rapid development of biocompatible nanoparticles, comprising several classes of materials, such as lipid-based liposomes, polymeric micelles, carbon-based nanotubes, graphene, quantum dots, and metal-based ferroferric oxide or gold nanoparticles (Bhandari et al., 2021; Conroy et al., 2024; Kong et al., 2017) for targeting the CB. Such nanoparticles can be functionalized to preferentially bind to specific populations of cells and release pharmacological agents (Conroy et al., 2024). Nanoparticle-based pharmacotherapy presents potential for local CB-directed drug delivery affecting specific chemosensitive glomus cells or sensory afferents with distinct phenotypes, at the same time avoiding systemic side-effects. Another option for selective and local targeting of the CB is genetic manipulation, which has recently been shown to be feasible. In the hypertensive canine model, the P2X3 receptor was not blocked but downregulated with CRISPR/Cas9 plasmid engineered for disruption of the P2X3 gene. The plasmid was delivered encapsulated within microbubbles and locally released in the CBs using low-intensity focused ultrasound allowing for targeted gene transfer in the CB (Xue et al., 2021). Downregulation of P2X3 receptor expression in the CB decreased systolic and diastolic blood pressures in dogs from 152 to 138 mmHg and from 97 to 87 mmHg, respectively (Xue et al., 2021) (Fig. 7). A future option would be to upregulate GLP1 signalling selectively within the CB, which should have a sympatho-inhibitory effect. Emerging new genetic approaches point to the clinical feasibility of selective targeting of specific genes for therapy of cardiovascular and neurological diseases in humans. Recently, results from a phase 1 clinical trial with zilebesiran, a therapeutic agent based on small interfering RNA to downregulate angiotensinogen expression in the liver, showed that it effectively lowered blood pressure in hypertensive humans (Desai et al., 2023). Several recent neurological treatments based on gene transfer to the peripheral nervous system have been either trialled or approved (Privolizzi et al., 2021). Genetic targeting of chemoreceptors or their afferents with specific phenotype poses a possibility for preferential silencing or augmenting given components of the arterial chemoreflex. More research is needed for proof that such

therapeutic approaches are effective. We propose that the CB is advantageous for such strategies because of its high blood flow, compact size, and accessible and relatively superficial location.

A percutaneous approach for CB ablation offers a less invasive way to ablate the CB than standard surgical resection. While a surgical strategy is free from the risk of baroreflex dysfunction, it still carries a small risk of vascular laceration, the hypoglossal nerve injury (Winter, 1972), and damage to spinal afferents resulting in hypoesthesia (our personal observations). Among proposed transcatheter modalities are ones using: radio-frequency (RF) current, cryoenergy or focused ultrasound to selectively destroy CBs without damage to adjacent structures. A single case of acutely successful CB ablation using a novel bipolar 'Y shaped' RF catheter was reported by Tubek et al. (2016). Blood pressure-lowering effects of intravascular ultrasound (IVUS)-guided catheter and application of therapeutic ultrasound energy for ablation of the right CB was recently described in a series of 39 hypertensive patients (Lobo, 2023).

Regardless of the energy or the approach (open surgical *vs.* transcatheter *vs.* non-invasive magnetic resonance imaging-guided focused ultrasound surgery; Jolesz, 2009) used for CB ablation, it will lead inevitably to the loss of HVR if done bilaterally. In this context, targeting structures that modulate CB function but that are not necessarily responsible for hypoxic reactivity appears as an interesting alternative. The GGN, which supplies the post-ganglionic sympathetic innervation to the CB, could be seen as such a potential target. In the rat model, sympathetic denervation of the CB resulted in a selective attenuation of CB hyperreflexia. Interestingly, the authors reported significant modulation of the sympathetic but not ventilatory reactivity (Felippe, Zera et al., 2023). By contrast, an *in vivo* animal model showed pronounced

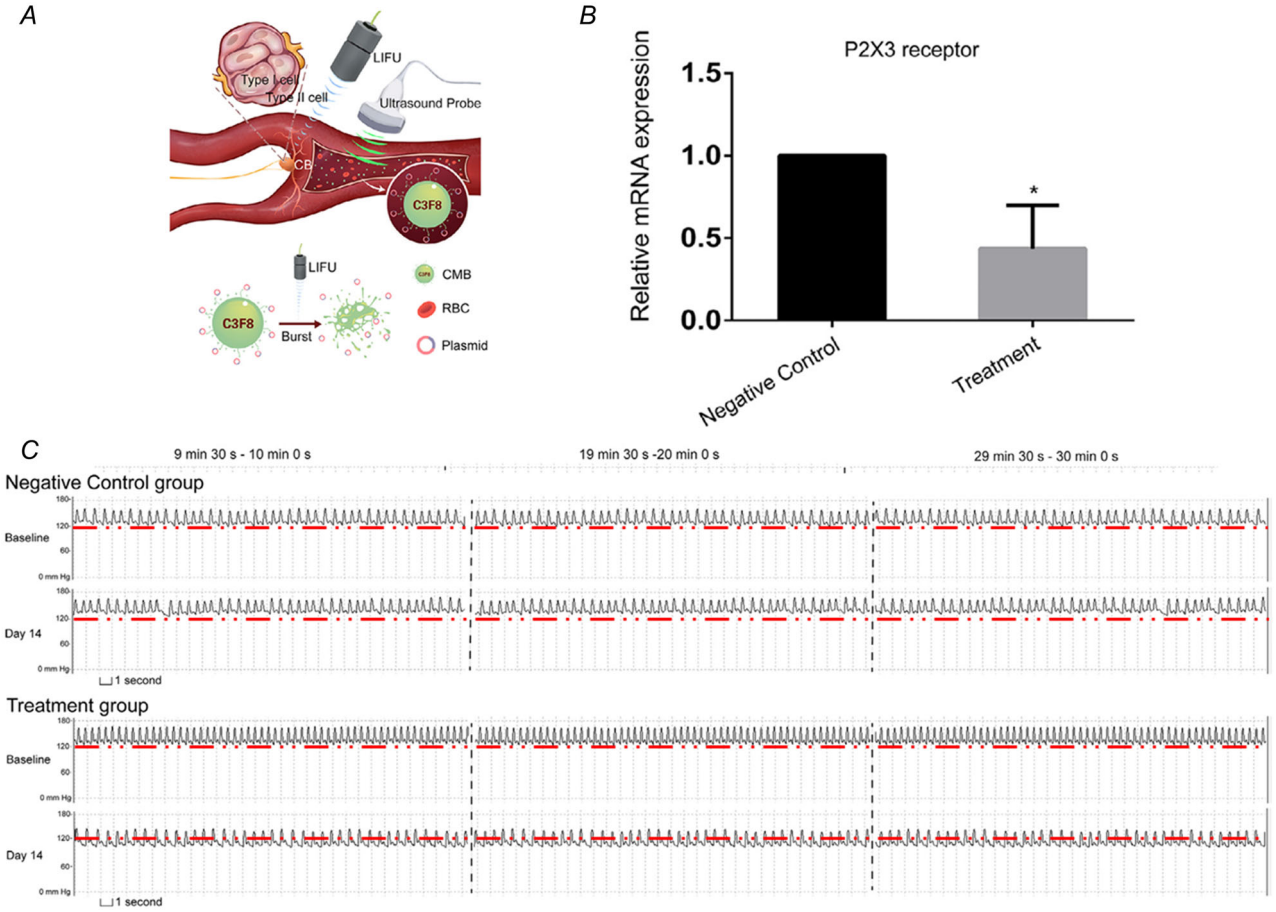



**Figure 7. Local down-regulation of P2X3 receptors in the CB decreases arterial blood pressure**
The CB-targeted local delivery of cationic microbubbles (CMBs) made of octafluoropropane (C3F8) with CRISPR/Cas9 plasmid engineered for disruption of the P2X3 gene with low-intensity focused ultrasound (LIFU) (*A*) effectively down-regulated mRNA expression of the P2X3 receptor in the CBs (*B*) and resulted in decreased arterial blood pressure evaluated at day 14 from baseline in a canine hypertension model as shown in pulsatile arterial pressure recordings (*C*) (Xue et al., 2021). Red dashed lines indicate 120 mmHg. Reproduced and modified with permission from Xue et al. (2021). [Colour figure can be viewed at wileyonlinelibrary.com]

changes in ventilatory responses to hypoxia following bilateral GGN resection. These changes, however, were limited to first 90–120 s of hypoxic exposure (Getsy et al., 2023).

Bioelectronic modulation of the carotid sinus nerve offers another exciting possibility for the modulation of CB afferent output. In a rat model, kilohertz pacing (specifically 40–50 kHz at 1–2 mA) from bilateral implantable cuff electrodes around the carotid sinus nerves provided inhibition of the cardiorespiratory response to hypoxia. Attenuation of the nerve traffic from the CBs translated into improved insulin sensitivity and better glucose tolerance. Importantly, this approach though being invasive was also dose-dependent and completely reversible (Conde et al., 2024; Sacramento et al., 2018). Whether this very high-frequency stimulation also blocked baroreceptor transmission altering blood pressure regulation remains unknown.

## Summary/conclusions

Unequivocally the data reviewed support the hypothesis that many diseases are associated with hyperexcitability of the CB that can cause autonomic imbalance and respiratory disturbances especially during sleep. In cardiometabolic disease, the literature supports the CB as a potential novel target for modulation. Human studies provide a stark warning that this cannot be ablation (unilateral or bilateral) due to worsening of apnoeas in patients with heart failure. However, most recent studies support the idea that the CB has separate lines of transmission for mediating the distinct components of the chemoreflex. These lines of transmission are characterized by unique transmitter and receptors that are ripe for interrogation of selective targeting of specific CB function. To date, the P2X3 and P2X2/3 receptors offer potential as a way to attenuate the CB and its hyperreflexia and hypertonicity in control of sympathetic activity, at least in hypertension and chronic heart failure. Also, ultrasound-guided genetic manipulation and high-frequency stimulation of the carotid sinus nerve may also provide approaches to quench CB aberrant activity. These approaches are encouraging and may restore autonomic balance without compromising ventilatory control which would be highly relevant to patients with comorbidities of hypertension, diabetes or heart failure with sleep apnoea.

## References


Abdala, A. P., McBryde, F. D., Marina, N., Hendy, E. B., Engelman, Z. J., Fudim, M., Sobotka, P. A., Gourine, A. V., & Paton, J. F. R. (2012). Hypertension is critically dependent on the carotid body input in the spontaneously hypertensive rat. *The Journal of Physiology*, **590**(17), 4269–4277.

Accorsi-Mendonca, D., Castania, J. A., Bonagamba, L. G. H., Machado, B. H., & Leao, R. M. (2011). Synaptic profile of nucleus tractus solitarius neurons involved with the peripheral chemoreflex pathways. *Neuroscience*, **197**, 107–120.

Acker, H., & O'Regan, R. G. (1981). The effects of stimulation of autonomic nerves on carotid body blood flow in the cat. *The Journal of Physiology*, **315**, 99–110.

