

## Ergoreflex Activity in Heart Failure

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### Abstract

A large body of evidence has suggested the existence of a reflex network that becomes hyperactive secondary to musculoskeletal alterations that occur in heart failure (HF) syndrome. Together with sympathoinhibitory cardiovascular reflexes, suppressed in the presence of the syndrome, heart failure can contribute to physical exercise intolerance. The hyperactivation of signals originated from receptors located in skeletal muscles (mechanoreceptors - metaboreceptors) is a recently proposed hypothesis to explain the origin of fatigue and dyspnea symptoms in HF. In HF, other alterations in the reflex control system, which are not mutually exclusive, contribute to dyspnea.

The inappropriate stimulation of the arterial baroreceptors, with the consequent lack of inhibition of the muscle metaboreflex and carotid chemoreflex unloading and the increase in the renal vasoconstriction with angiotensin II release can also be considered.

Although the functional alterations of the reflexes were used independently to illustrate the sympathetic excitation observed in HF, the interaction between these reflexes under normal and pathological conditions, especially its contribution to the sympathoexcitatory state found in HF, has not been broadly investigated.

Therefore, questions about a possible association between the muscle receptors (mechano and metaboreceptors) in the genesis of the ergoreflex exacerbation, observed in HF, remain. Thus, the objective of this review was to integrate the knowledge on the mechano and metaboreflex (ergoreflex) in HF syndrome, as well as to clarify the influence of HF drug therapy on the ergoreflex.

### Introduction

The existence of reflex network that becomes hyperactive underlying musculoskeletal alterations - which occur in heart failure (HF) syndrome - has been suggested by a large body of evidence<sup>1</sup>. These hyperactive reflexes, together with

### Keywords

Hyperventilation; heart failure; muscle fatigue; exercise.

sympathoinhibitory cardiovascular reflexes, suppressed in the HF syndrome, can contribute to exercise intolerance<sup>2,3</sup>.

During physical activity, patients with HF present a higher degree of ventilation for a certain workload, when compared to normal individuals<sup>4</sup>. This fact generates low ventilatory efficiency, associated with high ventilation related to the production of carbon dioxide (CO<sub>2</sub>), which is a strong predictor of poor prognosis, in addition to being an exercise limiting factor<sup>5-7</sup>. Hyperventilation can occur due to several causes, among which hyperactivity of reflexes originated from chemoreceptors, one of the several abnormalities in the cardiovascular reflex control related to the increased sympathetic tonus in HF<sup>4,8</sup>. The hyperactivation of signals originated from the receptors located in the skeletal muscles (mechanoreceptors - metaboreceptors) supports a hypothesis that has been recently proposed to explain the origin of fatigue and dyspnea symptoms and the beneficial effects of physical training on HF syndrome<sup>8</sup>.

The cardiovascular reflexes translate the increased sympathetic activity in individuals with HF. Although the alterations in these reflexes are constantly used to illustrate the sympathetic excitation observed in HF, the interaction between these reflexes under normal and pathological conditions, especially its contribution to the sympathoexcitatory state found in HF, has not been broadly studied<sup>9</sup>. Therefore, the aim of the present review is to integrate the knowledge on mechano and metaboreflex (ergoreflex) in heart failure syndrome and attempt to elucidate the influence of HF drug therapy on the ergoreflex.

### Cardiovascular reflexes

#### Cardiovascular and ventilatory control during exercise: general concepts

The autonomic nervous system allows the body to adjust its circulation and ventilation to maintain the oxygen supply to the tissues. With that, the autonomic balance is maintained through the complex interaction between the arterial baroreflex, central and peripheral chemoreflex, ergoreflex and pulmonary stretch reflex<sup>10</sup>. During the exercise, the central hemodynamics and the ventilatory responses are under the control of the autonomic nervous system, which depends on the interaction between the receptors of the brain's motor cortex and the peripheral afferences (baroreceptors, mechano and metaboreceptors)<sup>11</sup>. This system regulates the cardiac output, the vascular conductance and the ventilation, in an attempt to supply the adequate oxygenated blood flow to eliminate muscle metabolic byproducts.

