2023

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J Physiol 0.0 (2023) pp 1–25

The Journal of Physiology

REVIEW-SYMPOSIUM

Commonalities and differences in carotid body dysfunction in hypertension and heart failure

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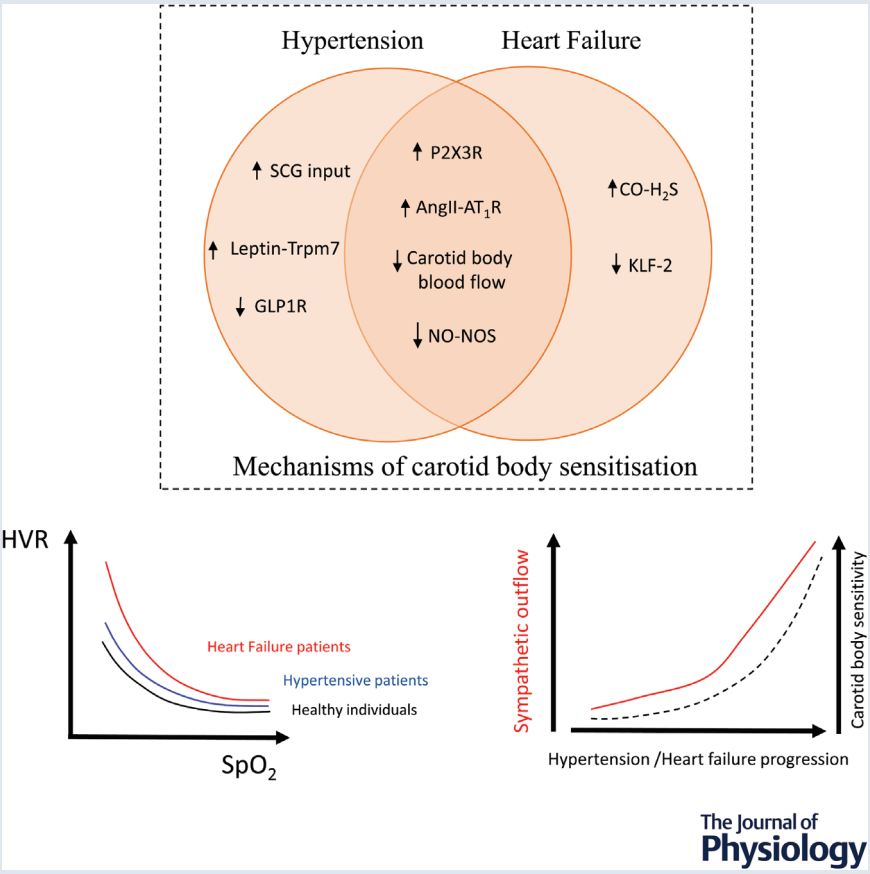
Handling Editors: Laura Bennet & Andrew Holmes

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP284114#support-information-section).



Abstract Carotid body pathophysiology is associated with many cardiovascular–respiratory–metabolic diseases. This pathophysiology reflects both hyper-sensitivity and hyper-tonicity.

DOI: 10.1113/JP284114

From both animal models and human patients, evidence indicates that amelioration of this pathophysiological signalling improves disease states such as a lowering of blood pressure in hypertension, a reduction of breathing disturbances with improved cardiac function in heart failure (HF) and a re-balancing of autonomic activity with lowered sympathetic discharge. Given this, we have reviewed the mechanisms of carotid body hyper-sensitivity and hyper-tonicity across disease models asking whether there is uniqueness related to specific disease states. Our analysis indicates some commonalities and some potential differences, although not all mechanisms have been fully explored across all disease models. One potential commonality is that of hypoperfusion of the carotid body across hypertension and HF, where the excessive sympathetic drive may reduce blood flow in both models and, in addition, lowered cardiac output in HF may potentiate the hypoperfusion state of the carotid body. Other mechanisms are explored that focus on neuro-transmitter and signalling pathways intrinsic to the carotid body (e.g. ATP, carbon monoxide) as well as extrinsic molecules carried in the blood (e.g. leptin); there are also transcription factors found in the carotid body endothelium that modulate its activity (Krüppel-like factor 2). The evidence to date fully supports that a better understanding of the mechanisms of carotid body pathophysiology is a fruitful strategy for informing potential new treatment strategies for many cardiovascular, respiratory and metabolic diseases, and this is highly relevant clinically.

(Received 31 March 2023; accepted after revision 29 August 2023; first published online 20 September 2023)
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Abstract figure legend The carotid body has been linked with the development of hypertension and heart failure in animals and humans. This review explores mechanisms of carotid body sensitisation across disease models. We ask whether these mechanisms are common or unique to distinct cardiovascular diseases; such knowledge could inform clinical treatment strategies. We propose that carotid body sensitivity increases progressively from health to hypertension and is maximal in heart failure and that there are both shared and distinct sensitisation mechanisms. This sensitisation is followed by an increase in systemic sympathetic outflow. It remains unknown whether the sensitised carotid body drives sympathetic overactivity or vice versa.

Introduction

Cardiovascular diseases are the leading killer in the developed world and cause a significant burden on healthcare systems and economies (Blakely et al., 2019; Ministry of Health, 2019; National Health Committee, 2013; Townsend et al., 2021). Heart failure (HF) is critical among cardiovascular diseases due to its high morbidity and mortality (Heidenreich et al., 2022; McDonagh et al., 2021; McMurray & Pfeffer, 2005; Mosterd & Hoes, 2007; Ziaeian & Fonarow, 2016). For instance, the Framingham heart study in the USA showed that men had less than a 50% chance of surviving for 5 years after the onset of HF, and survival was 60% for women (McKee et al., 1971). Although myocardial infarction is strongly associated with the development of HF, epidemiological studies have demonstrated that hypertension is the most significant contributor (Lloyd-Jones et al., 2002; McKee et al., 1971; Mosterd & Hoes, 2007; Pfeffer et al., 2019; Ziaeian & Fonarow, 2016) suggesting possible common mechanisms underpinning these co-morbidities.

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Hypertension is predominantly asymptomatic until it causes a cardiovascular event, which can be serious (Kalehoff & Oparil, 2020; Pokharel et al., 2022). According to Zhou et al. (2021), each 10 mmHg increase in systolic blood pressure is associated with a 45% higher risk of ischaemic heart disease and 65% higher risk of ischaemic or haemorrhagic stroke. The current treatment for hypertension and HF can be divided into non-pharmacological and pharmacological interventions. The former is characterised by lifestyle changes, including strategies to improve medication compliance, restrict sodium intake, stay physically active and vaccination (e.g. influenza, COVID-19, pneumococcal, etc.) (Heidenreich et al., 2022; McDonagh et al., 2021). The goals of pharmacological therapy are to reduce mortality and prevent recurrence of hospitalisation. The main classes of medication recommended are angiotensin receptor blockers, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor-neprilysin inhibitors (ARNI), beta-blockers, mineralocorticoid receptor antagonists, sodium–glucose co-transporter 2 (SGLT2) inhibitors such as dapagliflozin and empagliflozin, and loop diuretic for fluid retention (Heidenreich et al., 2022; McDonagh et al., 2021). However, there is no cure for HF, with prescribed medicines being able to only slow its progression, while for hypertension, target levels of blood pressure are not met in 50% of treated patients who remain at cardiovascular risk (Almgren et al., 2005; Brown et al., 2013; Lawlor et al., 2011). Given that current medications do not provide long-term reductions in sympathetic activity (Vongpatanasin et al., 2011) and do not prevent the exaggerated levels seen in exercise (Chant et al., 2018), with many frontline medications actually increasing sympathetic activity, we see an unmet clinical need to continue to find ways of sympathetic withdrawal (Grassi, 2016).

There is unequivocal evidence that both hypertension and HF not only originate from structural dysfunctions of the cardiovascular system (e.g. myocardial hypo- or hypertrophy leading to HF and vascular remodelling leading to hypertension) but also from an imbalance of the autonomic nervous system, including an augmented sympathetic outflow (Floras, 2009; Floras & Ponikowski, 2015; Jay et al., 2014; Kishi, 2012; Mancia & Grassi, 2014). The global impact of this autonomic dysfunction can be exemplified by a study from India demonstrating that 60% of patients with primary hypertension have sympathetic overactivity (Padmanabhan et al., 2014), and in Brazil, where a prospective study with HF patients showed that the incidence of muscle sympathetic nerve activity (MSNA) is an independent predictor of patients' mortality (Barretto et al., 2009). In this latter work, the authors demonstrated over a 12-month follow-up period that MSNA level >49 burst/min was associated with a survival rate below 50%, whereas patients with MSNA ≤ 49 burst/min had a survival rate above 90%. This is corroborated by works showing that plasma and cardiac noradrenaline spillover predict mortality in HF patients (Brunner-La Rocca et al., 2001; Cohn et al., 2010).

Although pharmacological options exist to temper the adverse effects of this augmented sympathetic activity, their efficiency is limited. As stated by Floras (2021): 'chronically administered beta-adrenoceptor blockade may partially restore the rhythmicity of muscle sympathetic discharge in heart failure but this drug class does not dampen muscle sympathetic nerve firing rates or block the vascular effects of the NE [noradrenaline] cotransmitters, neuropeptide Y, or adenosine triphosphate, or counter α-adrenoceptor-mediated neurogenic vasoconstriction' (Floras, 2021). Thus, it is important to understand the underlying mechanisms responsible for an increased sympathetic motor outflow, as its normalisation would provide a better target to improve clinical outcome for patients.

Many proposed mechanisms of autonomic imbalance lead to sympathetic overactivity in hypertension and HF (Floras & Ponikowski, 2015; Mancia & Grassi, 2014), but our focus in this review is on the carotid body. Herein, we review the literature correlating carotid body dysfunction with autonomic imbalance observed in hypertension and HF. We summarize the common and different pathophysiological mechanisms that lead to carotid body abnormalities in these two cardiovascular diseases to explore whether there are shared or distinct clinical interventions that could be proposed. The latter is relevant as hypertension can develop into HF.

Linking carotid body and autonomic imbalance in cardiovascular diseases

In humans, the carotid body is a rice grain-sized organ located at the bifurcation of both common carotid arteries (CCA) that senses arterial oxygen levels. It is well known for its ability to control respiration and the cardiovascular system by activating increased ventilation and sympathetic and parasympathetic motor outflows, respectively (for reviews, see Iturriaga et al., 2021; Machado, 2001; Zera et al., 2019). In both hypertension and HF, the carotid body becomes hyperactive, displaying both increased tonic neural input to central autonomic centres (hypertonicity) and exaggerated reflex responses (hyper-reflexia) (Pijacka et al., 2016b; Sun et al., 1999a).