Allen, A. M. (1998). Angiotensin AT1receptor-mediated excitation of rat carotid body chemoreceptor afferent activity. *The Journal of Physiology*, **510**(3), 773–781.

Alvarez-Buylla, R., & de Alvarez-Buylla, E. R. (1988). Carotid sinus receptors participate in glucose homeostasis. *Respiration Physiology*, **72**(3), 347–359.

Anderson, J. A., Chai, H., Claman, H. N., Ellis, E. F., Fink, J. N., Kaplan, A. P., Lieberman, P. L., Pierson, W. E., Salvaggio, J. E., Sheffer, A. L., & Slavin, R. G. (1986). Carotid body resection: Approved by the executive committee of the American academy of allergy and immunology. *Journal of Allergy and Clinical Immunology*, **78**(2), 273–275.

Atanasova, D. Y., Dandov, A. D., Dimitrov, N. D., & Lazarov, N. E. (2020). Histochemical and immunohistochemical localization of nitrergic structures in the carotid body of spontaneously hypertensive rats. *Acta Histochemica*, **122**(2), 151500.

Atanasova, D. Y., Dandov, A. D., & Lazarov, N. E. (2023). Neurochemical plasticity of the carotid body in hypertension. *Anatomical Record (Hoboken)*, **306**(9), 2366–2377.

Baby, S. M., Zaidi, F., Hunsberger, G. E., Sokal, D., Gupta, I., Conde, S. V., Chew, D., Rall, K., & Coatney, R. W. (2023). Acute effects of insulin and insulin-induced hypoglycaemia on carotid body chemoreceptor activity and cardiorespiratory responses in dogs. *Experimental Physiology*, **108**(2), 280–295.

Bardsley, E. N., Pen, D. K., McBryde, F. D., Ford, A. P., & Paton, J. F. R. (2021). The inevitability of ATP as a transmitter in the carotid body. *Autonomic Neuroscience*, **234**, 102815.

Bardsley, E. N., Schultz, H. D., Niewiński, P., & Paton, J. F. R. (2023). Chapter 134 - targeting carotid body chemoreceptors as a therapeutic intervention. In I. Biaggioni, K. Browning, G. Fink, J. Jordan, P. A. Low, J. F. R. Paton, (Eds.) *Primer on the Autonomic Nervous System*, (fourth ed., pp. 771–777). Academic Press. Available at: https://www.sciencedirect.com/science/article/pii/B9780323854924000788.

Bergmeijer, T. O., Janssen, P. W. A., van Oevelen, M., van Rooijen, D., Godschalk, T. C., Kelder, J. C., Deneer, V. H. M., Serebruany, V. L., & Berg, J. M. (2017). Incidence and causes for early ticagrelor discontinuation: A "real-world" Dutch registry experience. *Cardiology*, **138**(3), 164–168.

Bhandari, R., Sharma, A., & Kuhad, A. (2021). Novel nanotechnological approaches for targeting dorsal root ganglion (DRG) in mitigating diabetic neuropathic pain (DNP). *Frontiers in Endocrinology (Lausanne)*, **12**, 790747.

Bharucha, A. E., Charkoudian, N., Andrews, C. N., Camilleri, M., Sletten, D., Zinsmeister, A. R., & Low, P. A. (2008). Effects of glucagon-like peptide-1, yohimbine, and nitrergic modulation on sympathetic and parasympathetic activity in humans. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **295**(3), R874–R880.

Bin-Jaliah, I., Maskell, P. D., & Kumar, P. (2004). Indirect sensing of insulin-induced hypoglycaemia by the carotid body in the rat. *The Journal of Physiology*, **556**(1), 255–266.

Binet, L., & Dejours, P. (1962). [The role of arterial chemoreceptors in the control of pulmonary respiration in man]. *Archives Internationales De Pharmacodynamie Et De Therapie*, **139**, 328–335.

Biscoe, T. J., Purves, M. J., & Sampson, S. R. (1970). The frequency of nerve impulses in single carotid body chemoreceptor afferent fibres recorded in vivo with intact circulation. *The Journal of Physiology*, **208**(1), 121–131.

Bizzi, E., Libretti, A., Malliani, A., & Zanchetti, A. (1961). Reflex chemoceptive excitation of diencephalic sham rage behavior. *American Journal of Physiology-Legacy Content*, **200**(5), 923–926.

Bock, J. M., Ueda, K., Schneider, A. C., Hughes, W. E., Limberg, J. K., Bryan, N.S., & Casey, D. P. (2018). Inorganic nitrate supplementation attenuates peripheral chemoreflex sensitivity but does not improve cardiovagal baroreflex sensitivity in older adults. *American Journal of Physiology-Heart and Circulatory Physiology*, **314**(1), H45–H51.

Brognara, F., Felippe, I. S. A., Salgado, H. C., & Paton, J. F. R. (2021). Autonomic innervation of the carotid body as a determinant of its sensitivity: implications for cardiovascular physiology and pathology. *Cardiovascular Research*, **117**(4), 1015–1032.

Buttigieg, J., & Nurse, C. A. (2004). Detection of hypoxia-evoked ATP release from chemoreceptor cells of the rat carotid body. *Biochemical and Biophysical Research Communications*, **322**(1), 82–87.

Caballero-Eraso, C., Shin, M.-K., Pho, H., Kim, L. J., Pichard, L. E., Wu, Z.-J., Gu, C., Berger, S., Pham, L., Yeung, H.-Y. B., Shirahata, M., Schwartz, A. R., Tang, W.-Y. W., Sham, J. S. K., & Polotsky, V. Y. (2019). Leptin acts in the carotid bodies to increase minute ventilation during wakefulness and sleep and augment the hypoxic ventilatory response. *The Journal of Physiology*, **597**(1), 151–172.

Campanucci, V. A., Zhang, M., Vollmer, C., & Nurse, C. A. (2006). Expression of multiple P2X receptors by glossopharyngeal neurons projecting to rat carotid body O2-chemoreceptors: role in nitric oxide-mediated efferent inhibition. *Journal of Neuroscience*, **26**(37), 9482–9493.

Chang, A. J., Kim, N. S., Hireed, H., de Arce, A. D., Ortega, F. E., Riegler, J., Madison, D. V., & Krasnow, M. A. (2018). Chang et al. reply. *Nature*, **561**(7724), E41–E41.

Chang, A. J., Ortega, F. E., Riegler, J., Madison, D. V., & Krasnow, M. A. (2015). Oxygen regulation of breathing through an olfactory receptor activated by lactate. *Nature*, **527**(7577), 240–244.

Chen, Z., Zhao, H., Fu, N., & Chen, L. (2018). The diversified function and potential therapy of ectopic olfactory receptors in non-olfactory tissues. *Journal of Cellular Physiology*, **233**(3), 2104–2115.

Cheng, X., Prange-Barczynska, M., Fielding, J. W., Zhang, M., Burrell, A. L., Lima, J. D., Eckardt, L., Argles, I. L. A., Pugh, C. W., Buckler, K. J., Robbins, P. A., Hodson, E. J., Bruick, R. K., Collinson, L. M., Rastinejad, F., Bishop, T., & Ratcliffe, P. J. (2020). Marked and rapid effects of pharmacological HIF-2$\alpha$ antagonism on hypoxic ventilatory control. *Journal of Clinical Investigation*, **130**(5), 2237–2251.

Chua, T. P., Clark, A. I., Amadi, A. A., & Coats, A. J. S. (1996). Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *Journal of the American College of Cardiology*, **27**(3), 650–657.

Chua, T. P., Harrington, D., Ponikowski, P., Webb-Peploe, K., Poole-Wilson, P. A., & Coats, A. J. S. (1997). Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure. *Journal of the American College of Cardiology*, **29**(1), 147–152.

Chua, T. P., Ponikowski, P. P., Harrington, D., Chambers, J., & Coats, A. J. S. (1996). Contribution of peripheral chemoreceptors to ventilation and the effects of their suppression on exercise tolerance in chronic heart failure. *Heart*, **76**(6), 483–489.

Claps, A., & Torrealba, F. (1988). The carotid body connections: A WGA-HRP study in the cat. *Brain Research*, **455**(1), 123–133.

Colinas, O., Mombaerts, P., López-Barneo, J., & Ortega-Sáenz, P. (2024). Carotid body function in tyrosine hydroxylase conditional Olfr78 knockout mice. *Function (Oxford, England)*, **5**(3), zqae010.

Comroe, J. H. J., & Mortimer, L. (1964). The respiratory and cardiovascular responses of temporally separated aortic and carotid bodies to cyanide, nicotine, phenyldiguanide and serotonin. *Journal of Pharmacology and Experimental Therapeutics*, **146**(1), 33–41.

Conde, S. V., Monteiro, E. C., Rigual, R., Obeso, A., & Gonzalez, C. (2012). Hypoxic intensity: A determinant for the contribution of ATP and adenosine to the genesis of carotid body chemosensory activity. *Journal of Applied Physiology*, **112**(12), 2002–2010.

Conde, S. V., Obeso, A., & Gonzalez, C. (2007). Low glucose effects on rat carotid body chemoreceptor cells' secretory responses and action potential frequency in the carotid sinus nerve. *The Journal of Physiology*, **585**(3), 721–730.

Conde, S. V., Sacramento, J. F., & Guarino, M. P. (2018). Carotid body: A metabolic sensor implicated in insulin resistance. *Physiological Genomics*, **50**(3), 208–214.

Conde, S. V., Sacramento, J. F., Guarino, M. P., Gonzalez, C., Obeso, A., Diogo, L. N., Monteiro, E. C., & Ribeiro, M. J. (2014). Carotid body, insulin, and metabolic diseases: unraveling the links. *Frontiers in Physiology*, **5**, 418.

Conde, S. V., Sacramento, J. F., & Martins, F. O. (2020). Immunity and the carotid body: Implications for metabolic diseases. *Bioelectronic Medicine*, **6**(1), 24.

Conde, S. V., Sacramento, J. F., Zinno, C., Mazzoni, A., Micera, S., & Guarino, M. P. (2024). Bioelectronic modulation of carotid sinus nerve to treat type 2 diabetes: Current knowledge and future perspectives. *Frontiers in Neuroscience*, **18**, 1378473.

Conroy, L. J., McCann, A., Zhang, N., & de Gaetano, M. (2024). The role of nanosystems in the delivery of glucose-lowering drugs for the preemption and treatment of diabetes-associated atherosclerosis. *American Journal of Physiology-Cell Physiology*, **326**(5), C1398–C1409.

Contini, M., Apostolo, A., Cattadori, G., Paolillo, S., Iorio, A., Bertella, E., Salvioni, E., Alimento, M., Farina, S., Palermo, P., Loguercio, M., Mantegazza, V., Karsten, M., Sciomer, S., Magrì, D., Fiorentini, C., & Agostoni, P. (2013). Multiparametric comparison of CARvedilol, vs. NEbivolol, vs. BIsoprolol in moderate heart failure: The CARNEBI trial. *International Journal of Cardiology*, **168**(3), 2134–2140.

