J Physiol 595.1 (2017) pp 43–51

SYMPOSIUM REVIEW

Contribution of peripheral and central chemoreceptors to sympatho-excitation in heart failure

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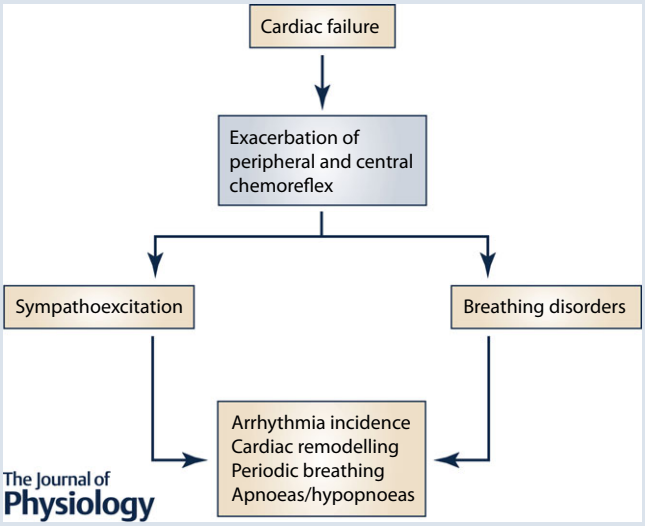

Abstract Chronic heart failure (CHF) is a major public health problem. Tonic hyper-activation of sympathetic neural outflow is commonly observed in patients with CHF. Importantly, sympatho-excitation in CHF exacerbates its progression and is strongly related to poor prognosis and high mortality risk. Increases in both peripheral and central chemoreflex drive are considered markers of the severity of CHF. The principal peripheral chemoreceptors are the carotid bodies (CBs) and alteration in their function has been described in CHF. Mainly, during CHF the CB chemosensitivity is enhanced leading to increases in ventilation and sympathetic outflow. In addition to peripheral control of breathing, central chemoreceptors (CCs) are considered a dominant mechanism in ventilatory regulation. Potentiation of the ventilatory and sympathetic drive in response to CC activation has been shown in patients with CHF as well as in animal models.

Rodrigo Del Rio obtained his PhD with Professor Rodrigo Iturriaga from the Pontificia Universidad Católica de Chile and trained as a postdoctoral fellow with Professor Harold D. Schultz at the Department of Cellular and Integrative Physiology at the University of Nebraska Medical Center. In 2014 he was appointed an Assistant Professor at the Center of Biomedical Research in the Universidad Autónoma de Chile where he is now the Head of the Laboratory of Cardiorespiratory Control. His group is interested in understanding the contribution of altered peripheral and central chemoreflex function on the progression of the pathophysiology of heart failure and other cardiovascular diseases.

This review was presented at the symposium "Targeting autonomic imbalance in pathophysiology: is the carotid body the new nirvana?", which took place at the meeting of International Society for Autonomic Neuroscience in Stresa, Italy, 26–29 September 2015.

DOI: 10.1113/JP272075

Therefore, improving understanding of the contribution of the peripheral and central chemoreflexes to augmented sympathetic discharge in CHF could help in developing new therapeutic approaches intended to attenuate the progression of CHF. Accordingly, the main focus of this review is to discuss recent evidence that peripheral and central chemoreflex function are altered in CHF and that they contribute to autonomic imbalance and progression of CHF.

(Received 23 December 2015; accepted after revision 20 April 2016; first published online 24 May 2016)
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Abstract figure legend Chronic heart failure is characterized by exacerbation of the peripheral and central chemoreflexes, which contributes to the establishment and progression of sympathoexcitation and breathing disorders. Importantly, chemoreflex activation is strongly associated with cardiac arrhythmogenesis, cardiac adverse remodelling, periodic breathing and central apnoeas and hypopnoeas.

Abbreviations ANG II, angiotensin II; CB, carotid body; CC, central chemoreceptor; CHF, chronic heart failure; MSNA, muscle sympathetic nerve activity; NTS, nucleus tractus solitarii; PVN, paraventricular nucleus; RTN, retrotrapezoid nucleus; RVLM, rostral ventrolateral medulla; $\dot{V}_E$, minute ventilation.

