Behavior of Central and Peripheral Chemoreflexes in Heart Failure

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Abstract
The heart failure (HF) syndrome can be defined as the final pathway of any type of heart disease. The sympatho-inhibitory cardiovascular reflexes, such as the arterial baroreceptor reflex, are significantly decreased in HF. Patients with HF present higher ventilation for a certain workload when compared with normal individuals. This fact generates low ventilatory efficiency and is related to higher ventilation associated with the carbon dioxide production, which is a predictor of bad prognosis, in addition to being a limiting factor for the practice of exercises. There is evidence that the autonomic imbalance contributes to the pathogenesis and the progression of heart failure. The chemoreflexes are the main mechanisms of control and regulation of the ventilatory responses to the changes in concentrations of arterial oxygen and carbon dioxide. The chemoreflex activation causes an increase in the sympathetic activity, heart rate, arterial pressure and minute volume. However, the increase in the minute volume and the arterial pressure, due to negative feedback, cause inhibition of the sympathetic response at the chemoreflex activation. In spite of the functional alterations of the reflexes, their behavior in normal and pathological conditions, especially their contribution to the sympathoexcitatory state observed in HF has not been broadly studied.

Therefore, this review aims at integrating the knowledge on central and peripheral chemoreflexes in HF syndrome, as well as clarifying the influence of the heart failure drug therapy on the chemoreflexes.

Introduction
The heart failure (HF) syndrome can be defined as the final pathway of any type of heart disease1, in which structural, functional and neurohumoral disorders of the heart lead to the decrease in the capacity of the ventricle to eject and/or fill with blood at the physiological filling pressures1,2. These alterations result in systolic and/or diastolic dysfunction and, consequently, in the loss of functional capacity, decrease in quality of life and increased morbidity and mortality4,5.

The HF syndrome is associated with hemodynamic disorders followed by systemic alterations, endothelial dysfunction, neurohormonal activation with increased catecholamine release, higher brain natriuretic peptide (BNP) levels5 and release of pro-inflammatory factors that contribute to heart dilation and poorer performance at physical exercises3,6. Patients with HF present higher levels of ventilation for a certain workload when compared to normal individuals7. This fact results in low ventilatory efficiency and is related with higher ventilation related to CO2 production, which is an important predictor of poor prognosis, in addition to being a limiting factor for the practice of exercises6,9.

Hyperventilation can occur due to several causes and among them, a hyperactive chemoreceptor reflex, one of the several abnormalities in the cardiovascular reflex control related to the increased sympathetic tonus in HF6,10. The signal hyperactivation originated from the receptors located in the skeletal muscles (mechanoreceptors - metaboreceptors) is a recently proposed hypothesis to explain the origin of symptoms of intolerance to physical exertion6.

The sympathoinhibitory cardiovascular reflexes, such as the arterial baroreceptor reflex, are significantly suppressed in HF. In turn, the sympathoexcitatory reflexes, including the arterial chemoreceptor reflex and the sympatheticafferent cardiac reflexes, are increased in HF. Although the functional alterations of the reflexes have been used independently to illustrate the sympathetic excitation observed in HF, the interaction between these reflexes in normal and pathological conditions, especially their contribution to the sympathoexcitatory state found in HF, has not been broadly studied11. Therefore, the objective of this study is to carry out a review of the action mechanism of peripheral and central chemoreceptors.