Cracchiolo, M., Sacramento, J. F., Mazzoni, A., Panarese, A., Carpaneto, J., Conde, S. V., & Micera, S. (2019). Decoding neural metabolic markers from the carotid sinus nerve in a type 2 diabetes model. *Institute of Electrical and Electronics Engineers Transactions on Neural Systems and Rehabilitation Engineering IEEE Engineering in Medicine and Biology Society*, **27**(10), 2034–2043.

Cramer, J. A., Wiggins, R. H., Fudim, M., Engelman, Z. J., Sobotka, P. A., & Shah, L. M. (2014). Carotid body size on CTA: Correlation with comorbidities. *Clinical Radiology*, **69**(1), e33-e36.

Critchley, J. A., Ellis, P., Henderson, C. G., & Ungar, A. (1982). The role of the pituitary-adrenocortical axis in reflex responses of the adrenal medulla of the dog. *The Journal of Physiology*, **323**(1), 533–541.

Critchley, J. A., Ellis, P., & Ungar, A. (1980). The reflex release of adrenaline and noradrenaline from the adrenal glands of cats and dogs. *The Journal of Physiology*, **298**(1), 71–78.

Cunha-Guimaraes, J. P., Guarino, M. P., Timóteo, A. T., Caires, I., Sacramento, J. F., Ribeiro, M. J., Selas, M., Santiago, J. C. P., Mota-Carmo, M., & Conde, S. V. (2020). Carotid body chemosensitivity: Early biomarker of dysmetabolism in humans. *European Journal of Endocrinology*, **182**(6), 549–557.

de Daly, M. B., & Scott, M. J. (1958). The effects of stimulation of the carotid body chemoreceptors on heart rate in the dog. *The Journal of Physiology*, **144**(1), 148–166.

Davidson, J. T., Whipp, B. J., Wasserman, K., Koyal, S. N., & Lugliani, R. (1974). Role of the carotid bodies in breath-holding. *New England Journal of Medicine*, **290**(15), 819–822.

Denjean, A., Canet, E., Praud, J. P., Gaultier, C., & Bureau, M. (1991). Hypoxia-induced bronchial responsiveness in awake sheep: Role of carotid chemoreceptors. *Respiration Physiology*, **83**(2), 201–210.

Desai, A. S., Webb, D. J., Taubel, J., Casey, S., Cheng, Y., Robbie, G. J., Foster, D., Huang, S. A., Rhyee, S., Sweetser, M. T., & Bakris, G. L. (2023). Zilebesiran, an RNA interference therapeutic agent for hypertension. *New England Journal of Medicine*, **389**(3), 228–238.

Despas, F., Lambert, E., Vaccaro, A., Labrunee, M., Franchitto, N., Lebrin, M., Galinier, M., Senard, J.-M., Lambert, G., Esler, M., & Pathak, A. (2012). Peripheral chemoreflex activation contributes to sympathetic baroreflex impairment in chronic heart failure. *Journal of Hypertension*, **30**(4), 753–760.

Dharia, S. M., & Brown, L. K. (2017). Epidemiology of sleep-disordered breathing and heart failure: What drives what. *Current Heart Failure Reports*, **14**(5), 351–364.

Ding, Y., Li, Y.-L. L., & Schultz, H. D. (2011). Role of blood flow in carotid body chemoreflex function in heart failure. *The Journal of Physiology*, **589**(1), 245–258.

Donoghue, S., Felder, R. B., Jordan, D., & Spyer, K. M. (1984). The central projections of carotid baroreceptors and chemoreceptors in the cat: A neurophysiological study. *The Journal of Physiology*, **347**(1), 397–409.

Drucker, D. J., & Holst, J. J. (2023). The expanding incretin universe: From basic biology to clinical translation. *Diabetologia*, **66**(10), 1765–1779.

Duffin, J. (2011). Measuring the respiratory chemoreflexes in humans. *Respiratory Physiology, & Neurobiology*, **177**(2), 71–79.

Edelman, N. H., Epstein, P. E., Lahiri, S., & Cherniack, N. S. (1973). Ventilatory responses to transient hypoxia and hypercapnia in man. *Respiration Physiology*, **17**(3), 302–314.

El-Medany, A., Adams, Z. H., Blythe, H. C., Hope, K. A., Kendrick, A. H., Abdala Sheikh, A. P., Paton, J. F. R., Nightingale, A. K., & Hart, E. C. (2024). Carotid body dysregulation contributes to Long COVID symptoms. *Communications Medicine*, **4**(1), 20.

Emans, T. W., Moraes, D. J. A., Ben-Tal, A., Barrett, C. J., Paton, J. F. R., & McBryde, F. D. (2024). Forgotten circulation: Reduced mesenteric venous capacitance in hypertensive rats is improved by decreasing sympathetic activity. *Hypertens (Dallas, Texas 1979)*, **81**(4), 823–835.

Erickson, J. T., & Millhorn, D. E. (1994). Hypoxia and electrical stimulation of the carotid sinus nerve induce fos-like immunoreactivity within catecholaminergic and serotoninergic neurons of the rat brainstem. *Journal of Comparative Neurology*, **348**(2), 161–182.

Farrar, T., Kirklin, J. W., Judd, E. S., & Devine, K. D. (1956). Resection of carotid-body tumors with preservation of the carotid vessels. *American Medical Association Archives of Surgery*, **72**(4), 595–599.

Felippe, I. S. A., Del Río, R., Schultz, H., Machado, B. H., & Paton, J. F. R. (2023). Commonalities and differences in carotid body dysfunction in hypertension and heart failure. *The Journal of Physiology*, **601**(24), 5527–5551.

Felippe, I. S. A., Zera, T., daSilva, M. P., Moraes, D., McBryde, F., & Paton, J. (2023). The sympathetic nervous system exacerbates carotid body sensitivity in hypertension. *Cardiovascular Research*, **119**(1), 316–331.

Fidone, S. J., & Sato, A. (1969). A study of chemoreceptor and baroreceptor A and C-fibres in the cat carotid nerve. *The Journal of Physiology*, **205**(3), 527–548.

Finley, J. C., & Katz, D. M. (1992). The central organization of carotid body afferent projections to the brainstem of the rat. *Brain Research*, **572**(1–2), 108–116.

Fletcher, E. C., Lesske, J., Behm, R., Miller, C. C. 3rd, Stauss, H., & Unger, T. (1992). Carotid chemoreceptors, systemic blood pressure, and chronic episodic hypoxia mimicking sleep apnea. *Journal of Applied Physiology*, **72**(5), 1978–1984.

Fletcher, E. C., Lesske, J., Qian, W., Miller, C. C. 3rd, & Unger, T. (1992). Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. *Hypertens (Dallas, Texas 1979)*, **19**(6_pt_1), 555–561.

Fukuda, Y., Sato, A., & Trzebski, A. (1987). Carotid chemoreceptor discharge responses to hypoxia and hypercapnia in normotensive and spontaneously hypertensive rats. *Journal of the Autonomic Nervous System*, **19**(1), 1–11.

Fung, M.-L. (2016). Angiotensin II in the carotid body – A friend or foe? *Experimental Physiology*, **101**(6), 675–676.

Gallego-Martin, T., Fernandez-Martinez, S., Rigual, R., Obeso, A., & Gonzalez, C. (2012). Effects of low glucose on carotid body chemoreceptor cell activity studied in cultures of intact organs and in dissociated cells. *American Journal of Physiology-Cell Physiology*, **302**(8), C1128–C1140.

Gallego, R., & Belmonte, C. (1979). The effects of blood osmolality changes on cat carotid body chemoreceptors in vivo. *Pflugers Archiv: European Journal of Physiology*, **380**(1), 53–58.

García-Fernández, M., Ortega-Sáenz, P., Castellano, A., & López-Barneo, J. (2007). Mechanisms of low-glucose sensitivity in carotid body glomus cells. *Diabetes*, **56**(12), 2893–2900.

García-Río, F., Racionero, M. A., Pino, J. M., Martínez, I., Ortuño, F., Villasante, C., & Villamor, J. (2000). Sleep apnea and hypertension. *Chest*, **117**(5), 1417–1425.

Gauda, E. B., Conde, S., Bassi, M., Zoccal, D. B., Almeida Colombari, D. S., Colombari, E., & Despotovic, N. (2020). Leptin: Master regulator of biological functions that affects breathing. *Comprehensive Physiology*, **10**(3), 1047–1083.

Gazzaniga, G., Menichelli, D., Scaglione, F., Farcomeni, A., Pani, A., & Pastori, D. (2023). Effect of digoxin on all-cause and cardiovascular mortality in patients with atrial fibrillation with and without heart failure: An umbrella review of systematic reviews and 12 meta-analyses. *European Journal of Clinical Pharmacology*, **79**(4), 473–483.

Gerlach, D. A., Manuel, J., Hoff, A., Kronsbein, H., Hoffmann, F., Heusser, K., Ehmke, H., Jordan, J., Tank, J., & Beissner, F. (2021). Medullary and hypothalamic functional magnetic imaging during acute hypoxia in tracing human peripheral chemoreflex responses. *Hypertension (Dallas, Texas 1979)*, **77**(4), 1372–1382.

Getsy, P. M., Coffee, G. A., & Lewis, S. J. (2023). Loss of ganglioglomerular nerve input to the carotid body impacts the hypoxic ventilatory response in freely-moving rats. *Frontiers in Physiology*, **14**, 1007043.

Gever, J. R., Cockayne, D. A., Dillon, M. P., Burnstock, G., & Ford, A. (2006). Pharmacology of P2X channels. *Pflugers Archiv: European Journal of Physiology*, **452**(5), 513–537.

Giannoni, A., Emdin, M., Bramanti, F., Iudice, G., Francis, D. P., Barsotti, A., Piepoli, M., & Passino, C. (2009). Combined increased chemosensitivity to hypoxia and hypercapnia as a prognosticator in heart failure. *Journal of the American College of Cardiology*, **53**(21), 1975–1980.

Giannoni, A., Emdin, M., Poletti, R., Bramanti, F., Prontera, C., Piepoli, M., & Passino, C. (2008). Clinical significance of chemosensitivity in chronic heart failure: Influence on neurohormonal derangement, Cheyne–Stokes respiration and arrhythmias. *Clinical Science*, **114**(7), 489–497.

Giannoni, A., Gentile, F., Buoncristiani, F., Borrelli, C., Sciarrone, P., Spiesshoefer, J., Bramanti, F., Iudice, G., Javaheri, S., Emdin, M., & Passino, C. (2022). Chemoreflex and baroreflex sensitivity hold a strong prognostic value in chronic heart failure. *Journal of the American College of Cardiology Heart Failure*, **10**(9), 662–676.

Gold, O. M. S., Bardsley, E. N., Ponnampalam, A. P., Pauza, A. G., & Paton, J. F. R. (2022). Cellular basis of learning and memory in the carotid body. *Frontiers in Synaptic Neuroscience*, **14**, 902319.

Gonzalez, C., Almaraz, L., Obeso, A., & Rigual, R. (1994). Carotid body chemoreceptors: From natural stimuli to sensory discharges. *Physiological Reviews*, **74**(4), 829–898.