Introduction

Chronic heart failure (CHF) is a global public health problem. Currently, it is estimated that 26 million people worldwide are living with this condition, affecting approximately 20% of the world population over 75 years of age, and resulting in more than 1 million hospitalizations annually in both the United State and Europe (Remme *et al.* 2001; Ambrosy *et al.* 2014). Chronic heart failure is a disease with very poor prognosis despite advances in treatment; half of the patients with CHF are likely to die in a 4 year time frame once diagnosed, while more than 50% with severe cardiac dysfunction are likely to die within 1 year (Swedberg *et al.* 2005). In addition, CHF patients often display frequent episodes of decompensation, needing complex therapeutic management, which are associated with poor prognosis and lower survival rates (Lloyd-Jones *et al.* 2002). Furthermore, while the ageing condition has improved in the global population, it has been estimated that the prevalence of CHF will increase to the point where it is one of the most prevalent diseases (Mann & Chakinala, 2012).

CHF is caused by myocardial dysfunction and often results in left ventricular dilatation, hypertrophy or both (Cohn *et al.* 2000). Autonomic imbalance and respiratory disorders are commonly observed in patients with CHF and are thought to contribute to CHF progression (Ponikowski *et al.* 1997; Esler & Kaye, 1998; Triposkiadis *et al.* 2009; Haack *et al.* 2014; Schultz *et al.* 2015*a*). Enhanced sympathetic stimulation of the heart in CHF is strongly associated with life threating cardiac arrhythmias (Esler, 1998) and is likely to account for the relationship between autonomic imbalance and sudden cardiac death in CHF (Vaseghi & Shivkumar, 2008). While there are many factors that contribute to autonomic imbalance in CHF, disordered oscillatory breathing patterns are likely to play a significant role. Importantly, both autonomic imbalance and oscillatory breathing in CHF have been linked to altered chemoreflex function (Kitzman *et al.* 2002; Zucker, 2006; Del Rio *et al.* 2013*a*; Marcus *et al.* 2014*a*). In a study performed by Giannoni and colleagues (2008), 60% of patients with CHF displayed enhanced ventilatory responses to hypoxia and/or hypercapnia when compared with controls. In support of this notion, animal studies have shown that tonic and hypoxia-evoked afferent activity recorded from the carotid body (CB) chemoreceptors is enhanced in experimental CHF (Del Rio *et al.* 2013*a*; Del Rio, 2015) suggesting that peripheral chemoreceptors may play a key role in the progression of autonomic imbalance in CHF. The CB-mediated chemoreflex pathway involved afferent projections to the commissural nuclei of the solitary tract (NTS) (Accorsi-Mendonça *et al.* 2011). It has been shown that the NTS drives the activation of the paraventricular nucleus (PVN) of the hypothalamus during CB chemoreceptor stimulation (Ciriello & Calaresu, 1980; Kubo *et al.* 1997; Chen *et al.* 2004). Furthermore, PVN postsynaptic neurones project to autonomic control regions within the central nervous system (Reddy *et al.* 2005), particularly to the rostral ventrolateral medulla (RVLM), the ultimate region of pre-sympathetic regulation. It has been shown that hyperactivation of pre-sympathetic neurones located in the RVLM during CHF represents a major contributor to the development of autonomic imbalance and decreased cardiac baroreflex sensivity (Zucker, 2006; Gao *et al.* 2010; Abbott *et al.* 2013). Remarkably, Del Rio and collegues (2013*a*) found that CB denervation decreases RVLM pre-sympathetic neuronal activation in CHF rats, improving autonomic function. Thus, it is plausible that CB-mediated effects on the RVLM also involved changes in the activation pattern of NTS and PVN neurones. Further studies will be needed to address this hypothesis.