Hypertension. In animals, the first work that linked the carotid body with hypertension was published by Przybylski (1978) using spontaneously hypertensive rats (SHR). The author examined the arterial blood gas and acid–base parameters in rats at different ages, i.e.

adult normotensive, adult and young SHRs. Przybylski found an increased P_{aO_2} and pH and a decreased P_{aCO_2} in blood samples taken from the abdominal aorta, which are the characteristic signs of alveolar hyperventilation. Interestingly, these changes were evident only in young SHRs and thus during the developmental stages of hypertension. Subsequently, in anaesthetised SHRs, Przybylski (1982) demonstrated that the minute ventilation ($\dot{V}_E$) was significantly higher during air breathing; in addition, hyperoxia, which inhibits the carotid body, produced a more remarkable fall in $\dot{V}_E$ of SHRs than in normotensive rats, suggesting that the carotid bodies in SHRs provide a continuous excitatory drive to breathe. Seminal contributions from Trzebski et al. during the 1980s were pivotal in advancing this research area (Fukuda et al., 1987; Tafil & Trzebski, 1984; Trzebski, 1992). Fukuda et al. (1987) and Trzebski et al. (1982) stimulated carotid body activity by exposing the rats to a hypoxic gas mixture. They observed that the chemoreceptor response to the hypoxic stimulus was larger quantitatively in SHRs than in normotensive rats. Moreover, both hypertonicity and hyper-reflexia were found in carotid body receptive petrosal neurones of SHRs *versus* Wistar rats (Pijacka et al., 2016b). All told, none of these studies addressed causality and the relationship between carotid body hyperexcitability and autonomic imbalance in hypertension. Indeed, one might question whether hypertension drives carotid body dysfunction rather than vice versa.

To approach this question, a series of complementary studies were carried out (Fig. 1) (Abdala et al., 2012; McBryde et al., 2013). First, hyperoxia, used to de-sensitise the carotid body, produced distinct effects in Wistar rats and SHRs (12 weeks old). In the former, systolic blood pressure was unchanged, whereas a 20% reduction from baseline renal sympathetic nerve activity (RSNA) occurred. In contrast, in SHRs, hyperoxia produced significant falls in both systolic blood pressure (i.e. −12 mmHg) and RSNA (i.e. 80%). After carotid body denervation, hyperoxia did not significantly affect these variables in either Wistar rats or SHRs. Second, in young pre-hypertensive SHRs (4 weeks old), carotid body denervation prevented the full development of hypertension at ages 11 and 13 weeks old (Abdala et al., 2012). Third, bilateral carotid body denervation in adult SHRs (12 weeks old) reduced both arterial pressure (by ∼20 mmHg) and RSNA. This led to the question of whether carotid body denervation lowered blood pressure in humans with hypertension. An important caveat that should be acknowledged is that carotid body denervation is not selective in eliminating carotid body sensory output, but also eliminates carotid baroreceptors afferents. Given this, we selectively removed the carotid bodies sparring the carotid sinus baroreceptors. This made no difference to the fall in arterial pressure observed (Pijacka et al., 2016a, 2018).

In humans, carotid body hyperactivity can be tested via measuring responses evoked by breathing a hypoxic gas mixture (i.e. hyper-reflexia) as the hypoxic ventilatory response (HVR, $\Delta\dot{V}_E/\Delta F_{iO_2}$) and/or the muscle sympathetic response (MSNA, Δ bursts/min/ΔF_{iO_2}). In addition, a reduction in baseline $\dot{V}_E$ or MSNA by inspired hyperoxia indicates the presence of carotid body hypertonicity. The patients' $\dot{V}_E$ plotted against their blood oxygen saturation (S_{pO_2}) produces a slope (i.e. $\dot{V}_E/S_{pO_2}$) that can be used as an index of chemosensitivity (Narkiewicz et al., 2016, 2017). Based on that, it was demonstrated that patients with hypertension have an exaggerated HVR and MSNA response to hypoxia (Somers et al., 1988; Trzebski et al., 1982). Moreover, in patients with hypertension, hyperoxia causes a transient fall in blood pressure and MSNA (Sinski et al., 2014, 2011). These results, alongside the animal studies of carotid body denervation, formed the basis for designing clinical trials targeting the carotid body. Historically, carotid bodies were surgically resected in patients with respiratory disorders with some level of safety and success (Winter, 1973); this led to the first-in-human trial of unilateral carotid body resection in patients with resistant hypertension (Narkiewicz et al., 2016).

In the study of Narkiewicz et al. (2016), 15 patients with resistant hypertension were recruited; after surgery to remove a carotid body unilaterally; around half responded with an average fall of 26 mmHg after 6 months. However, after 12 months, the average fall was 12 mmHg, thus suggesting compensation from the contralateral carotid body. This was accompanied by a reduction in total MSNA at 6 but not at the 12-month follow-up. Prior to the ablation surgery, the respondent patients had a higher HVR and baseline respiratory rate (f_R, indicative of carotid body hypertonicity) than those that showed no response in arterial pressure after carotid body resection (Narkiewicz et al., 2016).

In summary, these results support the notion that the carotid body contributes to the development and persistence of hypertension in both animal models and a cohort of human patients. The inference from these studies is that the carotid body will drive or exacerbate hypertension by prompting sympathetic outflow, thus creating a maladaptive autonomic imbalance in this disease state.

Heart failure. HF is a recognized health problem affecting millions of people worldwide. HF's main hallmarks include, but certainly are not limited to, impaired systolic and/or diastolic cardiac function, elevated sympathetic outflow and breathing disorders. Importantly, both autonomic and respiratory distress in HF have been strongly related to decreased quality of life, poor prognosis, and increased mortality (Corrà et al., 2006; Hanly & Zuberi-Khokhar, 2012; Triposkiadis et al., 2009).

Increases in the sympathetic drive during the progression of HF have been associated with enhanced peripheral and/or central chemoreflex drive in humans (Narkiewicz et al., 1999; Ponikowski et al., 2001a; Porter et al., 1990). In animal models of HF, both carotid body hypertonicity and hyper-reflexia were demonstrated (Marcus et al., 2014; Sun et al., 1999a, 1999b). Using a rabbit model of pacing-induced HF, Sun et al. (1999a, 1999b) recorded from the carotid sinus nerve (CSN) and reported an elevated baseline discharge under normoxia and raised chemosensitivity under isocapnic hypoxia compared to sham animals (Fig. 2*A* and *B*). Carotid body hypertonicity in HF has been found in pacing-induced pre-clinical animal models of HF (Sun et al. (1999a, 1999b) as well as in myocardial-infarcted animals (Del Rio et al., 2013a). Additionally, it has been shown that transient carotid body chemoreceptor unloading using brief hyperoxic gas stimulation (Dejour's test) results

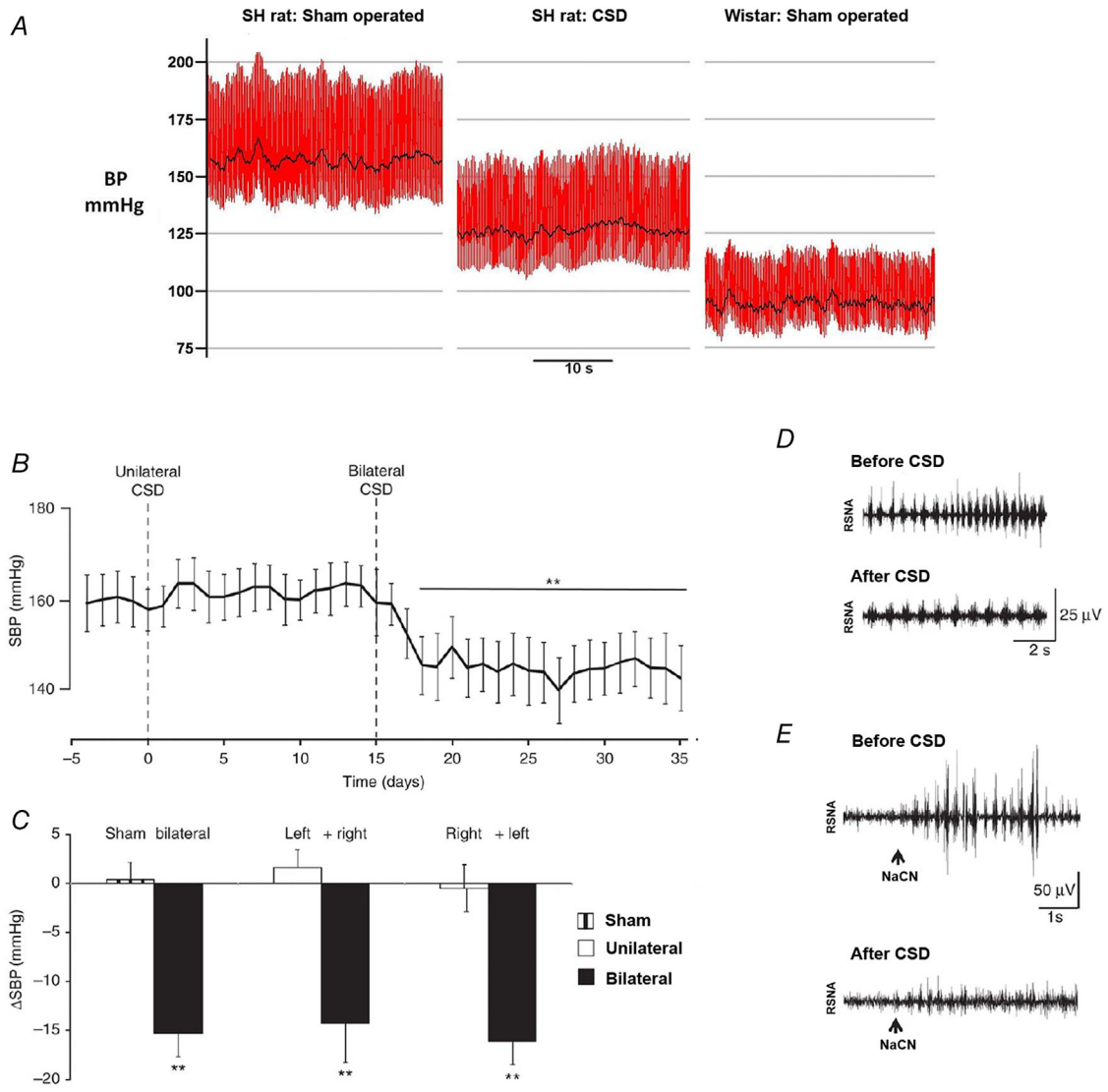

Figure 1. Carotid body sensitisation in hypertension
A, representative recordings of the arterial blood pressure (BP) in a spontaneously hypertensive (SH) rat, sham-operated SH rat, and sham-operated Wistar rat 10 weeks after carotid sinus denervation (CSD). The nerve was resected in 4-week-old rats, and thus before SHRs become hypertensive; data modified from Abdala et al. (2012) with permission. *B*, unilateral CSD was ineffective at lowering systolic blood pressure (SBP) in SHRs but when both carotid sinus nerves were sectioned arterial pressure fell. *C*, irrespective of which side (right or left) the CSD was performed first, there was no difference in the fall observed in SBP. *D*, raw activity levels of baseline renal sympathetic nerve activity (RSNA) before and after CSD in one SH rat showed a marked attenuation. *E*, carotid body sympathetic reflex evoked by bolus injection (I.V.) of sodium cyanide (NaCN) was greatly attenuated after CSD suggesting a substantial loss of carotid body input. Data in *B*–*E* modified from: McBryde et al. (2013) with permission.