Greenberg, H. E., Sica, A., Batson, D., & Scharf, S. M. (1999). Chronic intermittent hypoxia increases sympathetic responsiveness to hypoxia and hypercapnia. *Journal of Applied Physiology*, **86**(1), 298–305.

Haack, K. K. V., Marcus, N. J., Del Río, R., Zucker, I. H., & Schultz, H. D. (2014). Simvastatin treatment attenuates increased respiratory variability and apnea/hypopnea index in rats with chronic heart failure. *Hypertens (Dallas, Texas 1979)*, **63**(5), 1041–1049.

He, L., Dinger, B., & Fidone, S. (2000). Cellular mechanisms involved in carotid body inhibition produced by atrial natriuretic peptide. *American Journal of Physiology-Cell Physiology*, **278**(4), C845–C852.

Heindl, S., Lehnert, M., Criée, C. P., Hasenfuss, G., & Andreas, S. (2001). Marked sympathetic activation in patients with chronic respiratory failure. *American Journal of Respiratory and Critical Care Medicine*, **164**(4), 597–601.

Hennersdorf, M. G., Hillebrand, S., Perings, C., & Strauer, B. E. (2001). Chemoreflexsensitivity in chronic heart failure patients. *European Journal of Heart Failure*, **3**(6), 679–684.

Hilton, S. M., & Marshall, J. M. (1982). The pattern of cardiovascular response to carotid chemoreceptor stimulation in the cat. *The Journal of Physiology*, **326**(1), 495–513.

Hoka, S., Bosnjak, Z. J., Arimura, H., & Kampine, J. P. (1989). Regional venous outflow, blood volume, and sympathetic nerve activity during severe hypoxia. *American Journal of Physiology*, **256**(1 Pt 2), H162–70.

Honda, Y., Watanabe, S., Hashizume, I., Satomura, Y., Hata, N., Sakakibara, Y., & Severinghaus, J. W. (1979). Hypoxic chemosensitivity in asthmatic patients two decades after carotid body resection. *Journal of Applied Physiology*, **46**(4), 632–638.

Honigberg, M. C., Chang, L.-S., McGuire, D. K., Plutzky, J., Aroda, V. R., & Vaduganathan, M. (2020). Use of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes and cardiovascular disease: A review. *Journal of the American Medical Association Cardiology*, **5**(10), 1182–1190.

Ito, B. R., & Feigl, E. O. (1985). Carotid chemoreceptor reflex parasympathetic coronary vasodilation in the dog. *American Journal of Physiology*, **249**(6 Pt 2), H1167–H1175.

Iturriaga, R. (2018). Translating carotid body function into clinical medicine. *The Journal of Physiology*, **596**(15), 3067–3077.

Iturriaga, R. (2023). Carotid body contribution to the physio-pathological consequences of intermittent hypoxia: Role of nitro-oxidative stress and inflammation. *The Journal of Physiology*, **601**(24), 5495–5507.

Iturriaga, R., Alcayaga, J., Chapleau, M. W., & Somers, V. K. (2021). Carotid body chemoreceptors: Physiology, pathology, and implications for health and disease. *Physiological Reviews*, **101**(3), 1177–1235.

Iturriaga, R., Moya, E. A., & Del Río, R. (2010). Cardiorespiratory alterations induced by intermittent hypoxia in a rat model of sleep apnea. *Advances in Experimental Medicine and Biology*, **669**, 271–274.

Izdebska, E., Cybulska, I., Sawicki, M., Izdebski, J., & Trzebski, A. (1998). Postexercise decrease in arterial blood pressure, total peripheral resistance and in circulatory responses to brief hyperoxia in subjects with mild essential hypertension. *Journal of Human Hypertension*, **12**(12), 855–860.

Izdebska, E., Izdebski, J., & Trzebski, A. (1996). Hemodynamic responses to brief hyperoxia in healthy and in mild hypertensive human subjects in rest and during dynamic exercise. *Journal of Physiology and Pharmacology*, **47**(2), 243–256.

Jack, S., Rossiter, H. B., Pearson, M. G., Ward, S. A., Warburton, C. J., & Whipp, B. J. (2004). Ventilatory responses to inhaled carbon dioxide, hypoxia, and exercise in idiopathic hyperventilation. *American Journal of Respiratory and Critical Care Medicine*, **170**(2), 118–125.

Janssen, C., Beloka, S., Kayembe, P., Deboeck, G., Adamopoulos, D., Naeije, R., & van de Borne, P. (2009). Decreased ventilatory response to exercise by dopamine-induced inhibition of peripheral chemosensitivity. *Respiratory Physiology, & Neurobiology*, **168**(3), 250–253.

Janssen, C., Lheureux, O., Beloka, S., Deboeck, G., Adamopoulos, D., Naeije, R., & van de borne, P. (2010). Digoxin increases peripheral chemosensitivity and the ventilatory response to exercise in normal subjects. *Clinical and Experimental Pharmacology, & Physiology*, **37**(3), 303–308.

Jaźwiec, P., Gać, P., Jurdziak, M., Poręba, M., Mazur, G., Sobieszczańska, M., & Poręba, R. (2015). Volume of carotid bodies and cardiac autonomic function in patients with essential hypertension. *Autonomic Neuroscience*, **190**, 26–32.

Jaźwiec, P., Gać, P., Poręba, M., Sobieszczańska, M., Mazur, G., & Poręba, R. (2016). The volume of the carotid bodies and blood pressure variability and pulse pressure in patients with essential hypertension. *Clinical Radiology*, **71**(6), 616.e7–616.e13.

Jendzjowsky, N. G., Roy, A., Barioni, N. O., Kelly, M. M., Green, F. H. Y., Wyatt, C. N., Pye, R. L., Tenorio-Lopes, L., & Wilson, R. J. A. (2018). Preventing acute asthmatic symptoms by targeting a neuronal mechanism involving carotid body lysophosphatidic acid receptors. *Nature Communications*, **9**(1), 4030.

Jolesz, F. A. (2009). MRI-guided focused ultrasound surgery. *Annual Review of Medicine*, **60**(1), 417–430.

Kahler, R. L., Goldblatt, A., & Braunwald, E. (1962). The effects of acute hypoxia on the systemic venous and arterial systems and on myocardial contractile force. *Journal of Clinical Investigation*, **41**(7), 1553–1563.

Karim, F., Hainsworth, R., Sofola, O. A., & Wood, L. M. (1980). Responses of the heart to stimulation of aortic body chemoreceptors in dogs. *Circulation Research*, **46**(1), 77–83.

Karim, F., Poucher, S. M., & Summerill, R. A. (1987). The effects of stimulating carotid chemoreceptors on renal haemodynamics and function in dogs. *The Journal of Physiology*, **392**(1), 451–462.

Katayama, P. L., Leirão, I. P., Kanashiro, A., Luiz, J. P. M., Cunha, F. Q., Navegantes, L. C. C., Menani, J. V., Zoccal, D. B., Colombari, D. S. A., & Colombari, E. (2022). The carotid body detects circulating tumor necrosis factor-alpha to activate a sympathetic anti-inflammatory reflex. *Brain, Behavior, and Immunity*, **102**, 370–386.

Kato, H., Menon, A. S., & Slutsky, A. S. (1988). Mechanisms mediating the heart rate response to hypoxemia. *Circulation*, **77**(2), 407–414.

Keir, D. A., Duffin, J., & Floras, J. S. (2020). Measuring peripheral chemoreflex hypersensitivity in heart failure. *Frontiers in Physiology*, **11**, 595486.

Keir, D. A., Duffin, J., Millar, P. J., & Floras, J. S. (2019). Simultaneous assessment of central and peripheral chemoreflex regulation of muscle sympathetic nerve activity and ventilation in healthy young men. *The Journal of Physiology*, **597**(13), 3281–3296.

Kim, S. J., Fong, A. Y., Pilowsky, P. M., & Abbott, S. B. G. (2018). Sympathoexcitation following intermittent hypoxia in rat is mediated by circulating angiotensin II acting at the carotid body and subfornical organ. *The Journal of Physiology*, **596**(15), 3217–3232.

Kimura, A., Sato, A., Sato, Y., & Trzebski, A. (1993). Role of the central and arterial chemoreceptors in the response of gastric tone and motility to hypoxia, hypercapnia and hypocapnia in rats. *Journal of the Autonomic Nervous System*, **45**(1), 77–85.

Kline, D. D., King, T. L., Austgen, J. R., Heesch, C. M., & Hasser, E. M. (2010). Sensory afferent and hypoxia-mediated activation of nucleus tractus solitarius neurons that project to the rostral ventrolateral medulla. *Neuroscience*, **167**(2), 510–527.

Kong, F.-Y., Zhang, J.-W., Li, R.-F., Wang, Z.-X., Wang, W.-J., & Wang, W. (2017). Unique roles of gold nanoparticles in drug delivery, targeting and imaging applications. *Molecules (Basel, Switzerland)*, **22**(9), 1445.

Koyama, Y., Coker, R. H., Denny, J. C., Lacy, D. B., Jabbour, K., Williams, P. E., & Wasserman, D. H. (2001). Role of carotid bodies in control of the neuroendocrine response to exercise. *American Journal of Physiology-Endocrinology and Metabolism*, **281**(4), E742–E748.

Kubin, L., Trzebski, A., & Lipski, J. (1985). Split medulla preparation in the cat: Arterial chemoreceptor reflex and respiratory modulation of the renal sympathetic nerve activity. *Journal of the Autonomic Nervous System*, **12**(2–3), 211–225.

Kulej-Lyko, K., Niewinski, P., Tubek, S., & Ponikowski, P. (2022). Contribution of peripheral chemoreceptors to exercise intolerance in heart failure. *Frontiers in Physiology*, **13**, 878363.

Kumar, P., & Bin-Jaliah, I. (2007). Adequate stimuli of the carotid body: More than an oxygen sensor? *Respiratory Physiology, & Neurobiology*, **157**(1), 12–21.

Lam, S.-Y., Tipoe, G. L., Liong, E. C., & Fung, M.-L. (2006). Hypoxia-inducible factor (HIF)-1alpha and endothelin-1 expression in the rat carotid body during intermittent hypoxia. *Advances in Experimental Medicine and Biology*, **580**, 21–29.

Lataro, R. M., Brognara, F., Iturriaga, R., & Paton, J. F. R. (2024). Inflammation of some visceral sensory systems and autonomic dysfunction in cardiovascular disease. *Autonomic Neuroscience*, **251**, 103137.

Lataro, R. M., Moraes, D. J. A., Gava, F. N., Omoto, A. C. M., Silva, C. A. A., Brognara, F., Alflen, L., Brazão, V., Colato, R. P., do Prado, J. C. J., Ford, A. P., Salgado, H. C., & Paton, J. F. R. (2023). P2×3 receptor antagonism attenuates the progression of heart failure. *Nature Communications*, **14**(1), 1725.

Lewis, C., Neidhart, S., Holy, C., North, R. A., Buell, G., & Surprenant, A. (1995). Coexpression of P2×2 and P2×3 receptor subunits can account for ATP-gated currents in sensory neurons. *Nature*, **377**(6548), 432–435.