While changes in peripheral chemoreceptor function are likely to play an important role in autonomic

imbalance in CHF, numerous investigators have demonstrated important physiological changes in the central nervous system that contribute as well (Aggarwal *et al.* 2002; Lymperopoulos *et al.* 2013). Indeed, the pathophysiological relevance of the peripheral and central chemoreflex function in CHF has received considerable attention (Kristen *et al.* 2002; Schultz *et al.* 2007; Giannoni *et al.* 2008; Marcus *et al.* 2014*b*; Del Rio *et al.* 2015). Accordingly, the aim of this brief review is to document the role played by peripheral and central chemoreceptors on sympatho-excitation and oscillatory breathing patterns during the progression of CHF.

The carotid body in CHF: the peripheral master regulator. The CBs are the predominant arterial chemoreceptors in humans (Gonzalez *et al.* 1994; Schultz & Sun, 2000). The CB is composed of clusters of chemoreceptor cells (type I cells) surrounded by glial cell processes (type II cells) (Iturriaga & Alcayaga, 2004). The type I cells are considered polymodal receptors since they respond to a wide variety of stimuli such as changes in arterial levels of O_2, CO_2, pH, blood flow and temperature (Gonzalez *et al.* 1994). Upon activation, the CBs send afferent signals to the central nervous system, specifically to first-order NTS neurones leading to activation of the central pattern generator in the brainstem and a concomitant increase in ventilation (Ponikowski & Banasiak, 2001; Accorsi-Mendonça *et al.* 2011; Marcus *et al.* 2014*b*). In addition, during hypoxaemic/hypercapnic stimulation, the CBs also activate the sympathetic nervous system to maintain arterial pressure and to guarantee adequate blood flow to target organs, especially the heart and brain (Schultz & Sun, 2000). While normal CB function contributes to maintenance of homeostatic blood gas parameters and tissue perfusion, mounting evidence indicates that maladaptive changes in CB function contribute to a variety of cardiovascular and metabolic disease states (Haack *et al.* 2014; Schultz *et al.* 2015*b*).

Evidence of a role for the CB in the pathophysiology of CHF comes from studies showing that patients with CHF that exhibit high ventilatory responses to hypoxia (high CB chemoreflex drive) have significantly greater mortality rates compared to CHF patients that have normal chemoreflex drive (Ponikowski & Banasiak, 2001; Giannoni *et al.* 2008). In support of the notion that CBs contribute to CHF progression, Del Rio and colleagues recently showed that selective bilateral CB denervation in experimental CHF significantly improved cardiac function and decreased mortality rate (Del Rio *et al.* 2013*a*). The proposed mechanism underlying these improvements is a reduction in activation of the sympathetic nervous system. Accordingly, studies performed in animal models of CHF indicate that the CB chemoreceptors became tonically hyperactive, resulting in the activation of the pre-sympathetic neurones in the brainstem and increases in efferent sympathetic outflow to the kidneys and heart (Sun *et al.* 1999; May *et al.* 2013; Del Rio *et al.* 2013*b*; Marcus *et al.* 2014*b*). In addition to these promising findings in pre-clinical models, the therapeutic value of modulating the CB-mediated chemoreflex drive has also been addressed in human CHF. Niewinski and colleagues (2013) showed that 6 months after unilateral CB resection, autonomic balance, sleep disordered breathing, exercise tolerance and quality of life were markedly improved in one patient with systolic CHF (Niewinski *et al.* 2013). This evidence strongly supports a pivotal role of the CB chemoreceptor in the progression of CHF.

The mechanisms associated to the increased CB activity during CHF are not fully described. However, it has been proposed that both angiotensin II (ANG II) peptides and oxidative stress play a principal role in enhancing the CB-mediated chemoreflex drive in CHF (Schultz, 2015). It has been shown that elevation of ANG II levels and upregulation of the ANG II type 1 receptor contribute to the increased CB chemoreceptor activity through a mechanism related to the inactivation of voltage-sensitive K^+ channels (Li *et al.* 2006). Additionally, oxidative stress is increased in CB chemoreceptor cells and this appears to be related to increases in NADPH oxidase protein expression (Li *et al.* 2007) as well as a marked decrease in the expression of anti-oxidant enzymes (i.e. CuZn and Mn superoxide dismutase) (Ding *et al.* 2009, 2010; Lindley *et al.* 2004). Importantly, reduction in blood flow to the CB region due to impaired cardiac function has been hypothesized to be the key determinant in the altered CB function. Indeed, it has been elegantly shown by Ding and collagues that chronic reductions in CB blood flow in a healthy rabbits recapitulates the potentiation of CB-mediated chemoreflex drive up to levels seen in CHF rabbits (Ding *et al.* 2011).