Cardiopulmonary regulation
The cardiopulmonary receptors are located, basically, in association with the large arterial vessels in the chest and neck and transmit stimuli to the respiratory center to help regulate the respiratory activity. Most of them are found in the aortic and carotid bodies, along their afferent nervous connections with the respiratory cento. The carotid bodies are located bilaterally in the bifurcations of the main carotid arteries and their afferent fibers pass through Hering's nerves to the glossopharyngeal nerves and then to the medulla oblongata. The aortic bodies are located along the aortic arch and their nervous fibers pass into the medulla oblongata through
the vagus nerve and then to the spinal cord through the sympathetic nerves12 (Figure 1). Three sets of cardiopulmonary receptors can be identified: 1) non-myelinated vagal cardiac afferents, which are small nervous terminals scattered in the cardiac chambers, sensitive to mechanical distension due to alterations in the atrial pressure or diastolic-end pressure and, as they cause similar responses to the arterial baroreceptors, it is supposed that both use the same neuronal pathways; 2) myelinated vagal cardiac afferents, located especially at the junction of large vessels and atria, spontaneously active during systole and diastole and that supply information to the central nervous system on the degree of atrial filling and heart rate. In situations of increased volemia, they cause a decrease in the renal sympathetic nervous activity and, consequently, a decrease in the release of vasopressin by the neurohypophysis. In this condition there is also an increase in the levels of brain natriuretic peptide (BNP) levels, which induces increases in diuresis and natriuresis, in addition to the inhibition of renin and aldosterone release and 3) spinal afferents of which trajectory coincides with that of sympathetic ones and are distributed along the coronary arteries, the cardiac chambers and great vessels of the chest.

Chemoreflex control

The autonomous nervous system allows the body to adjust its circulation and ventilation to maintain the oxygen supply to the tissues. The autonomic balance is maintained by the complex interaction of the arterial baroreflex, central and peripheral chemoreflex, ergoreflex and lung stretch reflex (Figure 2). There is evidence that the autonomic imbalance contributes to the pathogenesis and progression of heart failure15.

The chemoreflexes are the main mechanisms of control and regulation of the ventilatory responses to the changes in arterial oxygen and CO₂ concentrations16. The peripheral
chemoreceptors located in the carotid and aortic bodies, with afferents to the respiratory center in the medulla oblongata and the nucleus of the solitary tract, respond primarily to hypoxia\textsuperscript{16,17}. The central chemoreceptors, located on the ventral surface of the spinal cord, respond primarily to hypercapnia\textsuperscript{18}. Both responses to alterations in the concentrations of \(O_2\) and \(CO_2\), respectively, increase pulmonary ventilation. Almost simultaneously, another set of neurons that reach the nucleus of the solitary tract induces the increase in the sympathetic nervous activity. Both chemoreceptor mechanisms have a strong influence on neural control of circulation, especially in situations involving significant changes in the arterial concentrations of oxygen and/or \(CO_2\). The chemoreflex activation causes an increase in the sympathetic activity, heart rate, arterial pressure and minute volume. However, the increase in the minute volume and the arterial pressure, by negative feedback, causes inhibition of the sympathetic response to the chemoreflex activation. Therefore, chemoreflexes trigger several cardiovascular and respiratory responses, with complex interactions between their responses. To define any abnormality in the chemoreflex function, it is essential to consider the individual contribution of each component that integrates this response. In patients with HF, the stimulation of the central and peripheral chemoreceptors causes a marked increase in pulmonary ventilation and the sympathetic nervous activity, characterized by a selective potentiation of these responses\textsuperscript{14,19}.

**Contribution of the chemoreceptors under normoxia**

The chemoreflexes (central and peripheral) have a crucial role in the control of alveolar ventilation to guarantee that the gas exchanges in the lungs continuously supply the metabolic demand through the oxygen uptake and \(CO_2\) removal.

Frequently overestimated, however, is the fact that these reflexes also have a significant effect on the cardiac and vascular control to regulate the blood flow and then the levels of tissue gas exchange. An important component for the activation of the chemoreflex is an increase in the sympathetic activity on the vascular beds. This response helps maintain the arterial blood pressure in the presence of the direct vasodilating effects of hypoxemia or hypercapnia and then helps to maintain the pressure adequate for the blood flow and tissue gas exchange.