in marked improvement in autonomic control in both experimental animals and human HF (Marcus et al., 2014; Ponikowski et al., 1997; Sun et al., 1999a; Trzebski & Baradziej, 1992). In humans, Ponikowski et al. (1997) reported that hyperoxia increased both low-frequency and high-frequency heart rate variability, as well as baroreflex sensitivity. In contrast, Van de Borne et al. (1996) failed to demonstrate a reduction in MSNA of HF patients with hyperoxia. It is well known that not all HF patients have increased peripheral chemosensitivity or baseline MSNA (Giannoni et al., 2008; Notarius et al., 2001). In HF patients with elevated HVR (i.e. >0.6 L/min/S_{pO_2}), carotid body resection was able to reduce MSNA incidence (Niewinski et al., 2017). The latter suggests that increased carotid body chemosensory drive in HF plays a major role in the development/maintenance of heightened sympathetic drive in the setting of HF.

Additionally, patients with HF often display a high incidence (>60%) of breathing disorders (i.e. apnoea, hypopnoea and breathing variability), and these have been closely related to the progression of the disease (Bradley & Floras, 2003a, 2003b; Leung et al., 2012). Therefore, it has been proposed that the exaggerated responses rising from hyper-reactive carotid bodies to apnoeas or hypopnoeas contribute to respiratory instability creating a feed-forward mechanism that sustains the maintenance of disordered breathing in HF (Solin et al., 2000).

Besides, it is worth noting that causal evidence supporting a definite contribution of carotid bodies on cardiorespiratory alterations in the setting of HF was not available until recently. Indeed, Del Rio et al. showed that the role played by carotid bodies on autonomic imbalance and breathing disorders using bilateral carotid body ablation in rats with HF (Del

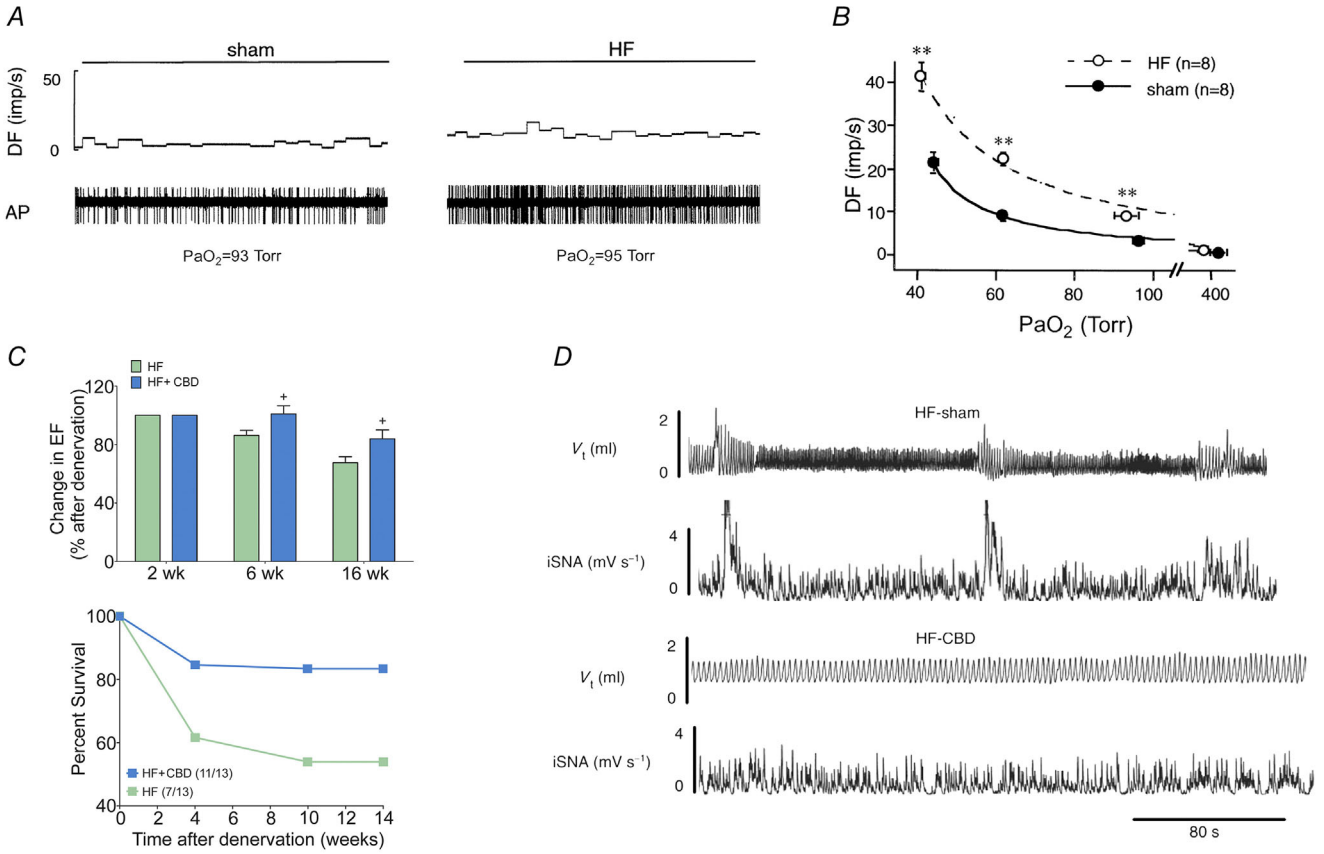

Figure 2. Enhanced carotid body activity in heart failure (HF)
A, during normoxia, HF rabbits have an increased carotid sinus nerve (CSN) afferent discharge compared to sham animals. *B*, carotid bodies of HF rabbits have a higher sensitivity to isocapnic hypoxia (i.e. hyper-reflexia) when compared to sham animals. Data in *A* and *B* were modified from Sun et al. (1999) with permission. *C*, in HF rats, early carotid body denervation attenuates the deterioration of left-ventricle ejection fraction (EF; top panel) and improves the survival rate when compared to intact carotid body HF rats (lower panel). Modified from Del Rio et al. (2013) with permission. *D*, in HF rabbits, carotid body denervation improved respiratory arrhythmias and reduced sympathetic discharge when compared to HF animals with CBs intact. Data modified from Marcus et al. (2014) with permission. CBD, carotid body denervation; DF, discharge frequency; iSNA, integrated renal sympathetic nerve activity; V_T, tidal volume.

Rio et al., 2013b) and rabbits (Marcus et al., 2014). Notably, when performed earlier during HF progression, carotid body ablation not only improved both autonomic and breathing function but also significantly improved survival rates in HF rats (Fig. 2*C*) (Del Rio et al., 2013b). Similarly, Marcus et al. (2014) showed that carotid body ablation reduces renal sympathetic nerve discharge, cardiac arrhythmogenesis, improved baroreflex sensitivity and normalized sympatho-respiratory coupling in rabbits with HF (Fig. 2*D*).

In the same line, Niewiński et al. (2013) presented the first-in-man study providing evidence showing that carotid body ablation can be safely translated into human HF studies. In this case report, unilateral carotid body ablation was performed in severe HF conditions. This case study supports the findings obtained in pre-clinical models showing that carotid body ablation offers the salutary potential for improving autonomic function. However, only modest effects were observed (Niewiński et al., 2013). Unfortunately, no follow-up measurements of this patient were performed to establish if, in the long term, the effects of carotid body ablation on autonomic function were larger. In later studies performed by the same group, they found that bilateral carotid body ablation significantly reduced both hypoxic-induced hypertension (Niewinski et al., 2014) and MSNA incidence, and improved exercise tolerance (Niewinski et al., 2017). These results confirm and extend previous results obtained in different experimental HF conditions (i.e. myocardial infarcted HF rats and pacing-induced HF rabbits) and human HF studies and add new data showing that the enhanced haemodynamic response to hypoxia observed in HF patients requires functional carotid bodies.

Together, findings obtained in experimental and human HF strongly support the role of carotid bodies in the development/maintenance of heightened resting sympathetic drive and disordered breathing. In addition, proof-of-principle studies using carotid body ablation as a tool to reduce peripheral chemosensory drive in HF resulted in marked improvements in both autonomic and respiratory regulation in pre-clinical and clinical studies. Whether this intervention reduces morbidity and mortality and increases life quality in HF patients remains to be determined.

Sleep apnoea. Although sleep apnoea is not the focus of this review, this cardio-respiratory condition deserves mentioning due to its link with carotid body dysfunction and its prevalence in patients with hypertension and HF. Sleep apnoea is a type of sleep-disordered breathing characterised by events of apnoea or hypopnoea during sleep. Some authors classify it as clinically relevant when patients present an apnoea – hypopnoea index (AHI) > 15 events/h (Floras & Ponikowski, 2015). Sleep apnoea can also be clinically sub-classified based on the nature of the apnoeic-hypopnoea event, with obstructive sleep apnoea (OSA) caused by the collapse of the pharynx. In contrast, central sleep apnoea (CSA) results from withdrawing the central respiratory drive in the ponto-medullary network.