Chemosensitive retrotrapezoid nucleus neurons: a novel player in sympathoexcitation in CHF. Central chemoreceptors (CCs) are mainly located on the ventral surface of the medulla and to a lesser extent in other locations within the brainstem, cerebellum, hypothalamus and midbrain (Nattie & Li, 2012). In cardiorespiratory research, the term central chemoreception usually refers to the process by which CO_2 activates cells that express the 'CO_2 sensors' (the receptors have not been definitively identified) modulating respiratory and cardiovascular control centres of the brainstem (Guyenet, 2014). Interestingly, Huckstepp and colleagues (2010) showed that ATP release in the ventral surface of the medulla oblongata, an event linked to the adaptive changes in ventilation in response to hypercapnia, was mediated by connexin 26 suggesting an important mechanism contributing to central respiratory chemosensitivity. Specifically, in conditions involving subtle changes in cerebrospinal fluid CO_2/H^+ content, central chemoreceptor neurones send

direct excitatory inputs to respiratory control centres to regulate the tidal volume and respiratory frequency (Guyenet *et al.* 2005). Stimulation of CCs also elicits an increase in sympathetic outflow. Central chemoreceptor neurones project to RVLM pre-sympathetic neurones (Moreira *et al.* 2006; Rosin *et al.* 2006), and it has been shown that activation of CCs can trigger respiratory synchronous modulation of sympathetic nerve activity, leading to respiratory-sympathetic coupling (Guyenet *et al.* 2010*a*,*b*). The nature of the CCs and of the circuits that mediate the ventilatory response to CO_2 is still controversial. Specific areas on the ventral surface of the medulla oblongata have been shown to play a major role in cardiorespiratory regulation (Mulkey *et al.* 2004; Guyenet & Mulkey, 2010). One of the plausible nuclei involved in breathing and haemodynamic control circuitry is the retrotrapezoid nucleus (RTN). The RTN is mainly composed of a group of neurones that are activated by changes in cerebrospinal fluid CO_2 and/or pH that projects to the respiratory central pattern generator (Lazarenko *et al.* 2009; Guyenet & Mulkey, 2010; Guyenet, 2012; Wang *et al.* 2013). Furthermore, the RTN is considered an extension of the ventrolateral medulla containing neurones that innervate the nucleus of the NTS and contribute to central respiratory chemoreception (Guyenet *et al.* 2013). In addition, the inhibition of RTN neurones attenuates the ventilatory chemoreflex drive in resting conscious rats without changing basal respiration suggesting that the RTN plays a pivotal role in central chemoreception (Basting *et al.* 2015; Takakura *et al.* 2014). The RTN chemosensitive neurones have a phenotype characterized by the presence of vesicular glutamate transporter 2 mRNA, the expression of the transcription factors Phox2b and Atoh1 and the absence of immunoreactivity for both tyrosine hydroxylase and choline acetyltransferase (Stornetta *et al.* 2006; Marina *et al.* 2010). In addition, these neurones have been shown to be activated by low pH *in vivo* and *in vitro* in slice preparations (Lazarenko *et al.* 2009; Wang *et al.* 2013). Also, RTN Phox2b/Atoh1-positive neurones are expressed early in embryonic development in regions associated with chemoreflex circuits (Ruffault *et al.* 2015). Importantly, this set of RTN neurons are essential for the development of ventilatory reflex responses to hypercapnic stimulation at birth and remain a major contributor to the adult hypercanic ventilatory response (Dubreuil *et al.* 2009).