Li, J., Yang, S., Yu, F., Ji, E. S., & Woodrow Weiss, J. (2019). Endothelin-1 enhanced carotid body chemosensory activity in chronic intermittent hypoxia through PLC, PKC and p38MAPK signaling pathways. *Neuropeptides*, **74**, 44–51.

Li, Y. L., Xia, X. H., Zheng, H., Gao, L., Li, Y. F., Liu, D., Patel, K. P., Wang, W., & Schultz, H. D. (2006). Angiotensin II enhances carotid body chemoreflex control of sympathetic outflow in chronic heart failure rabbits. *Cardiovascular Research*, **71**(1), 129–138.

Limberg, J. K., Ott, E. P., Pipkins, A. M., Lis, E. C., Gonsalves, A. M., Harper, J. L., & Manrique-Acevedo, C. (2024). Role of the peripheral chemoreceptors in cardiovascular and metabolic control in type 2 diabetes. *The Journal of Physiology*, **602**(19), 4849–4864.

Lincoff, A. M., Brown-Frandsen, K., Colhoun, H. M., Deanfield, J., Emerson, S. S., Esbjerg, S., Hardt-Lindberg, S., Hovingh, G. K., Kahn, S. E., Kushner, R. F., Lingvay, I., Oral, T. K., Michelsen, M. M., Plutzky, J., Tornøe, C. W., & Ryan, D. H. (2023). Semaglutide and cardiovascular outcomes in obesity without diabetes. *New England Journal of Medicine*, **389**(24), 2221–2232.

Lipski, J., McAllen, R. M., & Spyer, K. M. (1977). The carotid chemoreceptor input to the respiratory neurones of the nucleus of tractus solitarus. *The Journal of Physiology*, **269**(3), 797–810.

Lipski, J., McAllen, R. M., & Trzebski, A. (1976). Carotid baroreceptor and chemoreceptor inputs onto single medullary neurones. *Brain Research*, **107**(1), 132–136.

Lis, E. C., Ott, E. P., Harper, J. L., Manrique-Acevedo, C., & Limberg, J. K. (2022). Peripheral chemoreflex sensitivity is augmented in Human type 2 diabetes. *Federation of American Societies for Experimental Biology Journal*, **36**(S1).

Liu, M., King, B. F., Dunn, P. M., Rong, W., Townsend-Nicholson, A., & Burnstock, G. (2001). Coexpression of P2X(3) and P2X(2) receptor subunits in varying amounts generates heterogeneous populations of P2X receptors that evoke a spectrum of agonist responses comparable to that seen in sensory neurons. *Journal of Pharmacology and Experimental Therapeutics*, **296**(3), 1043–1050.

Liu, X., He, L., Stensaas, L., Dinger, B., & Fidone, S. (2009). Adaptation to chronic hypoxia involves immune cell invasion and increased expression of inflammatory cytokines in rat carotid body. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, **296**(2), L158–L166.

Liu, Y., Ji, E.-S., Xiang, S., Tamisier, R., Tong, J., Huang, J., & Weiss, J. W. (2009). Exposure to cyclic intermittent hypoxia increases expression of functional NMDA receptors in the rat carotid body. *Journal of Applied Physiology*, **106**(1), 259–267.

Lobo, M. D. (2023). Transcatheter carotid body denervation: first-in-man results and future directions. In R. R. Heuser, M. P. Schlaich, D. Hering, & S. C. Bertog (Eds), *Renal Denervation: Treatment and Device-Based Neuromodulation* (pp. 193–198). Springer International Publishing, Cham. Available at: https://doi.org/10.1007/978-3-031-38934-4_19.

López-Barneo, J. (2022). Neurobiology of the carotid body. *Handbook of Clinical Neurology*, **188**, 73–102.

López-Barneo, J., González-Rodríguez, P., Gao, L., Fernández-Agüera, M. C., Pardal, R., & Ortega-Sáenz, P. (2016). Oxygen sensing by the carotid body: mechanisms and role in adaptation to hypoxia. *American Journal of Physiology-Cell Physiology*, **310**(8), C629–C642.

Lu, Y., Whiteis, C. A., Sluka, K. A., Chapleau, M. W., & Abboud, F. M. (2013). Responses of glomus cells to hypoxia and acidosis are uncoupled, reciprocal and linked to ASIC3 expression: selectivity of chemosensory transduction. *The Journal of Physiology*, **591**(4), 919–932.

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 England Journal of Medicine*, **285**(20), 1105–1111.

Lusina, S.-J. C., Kennedy, P. M., Inglis, J. T., McKenzie, D. C., Ayas, N. T., & Sheel, A. W. (2006). Long-term intermittent hypoxia increases sympathetic activity and chemosensitivity during acute hypoxia in humans. *The Journal of Physiology*, **575**(3), 961–970.

Madden, C. J., & Morrison, S. F. (2005). Hypoxic activation of arterial chemoreceptors inhibits sympathetic outflow to brown adipose tissue in rats. *The Journal of Physiology*, **566**(2), 559–573.

Majcherczyk, S., Chruścielewski, L., & Trzebski, A. (1974). Effect of stimulation of carotid body chemoreceptors upon ganglioglomerular nerve activity and on chemoreceptor discharges in contralateral sinus nerve. *Brain Research*, **76**(1), 167–170.

Majcherczyk, S., & Willshaw, P. (1973). Inhibition of peripheral chemoreceptor activity during superfusion with an alkaline c.s.f. of the ventral brain stem surface of the cat. *The Journal of Physiology*, **231**, 26P–27P.

Mancini, D. M., Eisen, H., Kussmaul, W., Mull, R., Henry Edmunds, L., & Wilson, J. R. (1991). Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*, **83**(3), 778–786.

Marcus, N. J., Del Río, R., Ding, Y., & Schultz, H. D. (2018). KLF2 mediates enhanced chemoreflex sensitivity, disordered breathing and autonomic dysregulation in heart failure. *The Journal of Physiology*, **596**(15), 3171–3185.

Marcus, N. J., Del Río, R., Schultz, E. P., Xia, X.-H., & Schultz, H. D. (2014). Carotid body denervation improves autonomic and cardiac function and attenuates disordered breathing in congestive heart failure. *The Journal of Physiology*, **592**(2), 391–408.

Marcus, N. J., Del Río, R., & Schultz, H. D. (2013). Carotid body denervation attenuates oscillations in respiratory rate and sympathetic nerve activity, and decreases apnea/hypopnea index in congestive heart failure. *Federation of American Societies for Experimental Biology Journal*, **27**(S1), 1137.7.

Marcus, N. J., Del Río, R., & Schultz, H. D. (2014). Central role of carotid body chemoreceptors in disordered breathing and cardiorenal dysfunction in chronic heart failure. *Frontiers in Physiology*, **5**, 438.

Marotta, S. F. (1972). Roles of aortic and carotid chemorecept ors in activating the hypothalamo-hypophyseal-adrenocortical system during hypoxia. *Proceedings of the Society for Experimental Biology and Medicine*, **141**(3), 915–922.

Marshall, J. M. (1994). Peripheral chemoreceptors and cardiovascular regulation. *Physiological Reviews*, **74**(3), 543–594.

McBryde, F. D., Hart, E. C., Ramchandra, R., & Paton, J. F. R. (2017). Evaluating the carotid bodies and renal nerves as therapeutic targets for hypertension. *Autonomic Neuroscience*, **204**, 126–130.

McDonald, D. M., & Mitchell, R. A. (1975). The innervation of glomus cells, ganglion cells and blood vessels in the rat carotid body: A quantitative ultrastructural analysis. *Journal of Neurocytology*, **4**(2), 177–230.

McGarvey, L. P., Birring, S. S., Morice, A. H., Dicpinigaitis, P. V., Pavord, I. D., Schelfhout, J., Nguyen, A. M., Li, Q., Tzontcheva, A., Iskold, B., Green, S. A., Rosa, C., Muccino, D. R., & Smith, J. A. (2022). Efficacy and safety of gefapixant, a P2X(3) receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *The Lancet (London, England)*, **399**(10328), 909–923.

Melo, B. F., Sacramento, J. F., Capucho, A. M., Sampaio-Pires, D., Prego, C. S., & Conde, S. V. (2022). Long-term hypercaloric diet consumption exacerbates age-induced dysmetabolism and carotid body dysfunction: Beneficial effects of CSN denervation. *Frontiers in Physiology*, **13**, 889660.

Milsom, W. K., & Burleson, M. L. (2007). Peripheral arterial chemoreceptors and the evolution of the carotid body. *Respiratory Physiology, & Neurobiology*, **157**(1), 4–11.

Molnár, Z., Petheo, G. L., Fülöp, C., & Spät, A. (2003). Effects of osmotic changes on the chemoreceptor cell of rat carotid body. *The Journal of Physiology*, **546**(2), 471–481.

Moraes, D. J. A., daSilva, M. P., de Souza, D. P., Felintro, V., & Paton, J. F. R. (2021). Heightened respiratory-parasympathetic coupling to airways in the spontaneously hypertensive rat. *The Journal of Physiology*, **599**(12), 3237–3252.

Nakayama, K. (1961). Surgical removal of the carotid body for bronchial asthma. *Diseases of the Chest*, **40**(6), 595–604.

Nanduri, J., Peng, Y.-J., Wang, N., Khan, S. A., Semenza, G. L., & Prabhakar, N. R. (2018). DNA methylation in the central and efferent limbs of the chemoreflex requires carotid body neural activity. *The Journal of Physiology*, **596**(15), 3087–3100./bib>

Narkiewicz, K., van de Borne, P. J., Montano, N., Dyken, M. E., Phillips, B. G., & Somers, V. K. (1998). Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. *Circulation*, **97**(10), 943–945.

Narkiewicz, K., van de Borne, P. J., Pesek, C. A., Dyken, M. E., Montano, N., & Somers, V. K. (1999). Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. *Circulation*, **99**(9), 1183–1189.

Narkiewicz, K., Ratcliffe, L. E. K., Hart, E. C., Briant, L. J. B., Chrostowska, M., Wolf, J., Szyndler, A., Hering, D., Abdala, A. P., Manghat, N., Burchell, A. E., Durant, C., Lobo, M. D., Sobotka, P. A., Patel, N. K., Leiter, J. C., Engelman, Z. J., Nightingale, A. K., & Paton, J. F. R. (2016). Unilateral carotid body resection in resistant hypertension: A safety and feasibility trial. *Journal of the American College of Cardiology: Basic to Translational Science*, **1**(5), 313–324.

Narkiewicz, K., & Somers, V. K. (1997). The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. *Journal of Hypertension*, **15**(12), 1613–1619.

Nazaré Nunes Alves, M. J., dos Santos, M. R., Nobre, T. S., Martinez, D. G., Pereira Barretto, A. C., Brum, P. C., Rondon, M., Middlekauff, H. R., & Negrão, C. E. (2012). Mechanisms of blunted muscle vasodilation during peripheral chemoreceptor stimulation in heart failure patients. *Hypertens (Dallas, Texas 1979)*, **60**(3), 669–676.