At the start of the exercise, the motor cortex establishes a basal level of sympathetic and parasympathetic efferent

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Manuscript received December 19, 2009; revised manuscript received May 02, 2010; accepted July 13, 2010.

activity, which is, in turn, modulated by the signals originated from the arterial baroreceptors and articular, tendon and muscle receptors. The baroreceptors work with the control of muscle vasodilation and of heart rate through the sympathetic activation to maintain the blood pressure (BP) and counterbalance any disequilibrium between vascular resistance and cardiac output. On the other hand, the muscle receptors activate the nervous afferences, which, in turn, induce sympathetic-cardiovascular adjustments mediated in response to the mechanical and metabolic conditions of the working muscle<sup>8,11</sup>. There is evidence that the autonomic disequilibrium contributes to the pathogenesis and progression of heart failure. Initially, the disequilibrium leads to the increase in BP, ventilation, renal vascular resistance and peripheral vascular resistance. Consequently, one reaches the increase in heart rate and this disequilibrium might be responsible for the disease progression<sup>11</sup>. A summary of the autonomic alterations found in HF, as well as their interactions can be seen in Figure 1.

Two classes of neural mechanisms have been postulated as the origin of the increase in the ventilation rate, heart rate, sympathetic nerve discharge and heart contractility during exercise. The first is the system of central command that involves the direct activation of the locomotion and autonomic systems and ventilatory circuits through the nervous processes that occurred at the start of the exercise<sup>12,13</sup>. The second class of mechanisms is the reflex network that can activate autonomic circuits and medullary ventilatory centers through signals originating from the periphery, such as the type III and IV muscle afferent signals, which are activated during the exercise<sup>14</sup>.

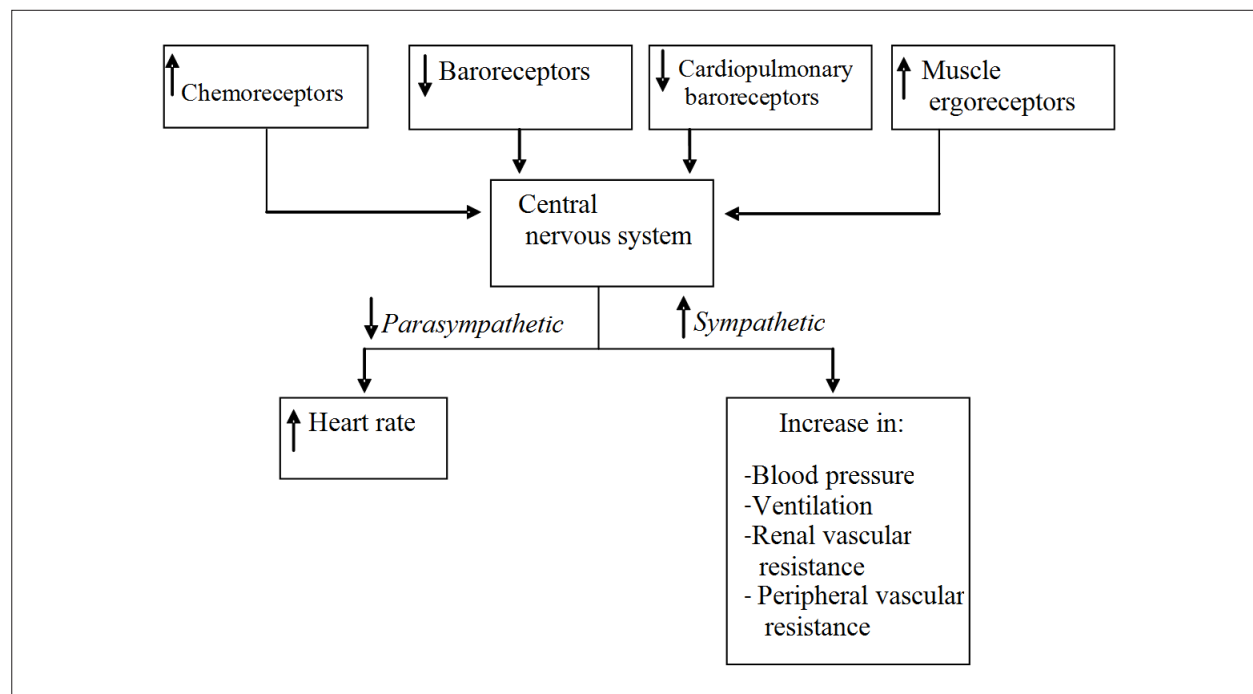
Evidence shows functions for both neural mechanisms in the cardiovascular and respiratory responses to exercise<sup>15</sup>. These type III and IV muscle afferences are defined as ergoreceptors, as they are stimulated by the muscle work. They were classified as mechanoreceptors, which are sensitive to movement; and metaboreceptors, which pick up chemical stimuli related to muscle work. The activation of these afferences can affect the heart rate, blood pressure, cardiac output, systolic volume, ventilation and the sympathetic nervous activity demonstrated by microneurography<sup>1,16</sup>.