In a pathological context, Narkiewicz and colleagues (1999) studied autonomic, haemodynamic, and respiratory responses to chemoreflex activation during CHF. They found that CHF patients showed a marked increase in the ventilatory and sympathetic responses elicited by brief exposure to a hypercapnic gas mixture (Narkiewicz *et al.* 1999). Hypercapnic stimulation induced significant increases in heart rate in CHF patients but not in control subjects suggesting an augmented central chemoreflex drive in response to CO_2 in the pathological condition (Narkiewicz *et al.* 1999). Also, both groups showed increases in minute ventilation ($\dot{V}_E$), blood pressure, and muscle sympathetic nerve activity (MSNA) in response to hypercapnia, but the increases in $\dot{V}_E$ and MSNA were significantly greater in the CHF patients, suggesting that the hypercapnic stimulus represents a potent mechanism for initiating sympathetic activation in CHF (Narkiewicz *et al.* 1999). Importantly, in the resting condition the arterial CO_2 levels remain unchanged in CHF patients compared to control subjects. In addition, in experimental CHF models, generated by aortocaval shunt or aortic banding, there was an increase in the hypercapnic central chemoreflex drive in CHF. This was shown by a large increase in the gain of the renal sympathetic nerve activity response to hypercapnic stimulation in both groups of CHF rats compared to the controls (Kristen *et al.* 2002). Interestingly, the increases in central chemoreflex gain in CHF seem to be independent of the aetiology of CHF since the aortocaval shunt model represents a diastolic form of cardiac failure (Abassi *et al.* 2011) and aortic banding represents a model of systolic heart failure (Patten & Hall-Porter, 2009). Accordingly, it has been shown that CHF patients displayed enhanced hypercapnic responses, which are positively correlated with the severity and progression of the disease (Giannoni *et al.* 2008).

The clinical implications of an enhanced sympathetic response to CO_2 relate first to the high prevalence of sleep apnoeas and Cheyne–Stokes/periodic breathing in CHF (Kasai *et al.* 2010). Then, the episodic stimulation of CC during each apnoea and hypoventilation episode leads to an exaggerated sympathetic response which adds further stress to the heart (Fig. 1). Furthermore, it has been proposed that repetitive stimulation of the sympathetic outflow could entrain the respiratory cycle regulation centrally to perpetuate breathing disorders (Bradley & Floras, 1996; Lorenzi-Filho *et al.* 1999).

In addition to central modulation, CHF patients display enhanced peripheral chemosensitivity that is strongly related to the incidence of breathing disorders (Corra *et al.* 2006; Marcus *et al.* 2014*a*). Interestingly, Del Rio and collagues showed in CHF rats that acute inhibition of the CB afferent activity by inhibition of the synthesis of H_2S stabilized breathing (Del Rio *et al.* 2013*b*) suggesting that CB chemoreceptors may modulate the central pattern generator (Fig. 1). In the same context, Blain and collegues (2010) showed that the sensitivity of the CCs is critically dependent on CB afferent activity evidenced by a hyper-additive ventilatory responses to central hypercapnia when CBs are stimulated (Blain *et al.* 2010). Together, this evidence strongly suggests an interrelationship between central and peripheral chemoreceptors and their possible contribution to altered sympathetic and respiratory control in pathophysiology.