Niewinski, P. (2014). Pathophysiology and potential clinical applications for testing of peripheral chemosensitivity in heart failure. *Current Heart Failure Reports*, **11**(2), 126–133.

Niewinski, P., Engelman, Z. J., Fudim, M., Tubek, S., Paleczny, B., Jankowska, E. A., Banasiak, W., Sobotka, P. A., & Ponikowski, P. (2013). Clinical predictors and hemodynamic consequences of elevated peripheral chemosensitivity in optimally treated men with chronic systolic heart failure. *Journal of Cardiac Failure*, **19**(6), 408–415.

Niewinski, P., Janczak, D., Rucinski, A., Jazwiec, P., Sobotka, P. A., Engelman, Z. J., Fudim, M., Tubek, S., Jankowska, E. A., Banasiak, W., Hart, E. C. J., Paton, J. F. R., & Ponikowski, P. (2013). Carotid body removal for treatment of chronic systolic heart failure. *International Journal of Cardiology*, **168**(3), 2506–2509.

Niewinski, P., Janczak, D., Rucinski, A., Tubek, S., Engelman, Z. J., Jazwiec, P., Banasiak, W., Sobotka, P. A., Hart, E. C. J., Paton, J. F. R., & Ponikowski, P. (2014). Dissociation between blood pressure and heart rate response to hypoxia after bilateral carotid body removal in men with systolic heart failure. *Experimental Physiology*, **99**(3), 552–561.

Niewinski, P., Janczak, D., Rucinski, A., Tubek, S., Engelman, Z. J., Piesiak, P., Jazwiec, P., Banasiak, W., Fudim, M., Sobotka, P. A., Javaheri, S., Hart, E. C. J., Paton, J. F. R., & Ponikowski, P. (2017). Carotid body resection for sympathetic modulation in systolic heart failure: results from first-in-man study. *European Journal of Heart Failure*, **19**(3), 391–400.

Niewinski, P., Tubek, S., Paton, J. F. R., Banasiak, W., & Ponikowski, P. (2021). Oxygenation pattern and compensatory responses to hypoxia and hypercapnia following bilateral carotid body resection in humans. *The Journal of Physiology*, **599**(8), 2323–2340.

Niu, W. Z., Engwall, M. J., & Bisgard, G. E. (1990). Two discharge patterns of carotid body chemoreceptors in the goat. *Journal of Applied Physiology*, **69**(2), 734–739.

Nussbaum, J. C., Hussain, A., Butera, P., Ford, A. P., Kitt, M. M., O'Neill, E. A., Smith, S., Vargas, G., O'Reilly, T., Wynne, C., Stoch, S. A., & Iwamoto, M. (2024). Single- and multiple-dose pharmacokinetics of Gefapixant (MK-7264), a P2×3 receptor antagonist, in healthy adults. *Journal of Clinical Pharmacology*, **64**(8), 1023–1029.

O'Rourke, D. A., & O'Rourke, H. M. (1964). Removal of the carotid body for asthma: An appraisal of results. *Medical Journal of Australia*, **2**(22), 869–870.

Ortega-Sáenz, P., & López-Barneo, J. (2020). Physiology of the carotid body: From molecules to disease. *Annual Review of Physiology*, **82**(1), 127–149.

Overholt, R. H. (1962). Resection of carotid body (cervical glomectomy) for asthma. *Journal of the American Medical Association*, **180**(10), 809–812.

Pachen, M., Abukar, Y., Shanks, J., Lever, N., & Ramchandra, R. (2021). Activation of the carotid body increases directly recorded cardiac sympathetic nerve activity and coronary blood flow in conscious sheep. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **320**(3), R203–R212.

Paleczny, B., Seredyński, R., Tubek, S., Adamiec, D., Ponikowski, P., & Ponikowska, B. (2019). Hypoxic tachycardia is not a result of increased respiratory activity in healthy subjects. *Experimental Physiology*, **104**(4), 476–489.

Pardal, R., & López-Barneo, J. (2002). Low glucose-sensing cells in the carotid body. *Nature Neuroscience*, **5**(3), 197–198.

Paton, J. F., Deuchars, J., Li, Y. W., & Kasparov, S. (2001). Properties of solitary tract neurones responding to peripheral arterial chemoreceptors. *Neuroscience*, **105**(1), 231–248.

Paton, J. F. R. (2016). Appeasing the carotid body after chronic intermittent hypoxia. *Hypertens (Dallas, Texas 1979)*, **68**(2), 315–317.

Paton, J. F. R., Ratcliffe, L., Hering, D., Wolf, J., Sobotka, P. A., & Narkiewicz, K. (2013). Revelations about carotid body function through its pathological role in resistant hypertension. *Current Hypertension Reports*, **15**(4), 273–280.

Paton, J. F. R., Sobotka, P. A., Fudim, M., Engelman, Z. J., Hart, E. C. J., McBryde, F. D., Abdala, A. P., Marina, N., Gourine, A. V., Lobo, M., Patel, N., Burchell, A., Ratcliffe, L., & Nightingale, A. (2013). The carotid body as a therapeutic target for the treatment of sympathetically mediated diseases. *Hypertens (Dallas, Texas 1979)*, **61**(1), 5–13.

Pauza, A. G., Murphy, D., & Paton, J. F. R. (2023). Transcriptomics of the carotid body. *Advances in Experimental Medicine and Biology*, **1427**, 1–11.

Pauza, A. G., Thakkar, P., Tasic, T., Felippe, I., Bishop, P., Greenwood, M. P., Rysevaite-Kyguoliene, K., Ast, J., Broichhagen, J., Hodson, D. J., Salgado, H. C., Pauza, D. H., Japundzic-Zigon, N., Paton, J. F. R., & Murphy, D. (2022). GLP1R Attenuates sympathetic response to high glucose via carotid body inhibition. *Circulation Research*, **130**(5), 694–707.

Pawar, A., Nanduri, J., Yuan, G., Khan, S. A., Wang, N., Kumar, G. K., & Prabhakar, N. R. (2009). Reactive oxygen species-dependent endothelin signaling is required for augmented hypoxic sensory response of the neonatal carotid body by intermittent hypoxia. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **296**(3), R735–R742.

Pelletier, C. L., & Shepherd, J. T. (1972). Venous responses to stimulation of carotid chemoreceptors by hypoxia and hypercapnia. *American Journal of Physiology*, **223**(1), 97–103.

Peng, Y.-J., Gridina, A., Wang, B., Nanduri, J., Fox, A. P., & Prabhakar, N. R. (2020). Olfactory receptor 78 participates in carotid body response to a wide range of low O(2) levels but not severe hypoxia. *Journal of Neurophysiology*, **123**(5), 1886–1895.

Peng, Y.-J., Nanduri, J., Raghuraman, G., Souvannakitti, D., Gadalla, M. M., Kumar, G. K., Snyder, S. H., & Prabhakar, N. R. (2010). H2S mediates O2 sensing in the carotid body. *Proceedings of the National Academy of Sciences of the USA*, **107**(23), 10719–10724.

Peng, Y.-J., Overholt, J. L., Kline, D., Kumar, G. K., & Prabhakar, N. R. (2003). Induction of sensory long-term facilitation in the carotid body by intermittent hypoxia: implications for recurrent apneas. *Proceedings of the National Academy of Sciences of the USA*, **100**(17), 10073–10078.

Peng, Y.-J., & Prabhakar, N. R. (2004). Effect of two paradigms of chronic intermittent hypoxia on carotid body sensory activity. *Journal of Applied Physiology*, **96**(3), 1236–1242; discussion 1196.

Peng, Y.-J., Raghuraman, G., Khan, S. A., Kumar, G. K., & Prabhakar, N. R. (2011). Angiotensin II evokes sensory long-term facilitation of the carotid body via NADPH oxidase. *Journal of Applied Physiology*, **111**(4), 964–970.

Peng, Y.-J., Su, X., Wang, B., Matthews, T., Nanduri, J., & Prabhakar, N. R. (2021). Role of olfactory receptor78 in carotid body-dependent sympathetic activation and hypertension in murine models of chronic intermittent hypoxia. *Journal of Neurophysiology*, **125**(6), 2054–2067.

Peng, Y.-J., Zhang, X., Gridina, A., Chupikova, I., McCormick, D. L., Thomas, R. J., Scammell, T. E., Kim, G., Vasavda, C., Nanduri, J., Kumar, G. K., Semenza, G. L., Snyder, S. H., & Prabhakar, N. R. (2017). Complementary roles of gasotransmitters CO and H2S in sleep apnea. *Proceedings of the National Academy of Sciences of the USA*, **114**(6), 1413–1418.

Pfoh, J. R., Tymko, M. M., Abrosimova, M., Boulet, L. M., Foster, G. E., Bain, A. R., Ainslie, P. N., Steinback, C. D., Bruce, C. D., & Day, T. A. (2016). Comparing and characterizing transient and steady-state tests of the peripheral chemoreflex in humans. *Experimental Physiology*, **101**(3), 432–447.

Pijacka, W., Moraes, D. J. A., Ratcliffe, L. E. K., Nightingale, A. K., Hart, E. C., daSilva, M. P., Machado, B. H., McBryde, F. D., Abdala, A. P., Ford, A. P., & Paton, J. F. R. (2016). Purinergic receptors in the carotid body as a new drug target for controlling hypertension. *Nature Medicine*, **22**(10), 1151–1159.

Plunkett, M. J., Holwerda, S., Young, B. E., Fadel, P. J., & Fisher, J. P. (2024). Respiratory modulation of sympathetic transduction to blood pressure in health and type 2 diabetes. *The Journal of Physiology*, **602**(16), 3909–3927.

Pokorski, M., & Lahiri, S. (1981). Effects of naloxone on carotid body chemoreception and ventilation in the cat. *Journal of Applied Physiology*, **51**(6), 1533–1538.

Pokorski, M., & Lahiri, S. (1983). Aortic and carotid chemoreceptor responses to metabolic acidosis in the cat. *American Journal of Physiology*, **244**(5), R652–658.

Pokorski, M., Pozdzik, M., Antosiewicz, J., Dymecka, A., Mazzatenta, A., & di Giulio, C. (2015). Hypoxic ventilatory reactivity in experimental diabetes. *Advances in Experimental Medicine and Biology*, **860**, 123–132.

Ponikowski, P., Anker, S. D., Chua, T. P., Francis, D., Banasiak, W., Poole-Wilson, P. A., Coats, A. J., & Piepoli, M. (1999). Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: Clinical implications and role of augmented peripheral chemosensitivity. *Circulation*, **100**(24), 2418–2424.

Ponikowski, P., Chua, T. P., Piepoli, M., Banasiak, W., Anker, S. D., Szelemej, R., Molenda, W., Wrabec, K., Capucci, A., & Coats, A. J. (1998). Ventilatory response to exercise correlates with impaired heart rate variability in patients with chronic congestive heart failure. *American Journal of Cardiology*, **82**(3), 338–344.