The idea that the chemoreflexes contribute to the sympathetic activity at rest in pathological states has been the hypothesis that the chemoreflexes would not be activated at rest (normoxia and isocapnia) and, therefore, they would have little influence on the sympathetic tonus under normal conditions. However, this hypothesis is quite controversial. In normal individuals at rest, the hyperoxia, which inhibits the activity of peripheral chemoreceptors, decreases the sympathetic nervous activity\textsuperscript{20}. However, individuals with sleep apnea present an increased chemoreflex activity under normoxia. Thus, it can be suggested that the chemoreflexes contribute to the increased sympathetic tonus in heart failure, even in the absence of hypoxia\textsuperscript{21}.

**Chemoreflexes and ventilatory abnormalities**

The respiration is stimulated by the chemoreflexes that include the central and peripheral receptors, the central nervous system and the respiratory muscles. The chemoreflexes are part of the negative feedback of a feedback cycle. The cycle is completed by the progression in which the alveolar ventilation controls the \(O_2\) extraction and the elimination of \(CO_2\). The cycle progression associates the dependence of \(PCO_2\) and \(PO_2\) in ventilation\textsuperscript{21}. The simulation of chemoreceptors results in an increased alveolar ventilation that leads to an increased elimination of \(CO_2\) and decrease in \(PCO_2\), stimulating the chemoreceptors por meiothrough the increased concentration of \(H^+\) ions; therefore, concluding the negative feedback designation of the system\textsuperscript{21} (Figure 3).

The increased sensitivity of the central and peripheral chemoreflexes can have an important role in the ventilatory control alteration observed in heart failure and a significant correlation can be found between the ventilatory response to exercise and the hypoxic chemosensitivity at rest\textsuperscript{24}. The inhibition of the peripheral chemoreflex has been shown to increase the performance at exercise and decrease the ventilatory response in patients with HF. These observations suggest that the marked hyperpnea at exercise can be influenced by the increased peripheral chemoreflex activity in these patients\textsuperscript{25,26}.

A significant positive correlation was observed between the central hypercapnic ventilatory response and the sleep time percentage in patients with HF and Cheyne-Stokes respiration. The fact that supplemental \(O_2\) and \(CO_2\) during sleep increase the Cheyne-Stokes respiration suggests a contribution of the increased chemosensitivity in this disorder. This increase can also explains the tendency of lower-than-normal \(PaCO_2\) observed during sleep and wakefulness in individuals with Cheyne-Stokes respiration\textsuperscript{26}.

In heart failure of Chagasic etiology, the ventilatory and autonomic responses increased with the stimulation of the peripheral chemoreflex. On the other hand, the ventilatory and autonomic responses decreased during hypercapnia, associated with the activation of central chemoreceptors in this group of patients\textsuperscript{27,28}.

Additionally, it is worth mentioning that, together with Chagas’ disease, diabetes mellitus is a disease that can course with autonomic neuropathy, leading to dysautonomy and very often, patients with HF present diabetes as a comorbidity.

There have been few studies associating diabetes and the chemoreflex function. Studies with experimental models have shown that the chemoreflex is decreased\textsuperscript{29}. In humans, it has been observed a decrease in the peripheral chemoreflex in individuals with type 2 diabetes, especially regarding the response to hypoxia\textsuperscript{30}.

**Influence of drug therapy on the central and peripheral chemoreflexes**

The drug therapy is crucial for a better prognosis in HF. The current treatment of HF includes beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI) and
angiotensin II receptor blockers (ARB). The treatment with beta-blockers significantly altered the morbidity and mortality of patients with HF, as shown in the COPERNICUS31, CIBIS-II32 and MERIT-HF studies33. The beta-blockers decrease the progression of left ventricular dysfunction, decrease the sympathetic activity and thus improve the prognosis of patients HF34. Their beneficial effects are evident, regardless of age or the low, intermediate or high risk that the patients present for HF35. However, that is not translated into exercise capacity improvement, at either submaximal or maximal exertion.