### Mechanoreflex and metaboreflex control

The circulatory and respiratory neural control of the mechanical and metabolic events that occur in the muscles involved in physical exercise are known as exercise pressor reflex. During the physical activity, the muscle mechanical stimulation, associated with contraction, can stimulate efferent nervous terminations and determine a cardiovascular reflex, the mechanoreflex.

The mechanoreceptors stimulate mainly the type II myelinated afferent fibers, which respond, in general, to mechanical stimulation. The type III afferent fibers fire at the start of the contraction (they present early activation in comparison to metaboreceptors) and their firing rate tends to adapt, when the muscle tension is maintained constant.

With the progression of metabolic effort, lactic acid, adenosine, phosphate, kinins and cations are produced in the skeletal muscle. In addition to the production, the blood flow to the skeletal muscle might not be sufficient, which can impair the kinetics of metabolic byproduct removal - lactic acid,



**Figure 1** - Autonomic control mechanisms in heart failure. The sensitivity of arterial baroreceptors and cardiopulmonary receptors is decreased, whereas the sensitivity of the chemoreceptors is increased and the increase in the muscle ergoreceptor activity is also observed (which triggers the ergoreflex). The response to this altered balance includes generalized increase in sympathetic activity, which results in the increase of blood pressure, ventilation, renal vascular resistance and peripheral vascular resistance, whereas there is a decrease in the parasympathetic activity, which causes heart rate increase.

hydrogen ions, adenosine, potassium, phosphate ions and arachidonic acid, among others. These substances accumulate when stress increases, and when the oxygen supply fails to meet the metabolic demands of the contracting muscle, the muscle metaboreceptors are activated. That, in turn, leads to the reflex regulation of the cardiovascular system, commonly called metaboreflex. Non-myelinated type IV afferent fibers are sensitive to metabolites, especially to acidosis, and to prostaglandins and bradykinins<sup>17</sup>. Once activated, they directly stimulate the sympathetic drive, which leads to the increase in pulmonary ventilation and vasoconstriction of muscles that are not being exercised. The combination of this effect takes more oxygenated blood to the skeletal muscles undergoing activity. The stimulation of the type III and IV afferent fibers seems to be essential for the normal hemodynamic response to exercise in healthy individuals. Most of the type III and IV afferent fibers enter the spinal cord via the dorsal horn; these fibers' impulses probably present several levels of integration and the reflex does not seem to need the brainstem, although there is a supraspinal level of integration.

During the exercise, there is a muscle contraction, followed by an accumulation of metabolites, and, therefore, mechano and metaboreflexes overlap. The spinal cord is probably the area that controls the cardiovascular response during the activation of the mechano and metaboreflex<sup>17,18</sup>.

Therefore, even in terms of anatomical differentiation and regarding the physiological triggers, there is a degree of overlapping between mechano and metaboreceptors and more recent observations have challenged the classic description of these receptors as distinct structures<sup>19,20</sup>. Hence, we use the terms "ergoreceptors", which contemplate both types of afferences and "ergoreflex", which is the reflex triggered by both types of receptors<sup>16,21-23</sup>.

### The muscle hypothesis

Heart failure results in limitations to usual activities, regarding the changes occurred in the oxygen transportation system from the center (heart, lungs and neural control) to the periphery (circulation, neurohormonal status, reflexes, autonomic nervous system and muscle metabolism). A key issue has been whether this imbalance is mechanically important or whether it is merely the result of the sum of the factors associated to the poor cardiac function and consequent physical inactivity.

The muscle hypothesis has developed in the last twenty years, which attributes the symptom origin and reflex abnormalities observed in heart failure to the peripheral muscle abnormalities. The skeletal muscle, when it becomes abnormal in heart failure, would indicate altered patterns of the cardiorespiratory control, thus resulting in symptoms such as dyspnea, fatigue and hyperpnea, usually reported by HF patients<sup>23</sup>.