Ponikowski, P., Chua, T. P., Piepoli, M., Ondusova, D., Webb-Peploe, K., Harrington, D., Anker, S. D., Volterrani, M., Colombo, R., Mazzuero, G., Giordano, A., & Coats, A. J. (1997). Augmented peripheral chemosensitivity as a potential input to baroreflex impairment and autonomic imbalance in chronic heart failure. *Circulation*, **96**(8), 2586–2594.

Ponikowski, P., Chua, T. P. P., Anker, S. D. D., Francis, D. P. P., Doehner, W., Banasiak, W., Poole-Wilson, P. A. A., Piepoli, M. F. F., & Coats, A. (2001). Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. *Circulation*, **104**(5), 544–549.

Ponte, J., & Purves, M. J. (1974). The role of the carotid body chemoreceptors and carotid sinus baroreceptors in the control of cerebral blood vessels. *The Journal of Physiology*, **237**(2), 315–340.

Potter, E. K., & McCloskey, D. I. (1987). Excitation of carotid body chemoreceptors by neuropeptide-Y. *Respiration Physiology*, **67**(3), 357–365.

Prabhakar, N. R. (2016a). Chapter 18 - O2 and CO2 detection by the carotid and aortic bodies. In F. Zufall, & S. D. Munger (Eds), *Chemosensory Transduction* (pp. 321–338). Academic Press. Available at: https://www.sciencedirect.com/science/article/pii/B9780128016947000184.

Prabhakar, N. R. (2016b). Carotid body chemoreflex: A driver of autonomic abnormalities in sleep apnoea. *Experimental Physiology*, **101**(8), 975–985.

Prabhakar, N. R., & Peng, Y.-J. (2004). Peripheral chemoreceptors in health and disease. *Journal of Applied Physiology*, **96**(1), 359–366.

Prabhakar, N. R., Peng, Y.-J., & Nanduri, J. (2022). Adaptive cardiorespiratory changes to chronic continuous and intermittent hypoxia. *Handbook of Clinical Neurology*, **188**, 103–123.

Prange-Barczynska, M., Jones, H. A., Sugimoto, Y., Cheng, X., Lima, J. D., Ratnayaka, I., Douglas, G., Buckler, K. J., Ratcliffe, P. J., Keeley, T. P., & Bishop, T. (2024). Hif-2$\alpha$ programmes oxygen chemosensitivity in chromaffin cells. *Journal of Clinical Investigation*, **134**(18), e174661.

Prasad, B., Morgan, B. J., Gupta, A., Pegelow, D. F., Teodorescu, M., Dopp, J. M., & Dempsey, J. A. (2020). The need for specificity in quantifying neurocirculatory vs. respiratory effects of eucapnic hypoxia and transient hyperoxia. *The Journal of Physiology*, **598**(21), 4803–4819.

Prasad, M., Fearon, I. M., Zhang, M., Laing, M., Vollmer, C., & Nurse, C. A. (2001). Expression of P2×2 and P2×3 receptor subunits in rat carotid body afferent neurones: Role in chemosensory signalling. *The Journal of Physiology*, **537**(3), 667–677.

Privolizzi, R., Chu, W. S., Tijani, M., & Ng, J. (2021). Viral gene therapy for paediatric neurological diseases: Progress to clinical reality. *Developmental Medicine and Child Neurology*, **63**(9), 1019–1029.

Proczka, M., Przybylski, J., Cudnoch-Jędrzejewska, A., Szczepańska-Sadowska, E., & Żera, T. (2021). Vasopressin and breathing: Review of evidence for Respiratory effects of the antidiuretic hormone. *Frontiers in Physiology*, **12**, 1828.

Przybylski, J. (1978). Alveolar hyperventilation in young spontaneously hypertensive rats. *International Research Communications System Medical Science*, **6**, 315.

Przybylski, J. (1981). Do arterial chemoreceptors play a role in the pathogenesis of hypertension? *Medical Hypotheses*, **7**(2), 127–131.

Przybylski, J., Trzebski, A., & Przybyszewski, A. (1980). Circulatory responses to acute hypoxia in spontaneously hypertensive and normotensive rats. *Acta Physiologica Polonica*, **31**(5), 463–468.

Raff, H., Shinsako, J., & Dallman, M. F. (1984). Renin and ACTH responses to hypercapnia and hypoxia after chronic carotid chemodenervation. *American Journal of Physiology*, **247**(3 Pt 2), R412–417.

Rakoczy, R. J., & Wyatt, C. N. (2018). Acute oxygen sensing by the carotid body: A rattlebag of molecular mechanisms. *The Journal of Physiology*, **596**(15), 2969–2976.

Rey, S., Del Río, R., Alcayaga, J., & Iturriaga, R. (2004). Chronic intermittent hypoxia enhances cat chemosensory and ventilatory responses to hypoxia. *The Journal of Physiology*, **560**(2), 577–586.

Rey, S., Tarvainen, M. P., Karjalainen, P. A., & Iturriaga, R. (2008). Dynamic time-varying analysis of heart rate and blood pressure variability in cats exposed to short-term chronic intermittent hypoxia. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **295**(1), R28–R37.

Ribeiro, M. J., Sacramento, J. F., Gallego-Martin, T., Olea, E., Melo, B. F., Guarino, M. P., Yubero, S., Obeso, A., & Conde, S. V. (2018). High fat diet blunts the effects of leptin on ventilation and on carotid body activity. *The Journal of Physiology*, **596**(15), 3187–3199.

Ribeiro, M. J., Sacramento, J. F., Gonzalez, C., Guarino, M. P., Monteiro, E. C., & Conde, S. V. (2013). Carotid body denervation prevents the development of insulin resistance and hypertension induced by hypercaloric diets. *Diabetes*, **62**(8), 2905–2916.

Del Río, R., Andrade, D. C., Lucero, C., Arias, P., & Iturriaga, R. (2016). Carotid body ablation abrogates hypertension and autonomic alterations induced by intermittent hypoxia in rats. *Hypertens (Dallas, Texas 1979)*, **68**(2), 436–445.

Del Río, R., Marcus, N. J., & Schultz, H. D. (2013a). Carotid chemoreceptor ablation improves survival in heart failure. *Journal of the American College of Cardiology*, **62**(25), 2422–2430.

Del Río, R., Marcus, N. J., & Schultz, H. D. (2013b). Inhibition of hydrogen sulfide restores normal breathing stability and improves autonomic control during experimental heart failure. *Journal of Applied Physiology*, **114**(9), 1141–1150.

Del Río, R., Moya, E. A., Parga, M. J., Madrid, C., & Iturriaga, R. (2012). Carotid body inflammation and cardiorespiratory alterations in intermittent hypoxia. *European Respiratory Journal*, **39**(6), 1492–1500.

Robbins, J. A., Sands, S., Maganti, L., Crumley, T., Fox-Bosetti, S., Hussain, A., Schwartz, H., Safirstein, B., Ahmad, M., Dragone, L., Nussbaum, J., Kushida, C., Iwamoto, M., & Stoch, S. A. (2024). Gefapixant as a P2×3 receptor antagonist treatment for obstructive sleep apnea: A randomized controlled trial. *Journal of Clinical Sleep Medicine JCSM Official American Academy of Sleep Medicine*, **20**(12), 1905–1913.

Sacramento, J. F., Andrzejewski, K., Melo, B. F., Ribeiro, M. J., Obeso, A., & Conde, S. V. (2020). Exploring the mediators that promote carotid body dysfunction in type 2 diabetes and obesity related syndromes. *International Journal of Molecular Sciences*, **21**(15), 5545.

Sacramento, J. F., Chew, D. J., Melo, B. F., Donegá, M., Dopson, W., Guarino, M. P., Robinson, A., Prieto-Lloret, J., Patel, S., Holinski, B. J., Ramnarain, N., Pikov, V., Famm, K., & Conde, S. V. (2018). Bioelectronic modulation of carotid sinus nerve activity in the rat: A potential therapeutic approach for type 2 diabetes. *Diabetologia*, **61**(3), 700–710.

Sacramento, J. F., Gonzalez, C., Gonzalez-Martin, M. C., & Conde, S. V. (2015). Adenosine receptor blockade by caffeine inhibits carotid sinus nerve chemosensory activity in chronic intermittent hypoxic animals. *Advances in Experimental Medicine and Biology*, **860**, 133–137.

Saito, M., Mano, T., Iwase, S., Koga, K., Abe, H., & Yamazaki, Y. (1988). Responses in muscle sympathetic activity to acute hypoxia in humans. *Journal of Applied Physiology*, **65**(4), 1548–1552.

dos Santos, E., Sacramento, J. F., Melo, B. F., & Conde, S. V. (2018). Carotid body dysfunction in diet-induced insulin resistance is associated with alterations in its morphology. *Advances in Experimental Medicine and Biology*, **1071**, 103–108.

Schultz, H. D., Marcus, N. J., & Del Río, R. (2013). Role of the carotid body in the pathophysiology of heart failure. *Current Hypertension Reports*, **15**(4), 356–362.

Schultz, H. D., Marcus, N. J., & Del Río, R. (2015). Mechanisms of carotid body chemoreflex dysfunction during heart failure. *Experimental Physiology*, **100**(2), 124–129.

Scott, M. J. (1966). The effects of hyperventilation on the reflex cardiac response from the carotid bodies in the cat. *The Journal of Physiology*, **186**(2), 307–320.

Seals, D. R., Johnson, D. G., & Fregosi, R. F. (1991). Hyperoxia lowers sympathetic activity at rest but not during exercise in humans. *American Journal of Physiology*, **260**(5 Pt 2), R873–878.

Sforza, E., & Roche, F. (2016). Chronic intermittent hypoxia and obstructive sleep apnea: An experimental and clinical approach. *Hypoxia (Auckland, NZ)*, **4**, 99–108.

Share, L., & Levy, M. N. (1966). Effect of carotid chemoreceptor stimulation on plasma antidiuretic hormone titer. *American Journal of Physiology-Legacy Content*, **210**(1), 157–161.

Shin, M.-K., Eraso, C. C., Mu, Y.-P., Gu, C., Yeung, B. H. Y., Kim, L. J., Liu, X.-R., Wu, Z.-J., Paudel, O., Pichard, L. E., Shirahata, M., Tang, W.-Y., Sham, J. S. K., & Polotsky, V. Y. (2019). Leptin induces hypertension acting on transient receptor potential melastatin 7 channel in the carotid body. *Circulation Research*, **125**(11), 989–1002.

Siebenmann, C., Ryrsø, C. K., Oberholzer, L., Fisher, J. P., Hilsted, L. M., Rasmussen, P., Secher, N. H., & Lundby, C. (2019). Hypoxia-induced vagal withdrawal is independent of the hypoxic ventilatory response in men. *Journal of Applied Physiology*, **126**(1), 124–131.

Sinski, M., Kowalczyk, P., Stolarczyk, A., Sawionek, L., & Przybylski, J. (2002). Influence of the stimulation of carotid body chemoreceptors on the gastric mucosal blood flow in artificially ventilated and spontaneously breathing rats. *Journal of Physiology and Pharmacology*, **53**(3), 359–369.