The beta-blockers can act on the beta-1 and/or beta-2 adrenergic receptors. The respiratory system is characterized by a prevalence of beta-2 receptors, which are characterized by regulating the bronchial tonus, whereas the alveolar beta receptors regulate the reabsorption of fluids that affect gas diffusion; however, more than 90% of the beta receptors are located in the alveoli, in which the beta-2 type predominate (70%)36,37. Although the treatment with beta-blockers is an effective therapy for HF, to date, only a few studies have evaluated the effect of beta-blockers on exercise-induced hyperventilation38. Additionally, there are no data regarding the effect of beta-blockers during exercise under hypoxia, when the arterial hypoxemia increases the activity of the chemoreceptors39.

The angiotensin-converting enzyme inhibitors (ACEI) inhibit the conversion of angiotensin I (AI) into angiotensin II (AII), decreasing the levels of the latter in the blood. The formation of AII involves the sequential cleavage of angiotensinogen. The angiotensinogen is transformed into angiotensin I through the action of renin, synthesized by the kidney, and then it is hydrolyzed into angiotensin II, through the action of the angiotensin-converting enzyme (ACE). The renin-angiotensin-aldosterone system can be blocked at different places and by several mechanism. The angiotensin-converting enzyme activity is predominantly found in the endothelium of lung vessels. The angiotensin II promotes aldosterone release by the adrenal glands. The agents that inhibit ACE interfere with the conversion of AI into AII, the latter being considered one of the most important systemic hormones, among which are noradrenaline, vasopressin and endothelin.

The angiotensin II receptor blockers (ARB) are drugs that act on AT1 receptors, responsible for all known actions of AII, including vasoconstriction, aldosterone release and effects on the myocardium and vasculature (Figure 4). There are hypotheses to explain their influence on the dynamics of central and peripheral chemoreflexes. Although the cell and molecular mechanisms involved in the increased sensitivity of the carotid chemoreceptors during HF are yet to be elucidated, there is evidence that the increased levels of angiotensin II in the central nervous system accentuates the peripheral chemoreflex sensitivity and increases the peripheral sympathetic nervous activity40,41.

The plasma and tissue levels of angiotensin II are increased in HF and, moreover, some studies have associated the

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**Figure 3** - Flow chart illustrating the influence of chemoreceptors in ventilation control. The pulmonary ventilation controls PCO$_2$ and PO$_2$, part of the cycle stimulation. The arterial and central concentration of the hydrogen ion ([H$^+$]) is determined by their respective PCO$_2$, ionic difference and concentrations of albumin ([Alb]) and phosphate ([PO$_4^-$]). The concentration of ions H$^+$ and PO$_2$ control the ventilation through the ventilatory stimulation of the chemoreflexes, apart from the negative feedback of the cycle.
hypersensitivity of chemoreceptors in HF to the increased levels of Ang II and the decreased levels of nitric oxide.

Recent studies demonstrated that the endogenous levels of Ang II and the expression of AT1 receptors are increased in the carotid bodies in animal models of HF and that mediates the increased sensitivity of chemoreceptors to hypoxia. Therefore, the drug treatment of with ARB can affect the chemoreflexes in HF, but most studies are experimental animal models, which limits the extrapolation of these conclusions regarding these mechanisms to humans.

Perspectives

In spite of the divergent results, currently the evidence points out to an increase in the activity of central and peripheral chemoreflexes in HF, which is correlated with disease severity. Although the mechanisms responsible for the altered central chemoreflex sensitivity are still unclear, the resulting alterations can be responsible, in part, for the increased ventilatory response at exercise, dyspnea, Cheyne-Stokes respiration and sympathetic hyperactivation observed in heart failure. As for the drugs used in the clinical management of HF, although they decrease the sympathetic hyperstimulation and the sensitivity of the central and peripheral chemoreflexes, they do not improve exercise performance, even if they attenuate symptoms such as dyspnea.

Therefore, the genesis of the signs and symptoms of the heart failure syndrome requires further clarification, so that we can intervene and treat the syndrome in order to improve prognosis, quality of life and the performance at activities of daily living.

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