This hypothesis proposes another cycle of deterioration similar to those of neuroendocrine activation. The decrease in the ventricular function causes metabolic effects, which ultimately deteriorate the skeletal muscle and generate abnormalities in metabolism and muscle function. In response to the early accumulation of metabolites in the exercising muscle, there is a marked activation of the

ergoreflex and that is perceived by the individual as muscle fatigue, as well as dyspnea.

Additionally, there is, as a reflex, an increase in the sympathetic tonus, tachycardia, vasoconstriction of the vascular beds distant from the muscles that are not being submitted to exercise and the excessive ventilatory response to exercise (Figure 2)<sup>1</sup>. These changes are initially beneficial to maintain the adequate blood pressure and perfusion in the most important areas. However, in the long term, this situation becomes harmful and causes permanent vasoconstriction, vascular and endothelial response, inflammation and necrosis, which alters the function of other organs, including kidneys, lungs and cardiac muscle<sup>18</sup>.

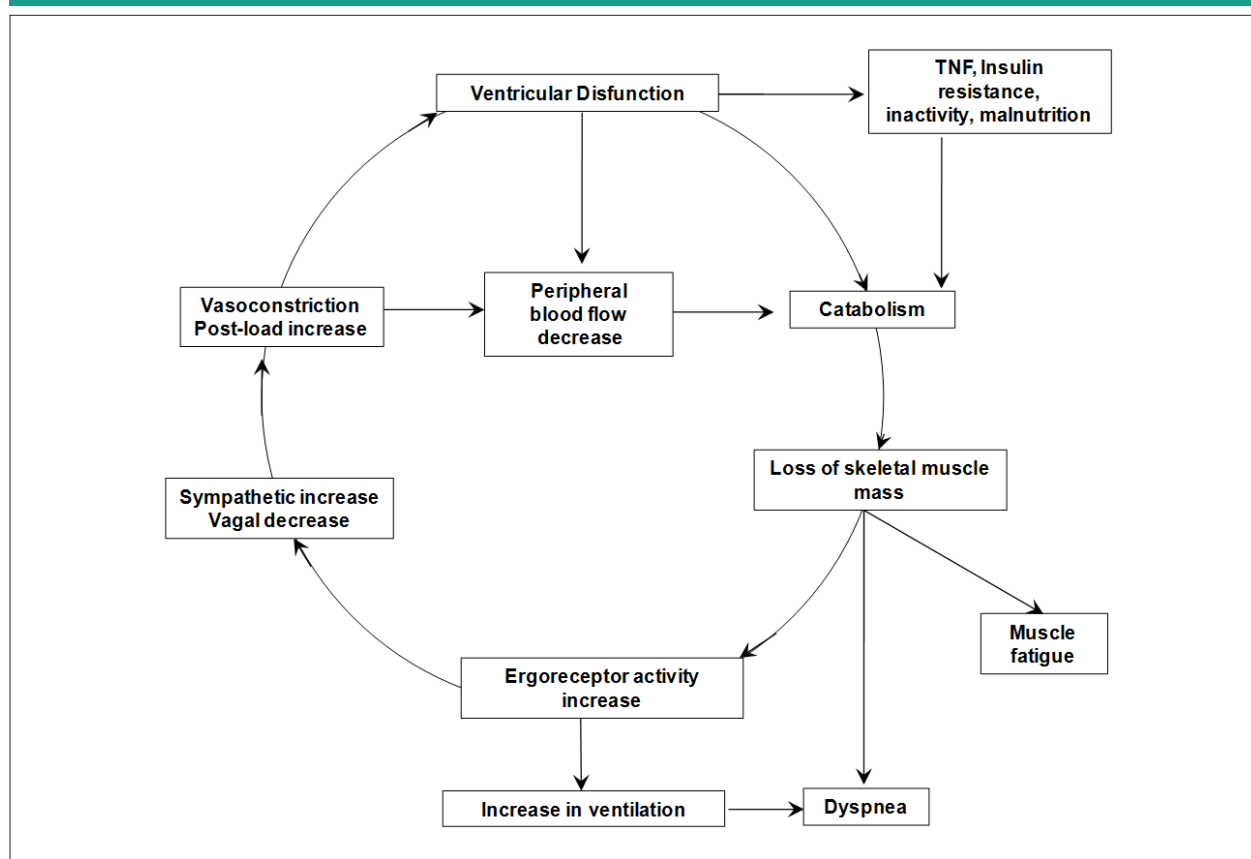
The previously described skeletal muscle abnormalities, observed in patients with HF, are mainly the prevailing of the oxidative metabolism over the glycolytic metabolism and ultra-structural changes in the muscle composition (type of fiber, number of mitochondria and endothelial function). Thus, early acidosis occurs, as well as depletion of the high-energy compounds developed during the exercise, which, in turn, trigger other compensatory mechanisms. In normal individuals, these compensatory mechanisms would keep the skeletal muscle performance and cause the stimulation of several afferents, such as muscle ergoreceptors, which communicate with the brainstem on the level of muscle work - which triggers the ergoreflex<sup>16,21-23</sup>.