The prevalence of this condition in patients with HF is about 50%, with half presenting OSA and the other half CSA (Yumino et al., 2009a). Sleep apnoea has been independently associated with an increased risk of death in patients with HF (Floras & Bradley, 2015; Yumino et al., 2009b). This causal link to autonomic dysfunction is suggested because sleep apnoea can further increase elevated MSNA incidence in these patients (Spaak et al., 2005). In a double-blind, randomised, vehicle-controlled trial, Narkiewicz et al. (1998) tested the hypothesis that OSA leads to high blood pressure and increased MSNA incidence by activating the carotid body chemoreceptors. The authors recruited non-HF patients diagnosed with OSA and gave them hyperoxia (i.e. 100% oxygen) to breathe; they observed significant reductions in blood pressure and MSNA. Collectively, the carotid body plays a considerable role in the autonomic imbalance of HF. This role can be further exacerbated if sleep apnoea is also present in patients (see Fig. 1 from Spaak et al., 2005).

As mentioned, when patients with OSA are exposed to hyperoxia, their blood pressure falls (Narkiewicz et al., 1998). In a prospective population-based study, data from 709 participants on AHI, blood pressure, habitus and health history were analysed at baseline and 4 years later (Peppard et al., 2000). The authors reported a 'dose-dependent' relationship between sleep apnoea and hypertension. Participants with AHI in the range of 0.1–4.9 events/h were 42% more likely to have hypertension than patients with no sleep-disordered breathing after 4 years. Moreover, participants with mild (AHI $=$ 5–14.9 events/h) and severe sleep apnoea (AHI $>$ 15 events/h) were respectively 2 and 3 times more likely to have hypertension after 4 years. Since this study, more recent evidence has confirmed the relationship between sleep apnoea and hypertension (Brown et al., 2022; Hou et al., 2018; Seravalle & Grassi, 2022; Yildiz et al., 2022). Perhaps, the most astonishing finding is the high prevalence ($\sim$80%) of sleep apnoea in patients with drug-resistant or refractory hypertension (Chedier et al., 2022; Logan et al., 2001; Parati et al., 2014).

Sleep apnoea generates cyclic periods of hypoxia that cause oxygen desaturation and carotid body activation. These cyclic periods of hypoxia are commonly termed intermittent hypoxia. In animal models (e.g, Wistar rats, goats, etc.), chronic intermittent hypoxia (CIH, i.e. $\sim$ 10 days exposition) is used to study the carotid body's cardio-respiratory adaptive and maladaptive responses (for review, see Prabhakar et al., 2022). Although this model of sleep apnoea is far from ideal (breathing

does not stop; conversely, hyperventilation and hypocapnia ensue), it remains an insightful model to understand how ischemia-reoxygenation impacts the carotid body sensory output. First, in rats, CIH causes increased HVR and hypertension (Fletcher et al., 1992a; Rey et al., 2004). Second, CIH drives hypertension by elevating systemic sympathetic outflow (Bao et al., 1997; Dick et al., 2007; Zoccal et al., 2007). Third, carotid body denervation prevents CIH-induced hypertension (Fletcher et al., 1992b; Leke et al., 1997). Finally, CIH was demonstrated to induce carotid body sensory plasticity (i.e. long-term facilitation), which is partially brought about by oxidative stress (Peng et al., 2003; Prabhakar, 2011). Interestingly, bilateral cryogenic ablation of carotid bodies in rats previously exposed to CIH abrogates hypertension and restores cardio-respiratory parameters and autonomic imbalance (Del Rio et al., 2016). These data indicate a causal relationship between CIH (a.k.a. sleep apnoea), carotid body-induced autonomic imbalance and secondary hypertension. How the carotid body leads to autonomic imbalance (i.e. exaggerated sympathetic outflow) and hypertension in the model of CIH is addressed next.

The CIH alters the sympathetic–respiratory coupling in the in situ *preparation of rats.* Using the arterially perfused *in situ* preparation known as the working heart–brainstem preparation (WHBP; Paton, 1996; Paton et al., 2022), Machado's group demonstrated that CIH leads to changes in the pattern of sympathetic–respiratory coupling (for review, see Moraes et al., 2012, 2014). The link between the increase in sympathetic outflow and its effect on the vascular tonus, and thereby blood pressure, depends on the discharge pattern of sympathetic motor neurones (Briant et al., 2015). Studies have demonstrated that more significant respiratory oscillations on sympathetic motor output (a.k.a. sympathetic–respiratory coupling), rather than an increased tonic discharge, produce more prominent changes in vascular resistance and blood pressure, thus leading to hypertension (Briant et al., 2015; Moraes et al. 2014*a*, 2014*b*, 2014*c*; Simms et al., 2009; Zoccal et al., 2009). These respiratory oscillations occur due to delicate interaction between inspiratory and expiratory neurones (located in the preBötzinger and Bötzinger complexes, respectively) and the premotor sympathetic neurones in the rostral ventrolateral medulla (RVLM) (Menuet et al., 2020; Sun et al., 1997), which adjusts the sympathetic outflow to the heart and vessels during each respiratory cycle (i.e. inspiration, post-inspiration and active expiration).

Machado et al. previously exposed young rats to a protocol of CIH and then conducted their experiments using the WHBP. They described changes in the central respiratory network that impact the pattern of sympathetic discharge and blood pressure (Machado et al., 2017; Moraes et al., 2013; Zoccal et al., 2008). First, CIH rats exhibited additional bursts of sympathetic activity during active expiration. Second, these changes were tightly associated with an additional burst of activity recorded from the abdominal nerve (Fig. 3). Third, augmented Traube–Hering waves were seen in the perfusion pressure of CIH animals (Moraes et al., 2012; Zoccal et al., 2008). Although the cardiac contractility was not directly measured in rats submitted to CIH during the phase of augmented sympathetic–respiratory coupling, we presume that the increased respiratory sympathetic coupling would increase myocardial contractility (i.e. increase in systolic pressure and cardiac output). This possibility is consistent with previous studies documenting that activation of peripheral chemoreceptors in the WHBP of normal rats induced a large increase in cardiac contractility (Braga et al., 2007). The latter, combined with an increase in peripheral vascular resistance, contributes to the development of CIH-induced hypertension. These findings open exciting perspectives for new studies to explore the possibility that an increase in the sympathetic drive to the heart in OSA patients, who are also subject to episodes of intermittent hypoxia, contributes to the increase of myocardial contractility and makes these patients prone to a higher rate of cardiac mortality (Yeghiazarians et al., 2021).

Previous studies reported that CIH-induced sympathetic overactivity and hypertension are associated with increased discharge frequency in RVLM neurones (Moraes et al., 2013). The latter depends on changes in the intrinsic excitability of precedent expiratory neurones that synapse on RVLM pre-motor sympathetic neurones and not elevated electrical excitability of these RVLM neurones themselves (Machado et al., 2017; Moraes et al., 2013; Paton et al., 2022). These data suggest that high carotid body sensory input can induce neuronal plasticity in a population of ponto-medullary expiratory neurones projecting to RVLM pre-motor sympathetic neurones, thus prompting the increase in sympathetic–respiratory coupling (Moraes & Machado, 2015; Moraes et al., 2014b, 2015). These findings strongly support the concept that carotid body-mediated changes in the central respiratory rhythm/pattern generator increase sympathetic outflow and contribute to the development of CIH-induced hypertension. This mechanism, however, does not exclude the presence of central circuit plasticity contributing to sympathetic overactivity, which is independent of the carotid body afferent drive, especially in hypertension and HF. For instance, an enhanced central chemoreflex sensitivity driving sympathetic outflow is reported in both hypertensive and HF patients, even in the absence of a sensitised peripheral chemoreflex (Narkiewicz et al., 1999; Sayegh et al., 2023; Van de Borne et al., 1996). In fact, a caveat that should be acknowledged is that although hypoxia and hyperoxia are commonly associated with the carotid body, there are central oxygen sensors that could modulate systemic sympathetic activity

(Barioni et al., 2022; Gourine & Funk, 2017). Given this mechanistic insight, we discuss whether carotid body dysfunction is the same or different in HF.

Characteristics of carotid body dysfunction in hypertension and HF

Quantitative comparison of carotid body hyperactivity in hypertension and HF. As previously mentioned, hyperactivity of the carotid body was demonstrated in both hypertension and HF (Pijacka et al., 2016; Sun et al., 1999). This hyperactivity can take the form of hypertonicity, which means the carotid body constantly sends elevated sensory input to the central nervous system, and/or hyper-reflexia, which means the carotid body has elevated sensitivity to a given stimulus and is comparable to allodynia in the perception of pain. For the latter, we can demonstrate a change in the gain of carotid body sensitivity by recording afferent activity or the amplitude of the chemoreflex motor responses.

Carotid body hypertonicity and hyper-reflexia are both present in the SH rat model (Pijacka et al., 2016b), two kidney-one clip (2K1C) model (Melo et al., 2020; Pijacka et al., 2016a), and CIH-induced hypertension, which is a model of sleep apnoea (see 'Sleep apnoea'). In contrast, using a renovascular ovine model of hypertension, Chang et al. (2020) could only demonstrate the presence of