Respiratory–sympathetic coupling in CHF: an integrative pathophysiological mechanism. Sympathetic discharge is actively modulated by respiration (Guyenet, 2014; Molkov *et al.* 2014). Recent studies suggest that enhanced coupling between sympathetic and respiratory neural drive contribute to augmented sympatho-excitation in CHF (Costa-Silva *et al.* 2012; Marcus *et al.* 2014*b*, 2015). In addition, respiratory–sympathetic coupling has been pointed out as a key pathophysiological mechanism in other disease conditions such as hypertension and sleep apnoea. Simms *et al.* (2009) showed that spontaneously hypertensive rats display an enhanced respiratory modulation of the renal sympathetic nerve discharges compared to normotensive animals. In rats exposed to intemittent hypoxia mimicking sleep apnoea, Zoccal *et al.* (2008) showed in an elegant study that respiratory–sympathetic coupling contributes to the development of CIH-dependent hypertension. Alterations in the coupling between the central control of respiration and sympathetic neural drive may underlie the pathophysiology of oscillatory breathing and related sympathetic activation in CHF. Central apnoeas and Cheyne–Stokes respiration, a form of episodic breathing during sleep, are commonly observed in patients with CHF and are thought to negatively impact autonomic and metabolic homeostasis (Brack *et al.* 2012). It has been proposed that oscillatory breathing patterns are associated with exaggerated carbon dioxide sensitivity (Javaheri, 1999). Indeed, it has been shown that a rise in CO_2 levels in the central nervous system increases sympathetic nerve discharge and blood pressure in anaesthetized and awake animals (Oikawa *et al.* 2005). Then, surges in sympathetic discharge could take place during acute stimulation of CCs. Therefore, in CHF the hypoxic/hypercapnic stimulation of central and peripheral chemoreceptors during the episodes of hypoventilation and apnoeas at rest (i.e. periodic breathing) may trigger an exaggerated sympathetic response to key end-organs. On the other hand, altered breathing patterns could also lead to sympathoexcitation due to the stimulation of the sympatho-inhibitory reflex elicited by lung stretch (Goso *et al.* 2001). Further studies should focus on the role of pulmonary receptors in the development of altered breathing patterns and autonomic imbalance in CHF.

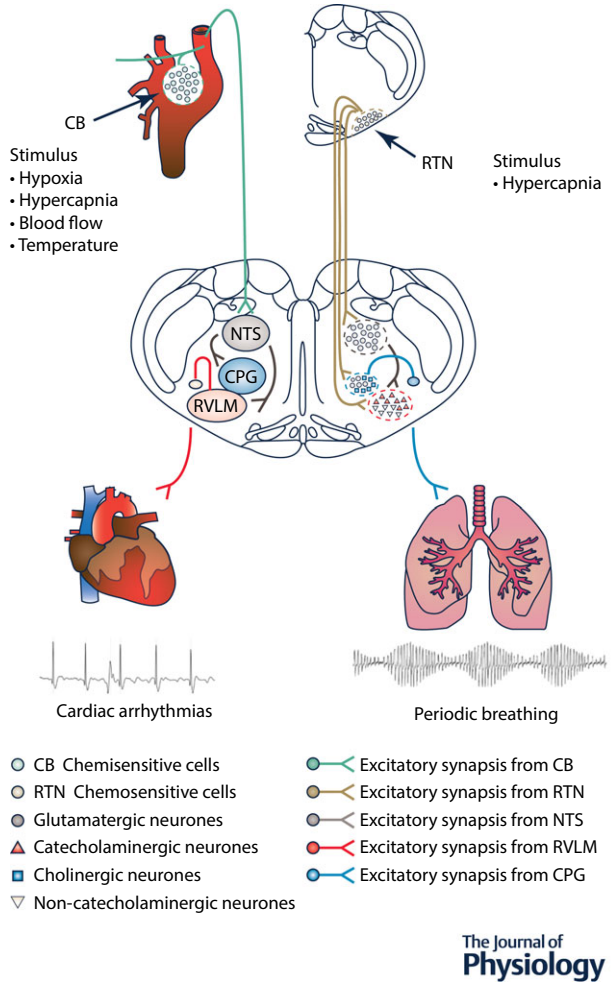

Figure 1. Schematic diagram showing the contribution of peripheral and central chemoreceptors in development of sympathoexcitation and breathing disorders
Carotid body and RTN neurons respond to changes in different signals from the bloodstream and cerebrospinal fluid, respectively. Upon activation, the chemoreflex drive increases and induces a reflex cardiorespiratory response. Integration of the chemosensory inputs takes place in brainstem areas including the NTS, RVLM and central pattern generator, which finally leads to an increase in sympathetic discharges and activation of phrenic motoneurones. In the pathophysiology of CHF, the enhanced activity from peripheral and central chemoreceptors induces an increase in the central symapatho-respiratory outflow triggering cardiac arrhythmias and breathing disorders. CB, carotid body; CPG, central pattern generator; NTS, nucleus tractus solitarii; RTN, retrotrapezoid nucleus; RVLM, rostral ventrolateral medulla.