### Factors that trigger the ergoreflex

The ergoreflex has been studied since the 90s, when the muscle hypothesis proposed that exercise intolerance would be related to alterations in the peripheral muscles<sup>24</sup>. Since then, the instrument to evaluate it has been the regional circulatory occlusion (RCO) after muscle contraction<sup>25,26</sup>.

In general, the technique includes two sessions of exercises developed randomly: (1) The control exercise, using upper-limb or lower-limb repetitive movements (arm or leg ergometer, handgrip) at submaximal intensity. (2) A pressure cuff is placed on one of the limbs submitted to exercise. The same control exercise protocol must be carried out, however, approximately ten seconds before the end of the stress and the pressure cuff of the limb submitted to exercise starts to be inflated. Then, the regional circulatory occlusion is maintained for three minutes through a pressure of at least 30 mmHg above the systolic pressure obtained at the last blood pressure measurement. After the cuff has been inflated, the individual is asked to relax. The exercise stops and the contribution of the ergoreceptors is evaluated by trapping the metabolites produced during the exercise. During the assessment of the ergoreflex activity, the individuals must breathe through a mouthpiece, with a nose clip and the expired gases and the ventilation must be measured, as well as the blood pressure and heart rate values. This protocol aims at setting the muscle metabolic status and prolonging the ergoreceptor activation<sup>1,23,27</sup>.

Two approaches can be used to study the ergoreflex: during exertion, through the reduction of blood flow to the muscle, or at the end of exertion, through the reduction of the blood flow and through the cause of post-exercise ischemia, which



**Figure 2** - In the muscle hypothesis, the initial decrease in the ventricular function and consequent inactivity activate the catabolic state and reduce the anabolic factors, leading to loss of muscle mass and musculoskeletal dysfunction. That, in turn, sensitizes the muscle ergoreceptors that lead to exercise intolerance and sympathetic excitation. As a consequence, the combined effects of the catabolic state and inactivity further worsen the structure and function of the skeletal muscle and might, eventually, lead to the progression of the disease (Adapted from Piepoli, M. and cols., *Circulation* 1996;93:940-9521).

traps the metabolites previously produced during the muscle contraction. The last approach, to cause post-exercise ischemia, isolates the central command and the mechanoreflex of the metaboreflex. The evaluation of the ergoreflex contemplates both the muscle mechano and the metaboreceptors and, as previously explained, their functions overlap during the exercise. However, at the start of the exercise, some authors consider only the evaluation of the mechanoreceptors to test the mechanoreflex. The technique consists in three minutes of passive exercise, followed by a period of three minutes of active exercise, separated by a three-minute resting period. In general, the movement is described in a lower-limb ergometer in both active and passive movements.

To quantify the ventilatory response attributed to muscle work, the increase in ventilation (VE) per unit increase in  $\text{VO}_2$  (dVE/d $\text{VO}_2$  ratio) is measured in both passive and active movements. The contribution of the mechanoreflex to exercise is quantified as the difference in the increase in the dVE/d $\text{VO}_2$  ratio between passive and active exercise<sup>28,29</sup>. However, the literature about the isolated evaluation of mechanoreceptors, as described, is scarce. Moreover, Scott et al<sup>28,29</sup> did not find a significant response of the mechanoreceptors, translated as ventilation increase, either in patients with HF or normal controls<sup>28</sup>. This can be attributed to the fact that the isolated activation is unusual,

as most daily activities are of submaximal nature, with an accumulation of metabolites in the skeletal muscle, thus activating not only the mechanoreceptors, but also the metaboreceptors. Therefore, the evaluation of the ergoreflex, which contemplates both mechano and metaboreceptors, is more frequent in the literature and more reproducible<sup>1,18,20,23</sup>.