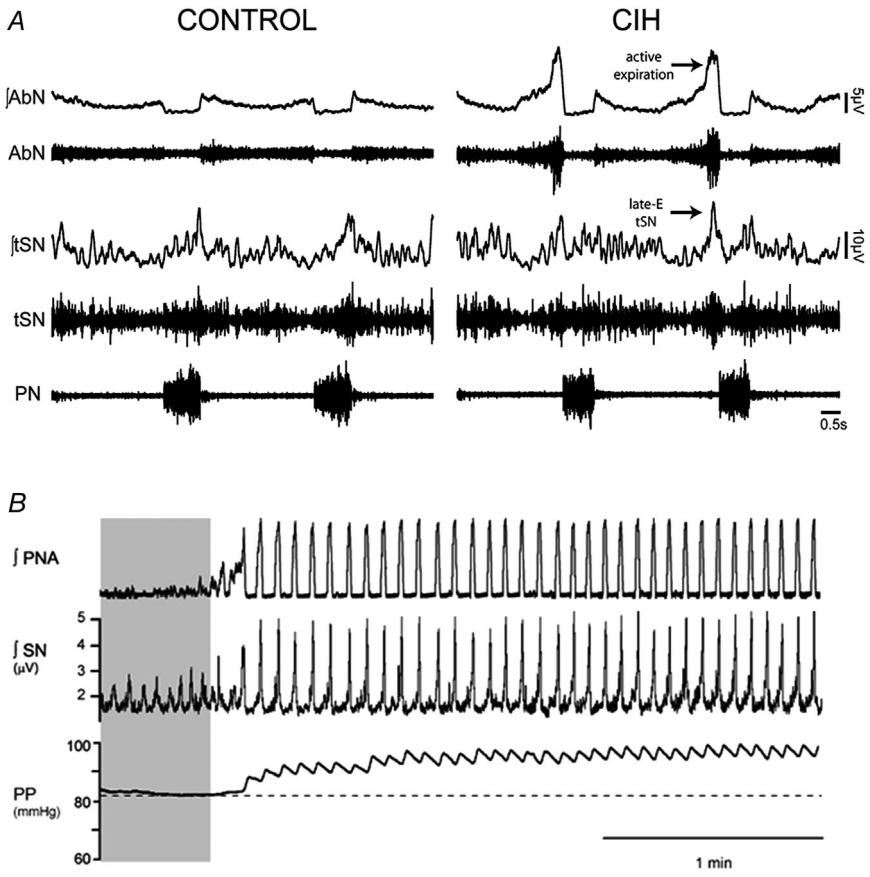

Figure 3. Enhanced respiratory–sympathetic coupling in chronic intermittent hypoxic (CIH) rat and in the spontaneously hypertensive rat (SHR) and its effect on arterial pressure
A, recordings from representative *in situ* preparations illustrating the pattern of raw and integrated (∫) activities of abdominal (AbN), thoracic sympathetic (tSN) and phrenic nerves (PN) from control and CIH rats. Note that the control rat presents low amplitude discharge from the AbN, indicating that the respiratory pattern is composed of active inspiration and passive expiration. The CIH rat presents enhanced AbN activity at the late part of expiration, indicating that expiration becomes an active process. As a consequence of the AbN discharge during expiration, the tSN of CIH rats exhibits a correlated peak of discharge during the same phase of respiratory cycle/late-expiratory (late-E) tSN peak. The latter augments Traube–Hering waves that summate to raise arterial pressure as illustrated in *B*. *B*, example showing the change in tSN activity in an SH rat during re-establishment of eupnoea. Note the Traube–Hering waves recover and summate to cause the perfusion pressure rise with the onset of eupnoea as a consequence of the respiratory – sympathetic coupling being re-engaged. Data in *A* from Machado et al. (2017) and *B* from Simms et al. (2009) with permission.

hypertonicity in sheep (2K1C), i.e. without chemoreflex hypersensitivity. In HF, carotid body hypertonicity and hyper-reflexia were both documented in the following animal models: pacing-induced HF in rabbits (Sun et al., 1999a); myocardial infarction in rats (i.e. via ligation of the left anterior descending coronary artery) (Del Rio et al., 2013a) and a genetic model of cardiomyopathy in mice (Wang et al., 2012).

Humans. Comparing the level of carotid body hyperactivity in humans with different cardiovascular diseases is confounded by the different methods employed. In patients with borderline hypertension, Somers et al. (1988) reported a 72% increase in $\dot{V}_E$ (baseline = 8.1 ± 0.5 L/m *vs.* response = 13.9 ± 1.0 L/m) using isocapnic hypoxia, while the MSNA raised by 20% in normotensive and 40% in hypertensive patients. Of note, the HVR was not different from normotensive patients. In contrast, Trzebski et al. (1982) reported an augmented HVR in hypertensive patients. These authors plotted a hyperbolic V_I–P_{AO_2} curve with the equation: $V_I = V_{Io} + A(P_{AO_2} - 4.3)$, where V_I is inspiratory minute ventilation, V_{Io} is the asymptote for ventilation obtained by extrapolation and a constant 4.3 representing in kPa the P_{AO_2} (32 mmHg) at which the slope of the V_I–P_{AO_2} curve usually approaches infinity, and they compared the ventilatory drive between hypertensive and normotensive patients through parameter *A*, which denotes the hyperbolic shape of the curve (normotensive = 28.8 ± 2.7 *vs.* hypertensive = 116.1 ± 10.5). Narkiewicz et al. (2016) assessed the HVR in patients with resistant hypertension using $\dot{V}_E/S_{pO_2}$; they reported a baseline of 0.44 ± 0.04 L/min/S_{pO_2}. After sorting patients into responders (i.e. to unilateral carotid body resection) and non-responders, the values of HVR were respectively 0.5 ± 0.05 and 0.32 ± 0.06 L/min/S_{pO_2}. Narkiewicz et al. (2016) did not control ET_{CO_2} to achieve an isocapnic hypoxia stimulus; instead, they gave patients 100% N_2 to breathe intermittently, aiming to evoke a quick fall in S_{pO_2} (to 75%). This would presumably lead to hypocapnia and diminished HVR.

Ponikowski et al. (2001) used the same method as Narkiewicz to assess the HVR in patients with HF; however, it was unclear whether they effectively controlled patients' ET_{CO_2} since they described monitoring O_2 and CO_2 at the mouth by mass spectrometry. The authors reported overall chemosensitivity of 0.69 ± 0.50 L/min/S_{pO_2}, whilst, in healthy individuals, HVR is approximately ∼0.35 L/min/S_{pO_2} (Keir et al., 2020), thus representing a 97% increase in the ventilatory response. In this study, the authors established an HVR threshold >0.72 L/min/S_{pO_2} to subclassify patients into augmented chemosensitivity. Based on this threshold, 27 out of 80 patients (i.e. 34%) were deemed to have abnormal peripheral chemosensitivity; their average $\dot{V}_E/S_{pO_2}$ was equal to 1.20 ± 0.53 L/min/S_{pO_2}. That is a 2.4-fold increase over healthy subjects. In another study, Chua et al. (1996) reported an HVR of 0.71 ± 0.076 L/min/S_{pO_2} in HF patients against 0.29 ± 0.056 L/min/S_{pO_2} in control subjects (i.e. 140% increase). Niewinski et al. (2013) reported a 2.4-fold increase in the HVR of HF patients against control subjects (0.58 (0.32–0.95) *vs.* 0.17 (0.06–0.29) l/min/S_{pO_2}). Interestingly, Giannoni et al. (2008) used progressive isocapnic hypoxia (i.e. ET_{CO_2} was maintained at a baseline) to demonstrate that 40% of HF patients had an HVR >1.1 L/min/S_{pO_2}. Collectively, these data show that, in humans, carotid body respiratory hyper-reflexia is quantitatively more elevated in HF patients than in hypertensive patients (Fig. 4), at least if we use the HVR as the metric to measure peripheral chemosensitivity (see 'Future clinical perspectives').

Animal models. If comparing the magnitude of carotid body chemosensitivity is challenging in humans, accomplishing this work in animals is even more equivocal due to the greater diversity of experimental methods and species (e.g. rats *vs.* rabbits). Recording from the CSN, Sun et al. (1999a) plotted the afferent discharge (i.e. impulse/s) against P_{aO_2} (in Torr) for both anaesthetised rabbits with pacing-induced HF and sham groups. By using the parameter *B* of their hyperbolic

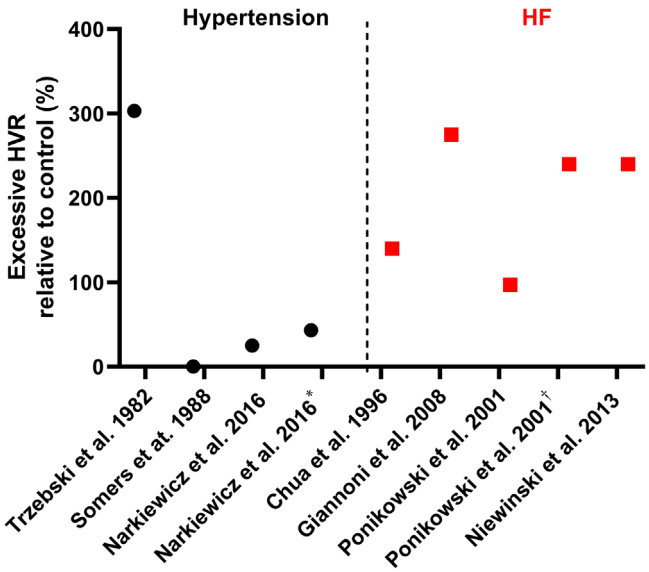

Figure 4. Hypoxic ventilatory response (HVR) of hypertensive *versus* heart failure (HF) patients
To compare carotid body sensitivity between different studies, we plotted the excessive ventilatory response as a percentage relative to its health controls. In the studies using the slope of minute ventilation ($\dot{V}_E$)/blood oxygen saturation (S_{pO_2}) as an index of peripheral chemosensitivity, we used 0.35 L/min/S_{pO_2} as a normal control response (Keir et al., 2020) as the study did not report any of its own. *Patients with resistant hypertension responsive to carotid body resection. †Grouping HF patients using HVR >0.72 L/min/S_{pO_2} as a threshold of abnormal chemosensitivity.

curve to compare the carotid body chemosensitivity between groups, they reported a 2.14-fold increase in HF rabbits relative to sham (309.6 ± 80.1 *vs.* 972.8 ± 89.2 impulses/s Torr; Sham *vs.* HF respectively). Similarly, Fukuda et al. (1987) also evaluated the carotid body chemosensitivity by recording the CSN afferent discharge in both anaesthetised SHR and normotensive rats. However, the authors plotted the carotid body sensory output (as a percentage of control activity) against the fraction of expired O_2 (i.e. F_{ETO_2}). For this analysis, the authors used an exponential regression $CSN = Ae^{-C.FETO2}$ and compared the chemosensitivity through parameters A (3574 ± 428 *vs.* 11,858 ± 2818% of control activity, normotensive rats *vs.* SHRs) and C (0.222 ± 0.008 *vs.* 0.282 ± 0.016, normotensive rats *vs.* SHRs). If we interpolate the values in the equation with a $F_{ETO_2} = 10\%$, we can calculate the CSN activity as 388% for normotensive and 707% for SHRs; therefore, SHRs have an excessive response 82% higher than normotensive rats.