Conclusions

CHF is characterized by a sustained elevation in sympathetic nerve traffic, which is recognized as an important component in the pathophysiology and progression of the disease independent of the aetiology of cardiac failure (Kristen *et al.* 2002; Del Rio, 2015; Floras & Ponikowski, 2015; Schultz *et al.* 2015*b*). The CBs have been suggested to be key mediators in the establishment and progression of autonomic dysfunction and breathing abnormalities in CHF (Ponikowski & Banasiak, 2001; Zucker, 2006; Schultz *et al.* 2007; Niewinski *et al.* 2013; Del Rio *et al.* 2013*a*; Marcus *et al.* 2014*b*). It is worth noting that the contribution of CB-mediated peripheral chemoreflex drive to autonomic imbalance and disordered breathing patterns has only been studied in systolic heart failure. Future studies should address the potential contribution of the CB chemoreceptors in other types of CHF.

Contrary to what is known about the contribution of the peripheral chemoreceptors in CHF progression, the role played by CCs in the development of autonomic and breathing disturbances in CHF is not well understood. The RTN in the ventral surface of the medulla has been pointed out as a key region involved in breathing control and CO_2 sensing (Onimaru *et al.* 2009; Guyenet & Mulkey, 2010). Exaggerated ventilatory and sympathetic responses to hypercapnia have been observed in both CHF patients and animal models of the disease, suggesting that central chemoreflex drive is enhanced during CHF (Narkiewicz *et al.* 1999; Kristen *et al.* 2002; Giannoni *et al.* 2008). More importantly, central chemoreflex drive seems to be augmented in both systolic and diastolic cardiac failure. Therefore, CCs are likely to play an important role in sympathoexcitation during CHF.

It has been shown that RTN neurones receive polysynaptic excitatory inputs from second-order NTS neurones, which in turn are modulated, at the NTS level, by CB afferent projections. Therefore, excitation of the CB may lead to sensitization of the RTN neurones. Indeed, it has been shown that activation of the CB afferent pathway results in the depolarization of RTN neurones (Takakura *et al.* 2006). It is also hypothesized that CB activity may regulate RTN neurone membrane potential and firing threshold (Guyenet, 2014). Therefore, it seems likely that interaction between peripheral and central chemoreflexes at the level of the RTN may be a key component in the respiratory regulation during hypoxic and hypercapnic challenges (Guyenet, 2014).

In addition, non-neuronal cells (i.e. astrocytes) have recently been recognized as taking part in several physiological functions, including pH detection in central chemosensitivity areas (Angelova *et al.* 2015). Recent evidence suggests that ATP-mediated purinergic signalling at the level of the RVLM contributes to cardiovascular and respiratory responses triggered by hypoxia and hypercapnia by activating pre-sympathetic catecholaminergic C1 neurones and CO_2/H^+-sensitive RTN neurones, respectively (Gourine *et al.* 2010; Moreira *et al.* 2015). Interestingly, Marina and collegues (2013) showed that ATP release from astrocytes activates pre-sympathetic brainstem neurones in the RVLM, thereby contributing to symphatoexcitacion, progression of ventricular remodelling and development of heart failure secondary to myocardial infarction (Marina *et al.* 2013). Together, this evidence strongly suggests that non-neuronal cells (i.e. astrocytes) actively participate in cardiorespiratory regulation in the central nervous system and may represent novel targets to control sympathoexcitation in CHF. In summary, numerous studies suggest that peripheral and central chemoreflex function is enhanced in CHF and contributes to increases in sympathetic nerve activity and the incidence of disordered breathing patterns. Future studies should focus on identifying autonomic mechanisms regulating cardiorespiratory patterns and how these mechanisms contribute to deterioration of cardiac function and increases in mortality in CHF. Understanding these mechanisms can aid in further development of therapeutic strategies to improve quality of life, morbity and mortality in the CHF population.

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Additional information

Conflict of interest

None of the authors have any conflicts of interests.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

R.D.R. is supported by Fondo de Desarrollo Cientifico y Tecnológico (Fondecyt no. 1140275).