Most authors recommend the use of submaximal exercises for the ergoreflex test (between 50 and 70% of  $\text{VO}_2$  peak). In a study carried out by our group, in patients with HF undergoing beta-blocker treatment, it was demonstrated that in RCO of a lower-limb after the six-minute walk test (6MWT) on a treadmill, representing daily activities, there was no activation of the ergoreflex mechanisms. This information can suggest that these mechanisms would be activated only at more intense or maximal exertion<sup>29,30</sup>. There has been no report in the literature on the evaluation of the ergoreflex during or after walking activity; however, this would be the most common physical activity performed by patients with heart failure. This activity can be reproduced by the 6MWT, as there is a correspondence with the metabolic demands of daily activities<sup>31,32</sup>.

Regarding the limb to be tested, whether the regional circulatory occlusion is to be performed in an upper or lower limb, there have been studies that used either one. However, previous studies used upper-limb localized exercise protocols and observed a variation in ventilation after the RCO<sup>1,22,33,34</sup>.

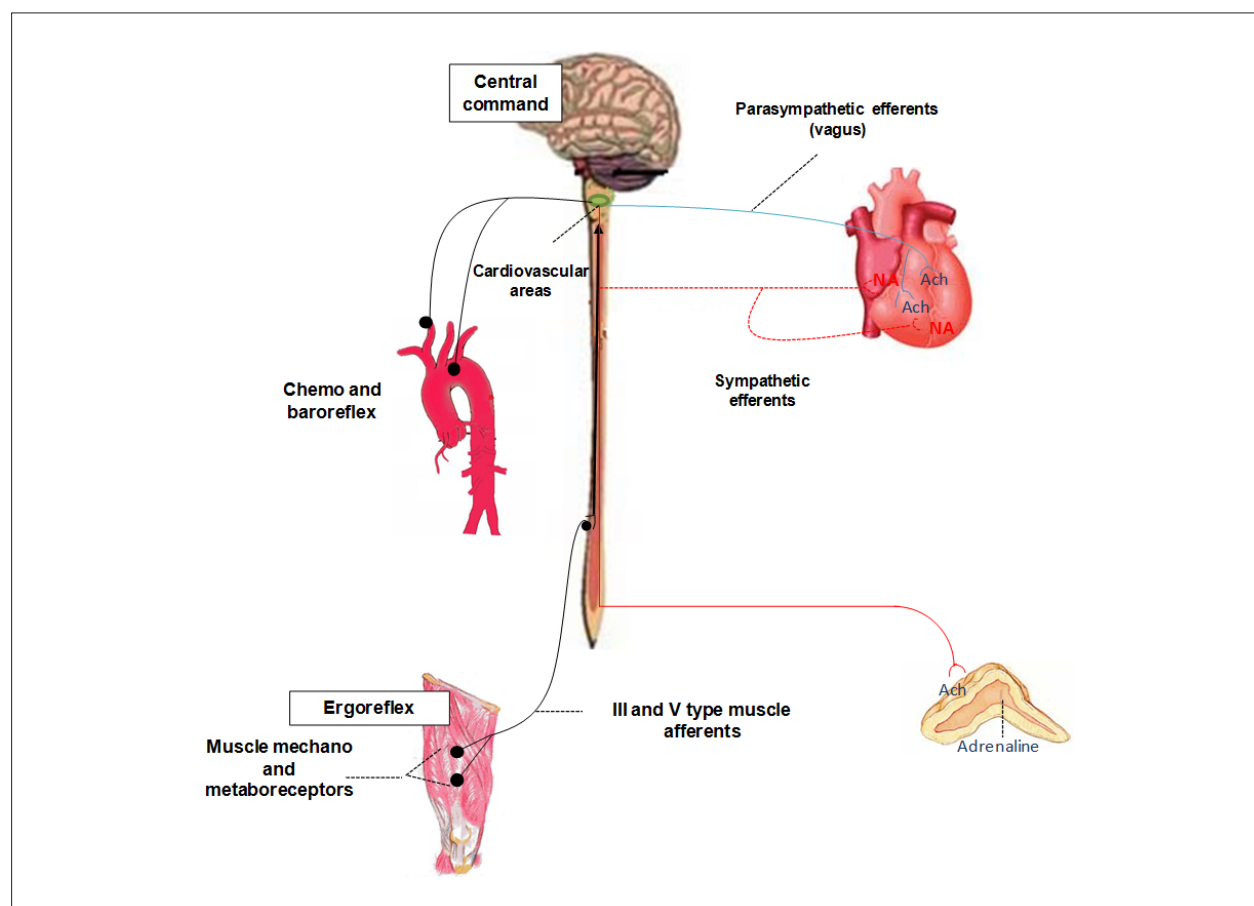
Nevertheless, this technique involves a small group of muscles and, perhaps, the anaerobic metabolism is predominant in this type of exercise, in order to overestimate the results. Other studies used protocols with ankle dorsiflexion and in a cycle ergometer, and found similar results<sup>35</sup>. The most adequate method to reliably test this reflex remains controversial in the literature. In a study that compared the ergoreflex in different muscle groups in the same patient with HF, it was observed that the results attributed to a higher or lower ergoreflex activity depended on the muscle group, type of fiber and oxidative or glycolytic metabolism involved in the exercise<sup>36</sup>.