Sinski, M., Lewandowski, J., Przybylski, J., Bidiuk, J., Abramczyk, P., Ciarka, A., & Gaciong, Z. (2012). Tonic activity of carotid body chemoreceptors contributes to the increased sympathetic drive in essential hypertension. *Hypertension Research*, **35**(5), 487–491.

Sinski, M., Lewandowski, J., Przybylski, J., Zalewski, P., Symonides, B., Abramczyk, P., & Gaciong, Z. (2014). Deactivation of carotid body chemoreceptors by hyperoxia decreases blood pressure in hypertensive patients. *Hypertension Research*, **37**(9), 858–862.

Somers, V. K., Mark, A. L., & Abboud, F. M. (1988). Potentiation of sympathetic nerve responses to hypoxia in borderline hypertensive subjects. *Hypertension*, **11**(6_pt_2), 608–612.

Spiller, P. F., daSilva, M.P., & Moraes, D. J. A. (2021). Lactate does not activate the carotid body of Wistar rat. *Respiratory Physiology, & Neurobiology*, **285**, 103593.

Sun, S. Y., Wang, W., Zucker, I. H., & Schultz, H. D. (1999a). Enhanced activity of carotid body chemoreceptors in rabbits with heart failure: Role of nitric oxide. *Journal of Applied Physiology*, **86**(4), 1273–1282.

Sun, S. Y., Wang, W., Zucker, I. H., & Schultz, H. D. (1999b). Enhanced peripheral chemoreflex function in conscious rabbits with pacing-induced heart failure. *Journal of Applied Physiology*, **86**(4), 1264–1272.

Tafil-Klawe, M., Thiele, A. E., Raschke, F., Mayer, J., Peter, J. H., & von Wichert, W. (1991). Peripheral chemoreceptor reflex in obstructive sleep apnea patients; a relationship between ventilatory response to hypoxia and nocturnal bradycardia during apnea events. *Pneumologie (Stuttgart, Germany)*, **45**(Suppl 1), 309–311.

Tafil-Klawe, M., Trzebski, A., Klawe, J., & Pałko, T. (1985). Augmented chemoreceptor reflex tonic drive in early human hypertension and in normotensive subjects with family background of hypertension. *Acta Physiologica Polonica*, **36**(1), 51–58.

Takakura, A. C. T., Moreira, T. S., Colombari, E., West, G. H., Stornetta, R. L., & Guyenet, P. G. (2006). Peripheral chemoreceptor inputs to retrotrapezoid nucleus (RTN) CO2-sensitive neurons in rats. *The Journal of Physiology*, **572**(2), 503–523.

Teppema, L. J., & Dahan, A. (2010). The ventilatory response to hypoxia in mammals: mechanisms, measurement, and analysis. *Physiological Reviews*, **90**(2), 675–754.

Thompson, E. L., Ray, C. J., Holmes, A. P., Pye, R. L., Wyatt, C. N., Coney, A. M., & Kumar, P. (2016). Adrenaline release evokes hyperpnoea and an increase in ventilatory CO2 sensitivity during hypoglycaemia: a role for the carotid body. *The Journal of Physiology*, **594**(15), 4439–4452.

Toledo, C., Andrade, D. C., Lucero, C., Schultz, H. D., Marcus, N., Retamal, M., Madrid, C., & Del Río, R. (2017). Contribution of peripheral and central chemoreceptors to sympatho-excitation in heart failure. *The Journal of Physiology*, **595**(1), 43–51.

Torres-Torrelo, H., Ortega-Saenz, P., Macias, D., Omura, M., Zhou, T., Matsunami, H., Johnson, R. S., Mombaerts, P., & Lopez-Barneo, J. (2018). The role of Olfr78 in the breathing circuit of mice. *Nature*, **561**(7724), E33–E40.

Trzebski, A. (1992). Arterial chemoreceptor reflex and hypertension. *Hypertens (Dallas, Texas 1979)*, **19**(6_pt_1), 562–566.

Trzebski, A., Tafil, M., Zoltowski, M., & Przybylski, J. (1982). Increased sensitivity of the arterial chemoreceptor drive in young men with mild hypertension. *Cardiovascular Research*, **16**(3), 163–172.

Tubek, S., Niewinski, P., Langner-Hetmanczuk, A., Jura, M., Kuliczkowski, W., Reczuch, K., & Ponikowski, P. (2023). The effects of P2Y12 adenosine receptors' inhibitors on central and peripheral chemoreflexes. *Frontiers in Physiology*, **14**, 1214893.

Tubek, S., Niewinski, P., Paleczny, B., Langner-Hetmanczuk, A., Banasiak, W., & Ponikowski, P. (2021). Acute hyperoxia reveals tonic influence of peripheral chemoreceptors on systemic vascular resistance in heart failure patients. *Scientific Reports*, **11**(1), 20823.

Tubek, S., Niewiński, P., Paleczny, B., Langner, A., Banasiak, W., & Ponikowski, P. (2018). Human carotid bodies as a therapeutic target: new insights from a clinician's perspective. *Kardiologia Polska*, **76**(10), 1426–1433.

Tubek, S., Niewinski, P., Reczuch, K., Janczak, D., Rucinski, A., Paleczny, B., Engelman, Z. J., Banasiak, W., Paton, J. F. R., & Ponikowski, P. (2016). Effects of selective carotid body stimulation with adenosine in conscious humans. *The Journal of Physiology*, **594**(21), 6225–6240.

Uchino, M., Kuwahara, M., Ebukuro, S., & Tsubone, H. (2006). Modulation of emetic response by carotid baro- and chemoreceptor activations. *Autonomic Neuroscience*, **128**(1–2), 25–36.

Di Vanna, A., Braga, A., Laterza, M. C., Ueno, L. M., Rondon, M., Barretto, A. C. P., Middlekauff, H. R., & Negrão, C. E. (2007). Blunted muscle vasodilatation during chemoreceptor stimulation in patients with heart failure. *American Journal of Physiology-Heart and Circulatory Physiology*, **293**(1), H846-H852.

Velez-Roa, S., Ciarka, A., Najem, B., Vachiery, J.-L., Naeije, R., & van de Borne, P. (2004). Increased sympathetic nerve activity in pulmonary artery hypertension. *Circulation*, **110**(10), 1308–1312.

Vidruk, E. H., Olson, E. B. J., Ling, L., & Mitchell, G. S. (2001). Responses of single-unit carotid body chemoreceptors in adult rats. *The Journal of Physiology*, **531**(1), 165–170.

Wade, J. G., Larson, C. P. J., Hickey, R. F., Ehrenfeld, W. K., & Severinghaus, J. W. (1970). Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. *New England Journal of Medicine*, **282**(15), 823–829.

Wang, B., Peng, Y.-J., Su, X., Zhang, C., Nagati, J. S., Garcia, J. A., & Prabhakar, N. R. (2021). Olfactory receptor 78 regulates erythropoietin and cardiorespiratory responses to hypobaric hypoxia. *Journal of Applied Physiology*, **130**(4), 1122–1132.

Wang, Z. Z., He, L., Stensaas, L. J., Dinger, B. G., & Fidone, S. J. (1991). Localization and in vitro actions of atrial natriuretic peptide in the cat carotid body. *Journal of Applied Physiology*, **70**(2), 942–946.

Wehrwein, E. A., Basu, R., Basu, A., Curry, T. B., Rizza, R. A., & Joyner, M. J. (2010). Hyperoxia blunts counterregulation during hypoglycaemia in humans: possible role for the carotid bodies? *The Journal of Physiology*, **588**(22), 4593–4601.

Weisbrod, C. J., Minson, C. T., Joyner, M. J., & Halliwill, J. R. (2001). Effects of regional phentolamine on hypoxic vasodilatation in healthy humans. *The Journal of Physiology*, **537**(2), 613–621.

Wilson, D. A., Hanley, D. F., Feldman, M. A., & Traystman, R. J. (1987). Influence of chemoreceptors on neurohypophyseal blood flow during hypoxic hypoxia. *Circulation Research*, **61**(5_supplement), II94-101.

Winter, B. (1972). Bilateral carotid body resection for asthma and emphysema. A new surgical approach without hypoventilation or baroreceptor dysfunction. *International Surgery*, **57**, 458–466.

Winter, B. (1973). Carotid body resection. *Annals of Thoracic Surgery*, **16**(6), 648–659.

Wolk, R., Shamsuzzaman, A. S. M., & Somers, V. K. (2003). Obesity, sleep apnea, and hypertension. *Hypertens (Dallas, Texas 1979)*, **42**(6), 1067–1074.

Xue, Q., Wang, R., Wang, L., Xiong, B., Li, L., Qian, J., Hao, L., Wang, Z., Liu, D., Deng, C., Rong, S., Yao, Y., Jiang, Y., Zhu, Q., & Huang, J. (2021). Downregulating the P2×3 receptor in the carotid body to reduce blood pressure via acoustic gene delivery in canines. *Translational Research*, **227**, 30–41.

Zera, T., Moraes, D. J. A., daSilva, M. P., Fisher, J. P., & Paton, J. F. R. (2019). The logic of carotid body connectivity to the brain. *Physiology (Bethesda, Md.)*, **34**(4), 264–282.

Zera, T., Przybylski, J., Grygorowicz, T., Kasarello, K., Podobinska, M., Mirowska-Guzel, D., & Cudnoch-Jedrzejewska, A. (2018). Vasopressin V1a receptors are present in the carotid body and contribute to the control of breathing in male Sprague-Dawley rats. *Peptides*, **102**, 68–74.

Zhang, M., Buttigieg, J., & Nurse, C. A. (2007). Neurotransmitter mechanisms mediating low-glucose signalling in cocultures and fresh tissue slices of rat carotid body. *The Journal of Physiology*, **578**(3), 735–750.

Zhang, M., Zhong, H., Vollmer, C., & Nurse, C. A. (2000). Co-release of ATP and ACh mediates hypoxic signalling at rat carotid body chemoreceptors. *The Journal of Physiology*, **525**(1), 143–158.

## Additional information

### Competing interests

Authors declare no conflict of interest to this report.

### Author contributions

All the authors contributed to writing the manuscript. All the authors have read and approved the final version of the manuscript submitted for publication.

### Funding

Manatu Hauora | Health Research Council of New Zealand (HRC): Julian F. R. Paton, 19/687; Sidney Taylor Trust: Julian F. R. Paton, 2019.

### Acknowledgements

T.Z. expresses gratitude and personally thanks Prof. Jacek Przybylski for countless fruitful discussions on arterial chemoreflex, cardiovascular system and physiology in general. J.F.R.P. is funded by the Health Research Council, the Royal Society Te Aparangi of New Zealand, the Sidney Taylor Trust and is a Partridge Family research laureate.

Open access publishing facilitated by The University of Auckland, as part of the Wiley - The University of Auckland agreement via the Council of Australian University Librarians.

### Keywords

carotid body, diabetes mellitus, heart failure, hypertension, hyperglycaemia, hypoxia, sleep apnoea, sympathetic nervous system

## 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:

**Peer Review History**