Del Rio et al. (2013a) investigated the HVR in awake rats with myocardial infarct induced-HF using whole-body plethysmography. The authors used a 10% inspired fraction of O_2 (i.e. F_{iO_2}) and 3% CO_2 (i.e. isocapnic hypoxia) as the stimulus. They reported an excessive 97% increase in ventilatory response when compared to sham animals (112.69 ± 12.23 *vs.* 222.10 ± 28.67 mL/min/100 g, sham *vs.* HF rats). Likewise, using whole-body plethysmography, Tian et al. (2019) reported an excessive 30% increase in the HVR of awake SHRs relative to control mates (627 ± 34 *vs.* 480 ± 24 μL/min/g, SHRs *vs.* Wistar–Kyoto rats). Care must be taken when evaluating the peripheral chemosensitivity using hypoxic hypoxia in awake rodents since this stimulus causes progressive metabolic decline measured by falls in $\dot{V}_{O_2}$ (i.e. O_2-uptake), $\dot{V}_{CO_2}$ (i.e. CO_2-production) and body core temperature (Morgan et al., 2014, 2016). According to Morgan et al. (2014), the optimal index for carotid body sensitivity in the unanaesthetised rodent is either $\Delta\dot{V}_E/\dot{V}_{CO_2}{:}\Delta S_{pO_2}$ or $\Delta V_T/T_i/\dot{V}_{CO_2}{:}\Delta S_{pO_2}$. Therefore, authors should assess the HVR by plotting the ventilatory equivalent for $\dot{V}_{CO_2}$ ($\dot{V}_E/\dot{V}_{CO_2}$) or $V_T/T_i/\dot{V}_{CO_2}$, with V_T being tidal volume and T_i inspiratory time, *versus* S_{pO_2} as the stimulus variable. Nevertheless, it seems clear that in animal models, the carotid body chemosensitivity follows the same trend as in humans, i.e. the level of hyperactivity is quantitatively 3 times higher in HF than in hypertension. Given these changes in sensitivity and this being greater in HF, this prompts the question of whether mechanisms are similar or distinct.

Insights from carotid body morphology. The carotid body has structural and functional plasticity. For example, it enlarges under specific environmental conditions or disease states (Cramer et al., 2014; Nair et al., 2013; Prabhakar et al., 2022). Carotid body hyperplasia is documented in people born and living at high altitudes compared to those at sea level (Arias-Stella & Valcarcel, 1976) and is also reported in humans and animals with cardio-metabolic diseases such as diabetes mellitus, hypertension and HF (Cramer et al., 2014; Pfeiffer et al., 1984). However, the same is not true for rats submitted to CIH (Peng et al., 2003) and patients with sleep apnoea (Welch et al., 2017).

While chronic hypoxia sensitises the carotid body, chronic sustained and intermittent hypoxia have different effects on the carotid body morphology and, perhaps, the underlying mechanisms of sensitisation. Moreover, the carotid body of hypertensive and HF patients might resemble the adaptive changes of individuals living at high altitudes. Hence, if the latter statement were true, then the carotid body of hypertensive and HF patients would be in a similar environment of chronic sustained hypoxia. But how would such an environment be created without chronic systemic hypoxemia (i.e. low P_{aO_2} and S_{pO_2})?

The first possibility is that, in hypertension and HF, the carotid body tissue P_{O_2} is normoxic, and chemical modulators within the blood alter the resting excitability level of chemoreceptor glomus cells. These modulators may be hormones or incretins released from the gastrointestinal tract (Pauza et al., 2022). Therefore, these putative chemical modulators would travel through the bloodstream, reaching the carotid body and, based on the chemoreflex response, may mimic chronic hypoxia's effects. Repeated exposure may even induce an epigenetic response. Evidence supports the existence of these chemical modulators, which are discussed below. A second possibility is that the carotid body tissue P_{O_2} would be dissociated from the levels of blood P_{aO_2} through reductions in blood flow supply to the carotid body, thus creating a localised chronic hypoxic environment. Both circulating modulators and local tissue hypoxia due to reduced carotid body blood flow are not mutually exclusive. It is feasible that both mechanisms co-exist in disease states, with changes in blood flow creating an environment of low carotid body P_{O_2} at the same time that paracrine modulators reach the chemoreceptors.

Mechanisms of carotid body dysfunction in hypertension and HF: unique or similar?

The mechanisms of carotid body dysfunction in HF have been extensively reviewed elsewhere (Schultz & Marcus, 2012; Schultz et al., 2015). Surprisingly, no reviews exist on the same topic for hypertension. In parallel, recent studies have proposed that metabolic modulators released in obesity and diabetes also drive carotid body sensitivity in hypertension (Pauza et al., 2022; Shin et al., 2019).

Shin et al. (2019) showed that leptin, a hormone produced by adipocytes in obesity, induces hypertension by activating the transient receptor potential melastatin 7 (Trpm7) on the glomus cells of the carotid body. Pauza et al. (2022) showed that activating the carotid body's glucagon-like peptide-1 receptor (GLP1R) inhibits hyperglycaemia-induced peripheral chemoreflex sensitisation and resting sympathetic overactivity in SHRs. Moreover, Pauza et al. (2022) demonstrated that GLP1R is expressed in both glomus cells and a subset of blood vessels in the carotid bodies of normotensive rats. In contrast, GLP1R is downregulated in SHRs, being absent in carotid body blood vessels. This may provide the elusive link between diabetes and carotid body sympathetically mediated hypertension. Another mechanism of carotid body dysfunction is linked to the upregulation of P2X3 receptors on sensory terminals of petrosal afferent neurones located in the carotid body of SHRs (Pijacka et al., 2016b). Whether these metabolic mechanisms exist in HF is unknown. However, in HF, recent evidence suggests that P2X3 receptor blockade attenuates carotid body afferent activity, reduces the augmented chemoreflex-evoked sympathetic responses, abolishes the apnoeas, reduces inflammation and improves cardiac pump function (Lataro et al., 2023). Future studies will need to assess whether drugs that modulate GLP1R or Trpm7 in the carotid body are therapeutic in animal models of HF.

Similar mechanisms. Zucker et al. (2022) raised the question of whether GLP1R could modulate carotid body sensitivity through changes in blood flow since these receptors are expressed in blood vessels. Using ultrasonic flow probes, Ding et al. (2011) recorded the CCA blood flow in HF rabbits and compared it against two groups of animals: sham and non-HF animals implanted with a cuff to occlude the CCA and reduce blood flow to the carotid bodies. The cuff was inflated to mimic the reduction in blood flow observed in HF rabbits. The authors reported similar levels of carotid body hyperactivity between HF animals and animals with CCA occlusion. They also reported increased baseline renal sympathetic nerve activity, decreased carotid body protein expression of nitric oxide synthase (NOS) and nitric oxide (NO) production, as well as increased carotid body production of angiotensin II (Ang II) and protein expression of Ang II receptor type 1 (AT_1R). The observed carotid body downregulation of NOS–NO and upregulation of Ang II–AT_1R pathways was not different between HF and CCA-occluded rabbits. This work strongly suggests that the reduced cardiac output in HF leads to hypoperfusion of the carotid body, which sensitises this organ. Felippe et al. (2023) demonstrated that increased sympathetic efferent input from the superior cervical ganglion (SCG) to the carotid body sensitises its reflex response via α_1-adrenoreceptors in both normotensive and hypertensive animals. Bilateral resection of the SCG in adult SHRs attenuated the sensitivity of evoked chemoreflex responses. It also caused significant falls in systolic and diastolic blood pressures at similar levels to those reported with carotid body denervation (McBryde et al., 2013). He proposed that an increased sympathetic outflow to the carotid body causes vasoconstriction, thereby reducing blood flow, which sensitises the carotid body. Testing whether the SCG also plays a role in HF carotid body hyperactivity remains to be explored. Recently, the SCG was also implicated with carotid body sensitisation during recovery from acute lung injury (Kamra et al., 2023); this indicates that the SCG may be involved in carotid body sensitisation in multiple pathological conditions, which could include HF. What seems quite clear is that regardless of whether the reason for carotid body hypoperfusion is a mechanical dysfunction of the heart's ability to deliver blood flow or pathological vasoconstriction of carotid body arteries (e.g. due to increased noradrenaline from sympathetic efferents, reduced vasodilatation by downregulation of NOS–NO or GLP1R pathways, etc.), reductions in carotid body blood flow is a potential common mechanism of dysfunction between hypertension and HF. Under these circumstances, we should consider the role that atherosclerosis could play in carotid body dysfunction. It is well known that the carotid artery bifurcation is prone to the development of atherosclerosis, which causes stenosis, thereby reducing the carotid body's blood flow (Lowe et al., 1987; Samuel, 1956; Zarins et al., 1983). Furthermore, concentrations of serum lysophosphatidic acid (LPA) are increased in patients with cardiovascular diseases such as acute coronary syndrome, and it was suggested to be involved with the development of atherosclerosis (Zhou et al., 2019). In addition, exogenous LPA infusion raised the blood pressure of rodents (Tokumura et al., 1978). Interestingly, increased plasma LPA was demonstrated to activate carotid bodies via both LPA receptors (LPAr) and transient receptor potential vanilloid one (TRPV1) (Jendzjowsky et al., 2018, 2021*a*, 2021*b*). Therefore, it would not be surprising if LPA was also involved with carotid body sensitisation during the development of atherosclerotic plaque in patients that are or will be hypertensive or develop HF in early stages. In a more progressed stage, atherosclerosis would further contribute to carotid body sensitisation via a reduction in carotid body blood flow.

Other similarities between HF and hypertension are the changes in NOS–NO and Ang II–AT_1R pathways. Atanasova et al. (2020, 2022) have demonstrated that SHRs have impaired carotid body NO production with a marked reduction of protein expression for both nNOS and eNOS in both chemoreceptor cells and blood vessels.

NO is an essential negative modulator of carotid body activity; it can attenuate its sensory output via either a direct effect on glomus cells or dilatation of blood vessels, thus increasing carotid body blood flow (Brognara et al., 2021; Campanucci & Nurse, 2007; Campanucci et al., 2012; Wang et al., 1993).