### Ergoreflex in heart failure

Muscle fatigue, even in the presence of moderate physical exercises, is a common problem associated with individuals that present HF. During exercise in HF, the cardiac output is decreased and the blood pressure control is intense through peripheral vascular responses that result from the increase in the sympathetic nervous activity and increase in the vasoactive hormone secretion. Moreover, the blood flow to the active skeletal muscle is decreased, which can lead to relative

ischemia<sup>37</sup>. Some studies have shown that part of the increase in the sympathetic tonus that occurs during moderate exercise in patients with HF results from the activation of the ergoreflex<sup>38,39</sup>. During the physical exercise, the capacity to dilate the peripheral musculature is related to the higher level of cardiac output (CO) and, in this process, the BP is maintained. However, if the capacity of the peripheral blood flow is higher than the CO, as recently suggested<sup>40</sup>, the influence of another control must be interposed between the heart and the skeletal muscle vessels to maintain the BP, which can guarantee that the cerebral and cardiac blood flow is preserved. The association between the sympathetic nervous system and vasoconstriction helps in this regulatory function (Figure 3). The main hemodynamic consequence of the ergoreflex activation is the increase in BP. This response is achieved primarily through the increase in the systemic vascular resistance, due to the peripheral vasoconstriction resulting from the increase in the sympathetic activity, whereas the effect on the heart rate is variable.

The neuromuscular stimulation of metaboreceptors through local physical-chemical changes causes reflex hyperpnea. In animals, the isolated lower-limb perfusion with blood in acidosis, hypercapnia or hypoxia, as well as the perfusion



**Figure 3** - Cardiovascular neural control during exercise. Neural signals originating in the brain (central command), in the aorta and carotid arteries (chemo and baroreflex) and in the skeletal muscles (ergoreflex) are known by modulating the sympathetic and parasympathetic activities during exercise. The alterations in the autonomic tonus induce changes in heart rate and contractility, in addition to altering vessel diameter and adrenalin release by the adrenal gland medulla. As a result, changes in heart rate, cardiac output and systemic vascular resistance mediate alterations in the appropriate mean blood pressure to determine exercise intensity. Ach - acetylcholine; NA - noradrenaline.



with venous blood previously collected from lower limb submitted to exercise, produce an increase in ventilation<sup>41</sup>. Similarly to what has been reported for the metaboreflex, the mechanoreflex has demonstrated the capacity to produce cardiovascular reflexes. The mechanical distortion of receptor fields of nervous terminations in contractile muscles can activate the mechanoreceptors, which, tonically activated, seem to be the main factors responsible for the reflex increase in BP induced by exercise (mechanoreflex)<sup>18,42</sup>.

In an experimental study, the activation of the muscle metaboreflex caused a significant increase in heart rate, with no alterations in systolic volume, thus resulting in a great increase in cardiac output and mean blood pressure. After the induced left ventricular ejection fraction decrease in these animals, much lower increases in CO occurred with the activation of muscle metaboreflex, and, although the heart rate (HR) increased, the systolic volume decreased. Moreover, when the HR was maintained constant, no increase in the CO was observed with the activation of the muscle metaboreflex, although the central venous pressure significantly increased.

After the beta-adrenergic blocking, the cardiac output (CO) and the systolic volume decreased with the activation of the muscle metaboreflex. Hence, the authors concluded that, in HF, the capacity of the muscle metaboreflex to increase the ventricular function through increases in contractility and filling pressure is evidently decreased<sup>43</sup>.

Scott et al<sup>29</sup> observed, in patients with moderate to severe HF, during lower-limb exercise in cycle ergometer, the activation of the ergoreflex demonstrated by the increased ventilatory response at exertion. This observation was developed in comparison with normal individuals and suggests that hyperactivation might be the origin of dyspnea and fatigue caused by exertion.

Piepoli et al<sup>23</sup> evaluated 107 patients with HF and, when compared to normal controls, they observed a higher degree of activity of the ergoreflex in ventilation, in addition to a decrease in muscle mass. However, the ergoreflex was particularly hyperactive in cachectic patients and suggested a strong correlation between muscle mass depletion and ergoreflex hyperactivation<sup>23</sup>.

### Influence of drug therapy on the ergoreflex

In HF, other alterations in the reflex control systems, which are not mutually exclusive, contribute to dyspnea. The inappropriately low stimulation of the arterial baroreceptors, with the consequent lack of inhibition of the muscle metaboreflex and carotid chemoreflex unloading and the increase in the renal vasoconstriction with angiotensin II release can also be considered<sup>23</sup>.

The beta-blockers used by most patients with HF (83%) are a well-acknowledged treatment and effective in these patients' survival, but have controversial effects in exercise tolerance. There is no information on their effect on ergoreflex. Based on the consideration that the ergoreflex is mediated by the sympathetic nervous system and that beta-blockers are adrenergic blockers, it can be suggested that these can affect their hyperactivation by decreasing the sympathetic tonus. Additionally, the studies on the activation of the ergoreflex in HF included, on average, only 30% of patients using beta-blockers<sup>1,8,22,28</sup>. There have been no studies that evaluated the

effect of treatment with beta-blockers on patients with HF and further studies are necessary to clarify this interrelation.

### Perspectives

As previously shown, many studies have demonstrated that the mechanoreflex involves the hemodynamic deregulation observed in heart failure. Therefore, the question whether both muscle receptors (mechano and metaboreceptors) correlate with the genesis of the exacerbation of the ergoreflex observed in HF is yet to be clarified.

From a clinical perspective, it would be useful to verify whether the chemical blocking of the receptors that mediate the metaboreflex can limit the sympathetic hyperactivity observed in patients with HF.

According to the muscle hypothesis, it would be more appropriate and effective to treat the cause, the musculoskeletal abnormalities, instead of treating the consequences of ergoreflex activation, such as peripheral vasoconstriction and sympathetic activation. Randomized and controlled trials have shown that physical training increases oxygen consumption and improves the neurohormonal balance in HF<sup>44</sup>. Particularly, it increases mitochondrial density and oxidative enzyme activity, increases capillary density and shifts towards the aerobic metabolism associated with the decrease in metaboreflex activation in HF. In a way, the muscle hypothesis is similar to other vicious circles in HF, in which many of the physiological responses seem to be adaptive at first, and then, throughout time, show to be deleterious adaptations.

By understanding the physiological basis of the symptoms of HF patients and developing strategies to improve these symptoms, we must start to solve the complex physiological processes that determine exercise incapacity. Apparently, the peripheral muscles, the endothelium, the lungs and the ventilatory control reflexes represent a key role in exercise-limiting factors.

At a time of aggressive interventions in clinical cardiology and focus on the molecular bases of cardiovascular disease, it must be supposed that complex and coordinated regulatory mechanisms determine the integrated functions of the cardiovascular system through the autonomic nervous system<sup>18</sup>. When this coordination is lost, exercise intolerance might be the precursor of many problems that will certainly appear.

Therefore, healthy life habits, which must include regular physical exercise, contribute to interrupt this vicious circle and successfully promote primary and secondary prevention.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

This study was partially funded by FAPESP.

### Study Association

This article is part of the thesis of doctoral submitted by Juliana Fernanda Canhadas Belli, from *Faculdade de Medicina da Universidade de São Paulo*.

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