It is well documented that Ang II acting via AT_1R increases carotid body excitability dose-dependently (Allen, 1998; Murali et al., 2014). As previously revealed in HF, the Ang II–AT_1R pathway was demonstrated to be upregulated and to play an essential role in carotid body hyperactivity (Li et al., 2006; Schultz, 2011). Ang II also sensitises the carotid body in CIH (Foster et al., 2010; Kim et al., 2018; Lam et al., 2014; Peng et al., 2011). First, intermittent hypoxia in humans raises blood pressure and this effect is prevented in patients treated with losartan (Foster et al., 2010). Likewise, in rats, intermittent hypoxia increases sympathetic nerve activity, which is also prevented by losartan (Kim et al., 2018). Second, intermittent injections of Ang II induce sympathetic overactivity, which is attenuated by carotid body denervation (Kim et al., 2018). Third, intermittent injections of Ang II *in vitro* evoke long-term facilitation in carotid body sensory discharge (Peng et al., 2011). Lastly, CIH evokes upregulation of angiotensinogen and AT_1R expression in glomus cells in rats (Lam et al., 2014). Further, glomus cells of CIH animals showed enhanced Ang II-induced $[Ca^{2+}]_i$ response, which was also abolished by losartan treatment (Lam et al., 2014). Interestingly, there is no data on the modulatory actions of Ang II/AT_1R on carotid body response in SHRs. Nonetheless, based on RNA-seq and qRT-PCR data, SHRs display increased transcript abundance of Ang-II type 2 (*Agtr2*) and type 1 A (*Agtr1a*) receptors relative to WKY rats (Pauza et al., 2022). Considering that Ang II plays a vital role in the pathophysiology and progression of the disease in SHRs (Mihailović-Stanojević et al., 2009), one can postulate that Ang II sensitises the carotid body in hypertension. This is corroborated by the work of Sohn et al. (2022), which demonstrated that blocking AT_1R with losartan reduces carotid body-evoked blood pressure response in hypertensive sheep (2K1C) challenged with bolus injection of cyanide. These data indicate that chronic carotid body hypoperfusion in hypertension and HF leads to maladaptive transcriptional gene expression, among which AT_1R is upregulated. Carotid body activation drives peripheral sympathetic outflow, which includes itself as a target organ as well as the kidneys; the latter activates the renin–angiotensin–aldosterone system, thus increasing Ang II production. Ang II will work as a feedforward mechanism contributing to sensitisation of the carotid body by two mechanisms: (i) direct activation of chemoreceptor cells (Allen, 1998; Murali et al., 2014) and (ii) further vasoconstricting arteries and reducing blood flow (Greenfield & Tindall, 1968). It is important to remember that any disease or pathological state that triggers the production of Ang II will most likely sensitise the carotid body.

Unique mechanisms. There are several mechanisms causing carotid body dysfunction that, to date, have been tested in either HF or hypertension but not in both disease states. Among these is the gaseous transmitter hydrogen sulphide (H_2S) (for review, see Schultz et al., 2012). In the field of carotid body chemo-transduction, studies carried out in cats and rats led Prabhakar's group to propose a critical balance between the gaseous messengers carbon monoxide (CO) and H_2S for setting the sensitivity to O_2 sensing. According to this theory, glomus cells express haem oxygenase-2 (HO-2), which catalyses the synthesis of CO, which inhibits the enzyme cystathionine-γ-lyase (CSE). CSE mediates the production of H_2S, which is proposed to inhibit O_2-sensitive-K^+ channels. Therefore, since the production of CO is regulated by the levels of O_2 (i.e. a substrate of the enzymatic reaction with HO-2), the levels of CO would drop during hypoxia, thus causing an increase in H_2S, which would then act on O_2-sensitive-K^+ channels to depolarise the glomus cells (Peng et al., 2018). Del Rio et al. (2013a) and Prabhakar & Peers (2014) used DL-propargylglycine (PAG), an irreversible inhibitor of CSE, to inhibit the production of H_2S in HF rats. They showed that PAG treatment restores breathing stability and cardiac autonomic function. It also reduces HVR *in vivo* and carotid body sensory output *in vitro*. Although the modulatory effect of the HO-2 system on carotid body sensitivity seems unquestionable, its role in oxygen sensing is debatable. Ortega-Sáenz et al. (2006) demonstrated the persistence of carotid body oxygen sensing in HO-2 null mice.

Another mechanism of carotid body dysfunction in HF concerns the transcription factor Krüppel-like factor 2 (KLF-2), which is decreased in the carotid body of HF rats (Haack et al., 2014). KLF-2 is a shear stress-sensitive transcription factor, and thus highly sensitive to changes in blood flow (Dekker et al., 2005). Marcus et al. (2018) overexpressed KLF-2 in carotid bodies of HF rabbits using adenoviral transfection. They showed that restoring KLF-2 reduced carotid body sensitivity and improved autonomic imbalance, corrected abnormal breathing patterns and reduced arrhythmia incidence associated with HF. Whether KLF-2 is also attenuated in the carotid bodies of SHRs awaits verification. However, it would not be surprising if it were. Anatomical studies undertaken on the carotid body of SHRs during the 1980s demonstrated many morphological abnormalities in blood vessels that would impair carotid body blood flow (Habeck & Holzhausen, 1985; Habeck et al., 1981, 1984, 1985; Honig et al., 1981; Smith et al., 1984). A brief

description of these morphological changes is presented next.

Underappreciated concepts: morphological alterations of carotid body blood vessels in SHRs

At the origin of the carotid body artery, there is a sphincter-like structure known as the intimal cushion, which is commonly seen in normotensive rats but either altered or missing in SHRs (Brognara et al., 2021; McDonald & Larue, 1983; Smith et al., 1984). When present, it is broader and shorter and hence less developed in SHRs (Habeck et al., 1984). In Wistar rats, cell proliferation of the intima at the origin of second-order branches can be observed. Together with smooth muscle cells, this intima proliferation forms intimal pads that surround and partially occlude the vessels (Honig et al., 1981; McDonald & Larue, 1983; Smith et al., 1984). Typically, carotid body arteries in SHRs have thicker walls (Habeck & Holzhausen, 1985; Habeck et al., 1981, 1984, 1985; Honig et al., 1981; Smith et al., 1984). In this strain, the most striking characteristic of carotid body arteries was the excessive cell proliferation in their intima; many of these cells had vacuolated material containing mucopolysaccharide (Habeck et al., 1984; Honig et al., 1981; Smith et al., 1984). The intimal proliferation in SHRs is so intense that it almost completely occludes the second-order branches immediately after the first-order vessel (Habeck et al., 1984; Honig et al., 1981; Smith et al., 1984). Furthermore, there was often local dilatation of the second-order vessels with thinning of the media and fragmentation of its elastic laminae. Interestingly, distal to the obstruction, the vessels were normal in structure (Smith et al., 1984).

As mentioned before, the origin of the carotid body artery contains the intimal cushion, which is described in the literature as a sphincter-like structure. However, this structure does not really resemble a sphincter since it is too narrow and projects toward the lumen of the external carotid artery. Although some authors suggest that intra-arterial cushions are involved with plasma skimming (i.e. to reduce blood haematocrit entering into collateral vessels such as the carotid body artery; McDonald, 1983; McDonald & Haskell, 1983; McDonald & Larue, 1983), other authors believe differently (Fourman & Moffat, 1961). Fourman & Moffat (1961) showed that the impact of intra-arterial cushions depends on their morphology: if the cushion projects towards the lumen of the main trunk, reaching the axial stream, this will produce a phenomenon called cell skimming instead. This means that the cushion will 'fish' the haematocrit of blood into the collateral vessels, presumably because this region is more oxygenated than the peripheral zone (Fourman & Moffat, 1961). On the other hand, if the cushion is not well-developed, plasma skimming will occur (Fourman & Moffat, 1961). This means that in the carotid body of SHRs, not only the blood flow is reduced, but the fraction of blood entering its microcirculation belongs to a less oxygenated bloodstream running through the carotid arteries.

Future clinical perspectives

An interesting fact from the first human trial performing unilateral carotid body resection is that blood pressure response wanes at 12 months, which could suggest compensation from the contralateral carotid body (Narkiewicz et al., 2016). This may imply that bilateral carotid body resection is required to maintain the fall in arterial pressure. This is, however, untenable based on the human studies in HF patients showing prolongation of sleep apnoeas and lowering of oxygen saturation (Niewinski et al., 2017, 2021). As mentioned previously, Felippe et al. (2023) identified that an increase in sympathetic outflow to the carotid body from the SCG works as a feed-forward mechanism leading to the carotid body hyperactivity in SHRs. After bilateral resection of the SCG, he observed a drop in blood pressure of the same magnitude as bilateral denervation of the carotid body. Based on that, Felippe et al. (2023) proposed that, in humans, instead of resecting the entire SCG (which would trigger Horner's syndrome), cutting the connection between the carotid body and SCG bilaterally could be an attractive target-specific interventional approach, which would allow the carotid body to maintain its essential protective ventilatory function against hypoxia and at the same time most likely prevent the compensatory effect in arterial blood pressure. However, we acknowledge that further neuroanatomical details are required to illustrate the feasibility of this selective resection to preserve the ventilatory response but not the autonomic compensatory effect under hypoxic conditions.

As the carotid body is a multi-modal receptor controlling multiple functions, its resection, whether unilateral or bilateral, is not a preferred option. Unilateral resection may result in compensation from the contralateral carotid body thereby reducing any therapeutic gains. Bilateral resection in HF patients has worsened oxygen desaturation in patients with sleep apnoea. Thus, pharmacological targeting of the carotid body continues to be of high interest. The clinical implication of using a purinergic P2X3 antagonist for treating carotid body-related autonomic dysfunction in cardiovascular diseases continues to be promising, as demonstrated in preclinical studies (Lataro et al., 2023; Pijacka et al., 2016b). Additionally, the use of genetic tools like single-cell RNAseq to find new molecular targets, as demonstrated by Pauza et al. (2022), could revolutionise

the field of carotid body drug discovery and development. For example, we revealed glucagon-like 1 peptide receptors in the carotid body, and their activation depressed chemoreflex gain and sympathetic activity in conditions of hyperglycaemia. Finally, device-based therapy is another interesting approach for controlling carotid body-mediated cardio-metabolic diseases (Conde, 2021; Conde et al., 2022; Heusser et al., 2020). Preclinical studies have demonstrated that electrical stimulation using KiloHertz frequency alternate current is capable of blocking CSN activity, thus opening the possibility for electrical neuromodulation of carotid body activity (Conde, 2022). The clear advantage of this approach would be the possibility of attenuating the carotid body to a certain activity level rather than completely abolishing it. However, it needs to be determined how feasible it is to implant a device such as this one around the CSN of humans.

Previously, we discussed how the carotid bodies in HF and hypertensive patients might resemble the (mal)adaptive changes seen in individuals living at high altitudes. Animal models used to study these adaptive changes use hypobaric and normobaric chronic sustained hypoxia (Prabhakar et al., 2022). In sojourners at high altitudes or animals exposed to chronic sustained hypoxia, a first immediate increase in $\dot{V}_E$ (i.e. HVR) is seen, and then it is followed by a further progressive increase in ventilation, known as ventilatory acclimatisation that might take hours or days to stabilise (Bishop et al., 2013; Cheng et al., 2020; Fielding et al., 2018; Hodson et al., 2016). Carotid body hyperplasia, ventilatory sensitivity and ventilatory acclimatisation during chronic sustained hypoxia (i.e. at high altitude) are regulated by the post-translational hydroxylation of the transcription factor hypoxia-inducible factor-2α (HIF-2α) by the prolyl hydroxylase domain 2 (PHD2) (i.e. the PHD2/HIF-2α pathway) (Hodson et al., 2016). Interestingly, Cheng et al. (2020) used a HIF-2α blocker (i.e. PT2385) to prevent and reverse the already established ventilatory acclimatisation of sustained hypoxia in mice. In unacclimatised animals, PT2385 also attenuated the HVR. Surprisingly, there was a rapid effect on HVR. After 1 h of treatment with the dose of 10 mg/kg (via oral gavage), the HVR was significantly attenuated in mice exposed to acute hypoxia, i.e. 5 min of 10% O_2–3% CO_2. Recently, the FDA approved Welireg (belzutifan), an oral HIF-2α inhibitor, for treating some rare types of cancers (Anon, 2021). Could belzutifan be repurposed in the market to treat resistant/refractory hypertension or HF and restore autonomic imbalance? That awaits experimental support.

As mentioned before ('Quantitative comparison of carotid body hyperactivity in hypertension and HF'), chronic sustained and intermittent hypoxia have different effects on the carotid body morphology and, perhaps, the underlying mechanisms of sensitisation; therefore, one would reckon that distinct therapeutic approaches are necessary. This is supported at some level by the carotid body resection clinical trials (Narkiewicz et al., 2016, 2017). In patients with resistant hypertension and most HF (i.e. chronic sustained hypoxia), carotid body resection was safe and reduced MSNA. However, profound oxygen desaturation during the night was observed in patients co-diagnosed with sleep apnoea. It is only logical that in sleep apnoea (i.e. chronic intermittent hypoxia), resecting the carotid body would not be desired because patients would lose their ability to wake up when S_{pO_2} is getting too low. Since the PHD2/HIF-2α pathway is involved with carotid body hyperplasia and ventilatory sensitivity in models of chronic sustained hypoxia, we speculate that this pathway might also be driving carotid body hyperplasia and sensitivity in hypertension and HF. In contrast, this pathway should not play the same role in carotid body dysfunction of sleep apnoea since carotid body hyperplasia is reported neither in patients with sleep apnoea nor in CIH animals. In fact, wild-type mice exposed to CIH revealed that HIF-2α levels are decreased in the carotid body (Nanduri et al., 2009). Of note is that Prabhakar's group have shown that the balance between HIF-1α and HIF-2α contributes to the cellular redox state, in which CIH favours the increase in reactive oxygen species, thus leading to carotid body activation (for review, see Semenza & Prabhakar, 2015). With that in mind, it does not seem rational to 'put everything in the same basket' and treat patients with carotid body dysfunction similarly. Future research should focus on unravelling distinct therapeutic strategies for cases where carotid body dysfunction originates from sustained *versus* intermittent hypoxia. Before, we mentioned that sleep apnoea is highly prevalent in patients with resistant/refractory hypertension (Logan et al., 2001); therefore, prior to any carotid body intervention, patients should first be screened for sleep apnoea.

The most crucial aspect of future clinical interventions that we should consider is the criteria for assessing and recruiting patients with carotid body hyperactivity. Keir et al. (2019) demonstrated that the sensitivity of the carotid body reflex sympathetic responses could not be predicted from the HVR in normotensive patients. John Floras argues that 'If such correlation is absent also in patients with heart failure (or with hypertension), the present enthusiasm for clinical interventions targeting the peripheral chemoreflex, solely on the basis of ventilatory responses to nonspecific chemoreflex stimulation should be tempered' (Floras, 2021). This notion is corroborated by the work of Somers et al. (1988), who reported that the HVR was not different between normotensive and hypertensive patients but the sympathetic response to hypoxia was exaggerated (i.e. twice higher) in hypertensive patients. In practical terms, because HVR is used as an index of abnormal peripheral chemosensitivity and as

a criterion for inclusion/exclusion in studies of carotid body intervention (e.g. carotid body resection) (Niewinski et al., 2017), this means that patients who would presumably benefit from these interventions (i.e. exaggerated sympathetic response to hypoxia) are probably being excluded from studies only because they have normal HVR, which would decrease the study's statistical power. Also, patients who would not benefit from such interventions might undergo unnecessary risk in clinical trials. Hence, in future studies of carotid body autonomic dysfunction in humans, a new index of carotid body hyperactivity should be pursued by researchers, and that is one that involves the hypoxic sympathoexcitation response (HSR) (e.g. $\Delta MSNA/\Delta S_{pO_2}$) together with hyperoxia-mediated sympathoinhibition.

Conclusion

The carotid body is sensitised in many cardio-respiratory diseases such as hypertension, HF and sleep apnoea. This hyperactivity drives autonomic imbalance with an exaggerated systemic sympathetic outflow, which has been demonstrated to worsen prognosis and independently predicts mortality in patients. While pharmacological sympatholytic agents exist, their efficiency is limited for an array of reasons, which include their competitive antagonist characteristic and their inability to block co-transmitter (ATP, neuropeptide-Y, etc.) released from sympathetic nerve endings. Hence, targeting the underlying mechanisms responsible for an increased sympathetic outflow and providing evidence that is of carotid body origin would provide better patient outcomes and a much-needed way to lower sympathetic activity.

The carotid body is a multi-modal sensor, which makes it prone to various interventions. In hypertension and HF, multiple maladaptive molecular pathways converge in the carotid body to yield an exaggerated chemoreflex motor response. Among these mechanisms of carotid body dysfunction, a few are similar between both diseases: reduced carotid body blood flow, downregulation of NOS–NO, upregulation of Ang II-AT_1R pathways and P2X3 receptors. Other mechanisms cannot be classified as distinct in hypertension or distinct in HF only because they have not been investigated in both diseases. For hypertension, we can list increased efferent input from the SCG, downregulation of GLP1R and increased leptin–Trpm7 signalling pathway. Alternatively, the following mechanisms for HF can be pointed out as exclusive: raised CO–H_2S signalling pathway and downregulation of KLF-2 (Fig. 5).

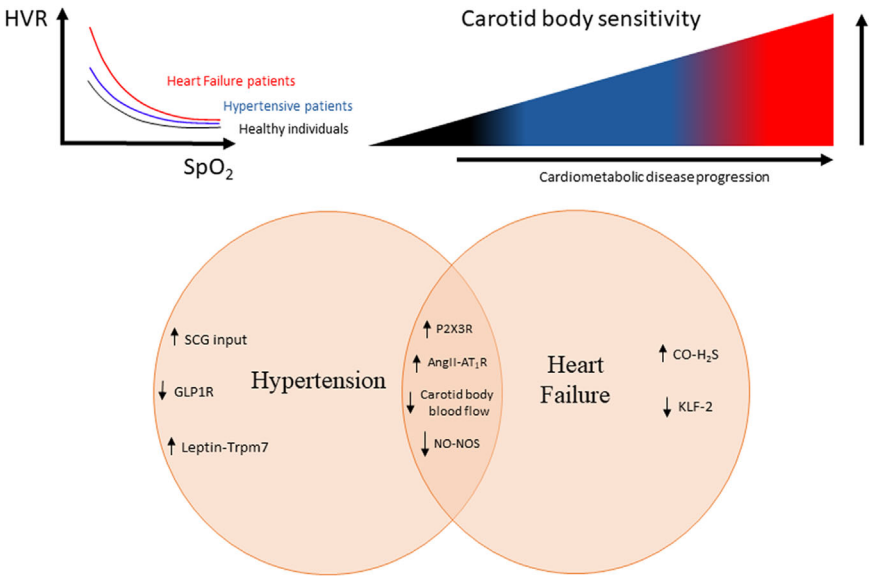

Figure 5. Schematic summary of carotid body dysfunction in hypertension and heart failure
A, carotid body sensitivity increases from healthy individuals up to heart failure patients. In hypertensive patients (in blue), hypoxic ventilatory response (HVR) is either no different or elevated when compared with healthy individuals (in black). In contrast, heart failure patients (in red) display a substantial elevation in HVR and other assessment methods of carotid body sensitivity (e.g. carotid sinus nerve recordings from animal models). Although hypertensive patients show moderate elevations in HVR, they still have elevated carotid body-mediated sympathetic outflow at rest and an excessive hypoxic reflex sympathoexcitation response (Narkiewicz et al., 2016; Somers et al. 1988). *B*, similar and dis-similar mechanisms of carotid body dysfunction in hypertension and heart failure. AngII, angiotensin II; AT_1R, angiotensin II type 1 receptor; CO, carbon monoxide; GLP1R, glucagon-like-peptide 1 receptor; H_2S, hydrogen sulphide; KLF-2, Krüppel-like factor 2; NO, nitric oxide; NOS, nitric oxide synthase; P2X3, purinergic receptor type P2X3; SCG, superior cervical ganglion; Trpm7, transient receptor potential melastatin 7.

These similar and distinct mechanisms of carotid body dysfunction unravel an intriguing connection between the pathophysiology of hypertension and HF with carotid body (mal)adaptive changes during chronic sustained hypoxia, which includes high baseline $\dot{V}_E$ (i.e. ventilatory acclimatisation), sensitised HVR and carotid body hyperplasia. The clinical relevance of this may be apparent if HIF-2α blockers are proven to modulate carotid body-mediated autonomic imbalance. Nevertheless, no clinical intervention should be pursued without carefully revising the clinical assessment of carotid body hyperactivity in patients with cardio-respiratory diseases.

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Additional information

Competing interests

No conflict of interest to report.

Author contributions

H.S. and R.D.R. were responsible for section 'Heart failure'. B.M. was responsible for section 'Sleep apnoea'. I.F. and J.P. were responsible for the other sections. All authors contributed to the editing of all sections. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

R.D. – ANID-FONDECYT: #1220950; J.F.R.P. – Health Research Council of New Zealand: 19/687 and Sidney Taylor Trust; B.H.M. – FAPESP: 2018/15957-2 and CNPq: 309338/2020-4; H.D.S. – Program Project Grant from the Heart, Lung, and Blood Institute of NIH: PO1-HL62222.

Acknowledgements

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

autonomic nervous system, blood flow, cardiovascular diseases, carotid body, heart failure, hypertension, sympathetic nervous system

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