The ergoreflex: how the skeletal muscle modulates ventilation and cardiovascular function in health and disease

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The control of ventilation and cardiovascular function during physical activity is partially regulated by the ergoreflex, a cardiorespiratory reflex activated by physical activity. Two components of the ergoreflex have been identified: the mechanoreflex, which is activated early by muscle contraction and tendon stretch, and the metaboreflex, which responds to the accumulation of metabolites in the exercising muscles. Patients with heart failure (HF) often develop a skeletal myopathy with varying degrees of severity, from a subclinical disease to cardiac cachexia. HF-related myopathy has been associated with increased ergoreflex sensitivity, which is believed to contribute to dyspnoea on effort, fatigue and sympatho-vagal imbalance, which are hallmarks of HF. Ergoreflex sensitivity increases significantly also in patients with neuromuscular disorders. Exercise training is a valuable therapeutic option for both HF and neuromuscular disorders to blunt ergoreflex sensitivity, restore the sympatho-vagal balance, and increase tolerance to physical exercise. A deeper knowledge of the mechanisms mediating ergoreflex sensitivity might enable a drug or device modulation of this reflex when patients cannot exercise because of advanced skeletal myopathy.
The ergoreflex in health and disease

Introduction

As stated by Charles Sherrington, ‘To move things is all that mankind can do, and for this task the sole executant is a muscle, whether it be whispering a syllable or felling a forest’. However, the muscle could mediate almost no expression of human nature if haemodynamics and ventilation were not modulated according to exercise intensity. In fact, sympathetic outflow and ventilatory rate increase proportionally to exercise intensity in order to meet the metabolic demands of exercising skeletal muscles. This response is possible because of three cardio-respiratory reflexes that are highly centrally integrated: baroreflex, chemoreflex and ergoreflex, the last originating from the exercising muscle (from the Greek word ‘èrgon’, meaning work).

Although known for about 80 years, the role of the ergoreflex in disease has only been investigated quite recently. The ergoreflex has been evaluated mostly in chronic heart failure (HF). In this setting, the demonstration of enhanced ergoreflex sensitivity provided a theoretical framework for exercise training (ET) as a novel therapeutic option, as ET may reduce ergoreflex sensitivity by improving muscle structure and function.1 On a similar note, muscle wasting and reduced exercise tolerance are prominent features of neuromuscular disorders, where increased ergoreflex sensitivity has been reported.4–7 A better understanding of the mechanisms mediating ergoreflex sensitivity in health and disease states is needed also to search for possible targets to be challenged by either pharmacological modulation or implantable devices when ET is not an option because of an advanced disease.

The ergoreflex: physiology

Discovery of the ergoreflex and its components

The existence of a reflex triggered by muscle activity was proposed by Alam and Smirk in 1937.8 Healthy volunteers were asked to perform a dynamic exercise while vessels in the limbs involved were occluded by inflating a sphygmomanometer cuff. The exercise lasted about 4 min, and circulatory occlusion was maintained for another 11 min. After the end of exercise, pressure values reached during exercise were maintained, and further increased after 3–4 min. Conversely, blood pressure dropped after removal of circulatory occlusion.8 This phenomenon was attributed to the trapping of metabolites into the muscles. Indeed, it could neither be due to the central command, as the exercise had ended, nor to the direct effect of an increase in peripheral resistance due to occlusion itself, since some limb perfusion had to be maintained to make exercise tolerable, and not even to ischaemic pain, as patients experienced severe pain only toward the end of the period of circulatory occlusion.8 One year later, the same Authors reported a sustained increase of heart rate during circulatory occlusion.9 Overall, these experiments suggested the existence of a reflex activated by the accumulation of metabolites in the exercising muscles and able to...
The ergoreflex is a cardiorespiratory feedback system. It is composed of the metaboreflex (activated by the accumulation of metabolites in the skeletal muscle) and the mechanoreflex (elicited by mechanical stretch of muscle and tendons). Signals from both components reach the central nervous system [e.g. nucleus of the solitary tract (NTS), rostral and ventral portions of the medulla (RVLM), caudal ventrolateral medulla (CVLM), lateral tegmental field (LTF)] where they are integrated with other peripheral and central afferences (e.g. chemoreflex, baroreflex, cortical areas). The final output consists in increased ventilation, increased peripheral resistances and cardiac output, resulting in increased systemic blood pressure (BP). HR, heart rate; MSNA, muscle sympathetic nerve activity.

In the 1980s, some experiments on animals revealed that the mechanical stimulation of muscles and tendons elicited increases in heart rate and blood pressure. This reflex occurs in an earlier phase of physical exercise compared to the metaboreflex, and was named ‘mechanoreflex’. The combination of metaboreflex and mechanoreflex constitutes the ergoreflex, a neural mechanism coupling cardiovascular function and ventilation to exercise intensity.

Afferences

Figure 1 provides a schematic representation of the two components of the ergoreflex. The metaboreflex is activated by several metabolites produced in the exercising muscles, including lactic acid, hydrogen and potassium ions, bradykinin, prostaglandins, and adenosine. The accumulation of these molecules is believed to be sensed by receptors located on free nerve endings in the muscle interstitial spaces, such as cannabinoids, μ-opioid, acid-sensing ion channels, transient receptor potential vanilloid-1, and purinergic ligand-gated ion channels. The impulses are conveyed by group IV (small, non-myelinated) fibres, which are activated during exercise with a period of latency due to the need for metabolite accumulation. In a study on healthy volunteers, a threshold for metaboreflex activation has been detected, corresponding to a muscle pH of 6.9 (as estimated based on 31P magnetic resonance spectroscopy). Indeed, during experimental ischaemia, muscle pH decreased linearly along with contraction time, but mean arterial pressure did not initially change. Instead, mean arterial pressure significantly increased when a muscular pH of about 6.9 was reached, and pH values below this threshold were inversely correlated with mean arterial pressure, presumably because of a progressive increase in the firing rate of group IV fibres, which was not examined in this study. To our knowledge, the relationship between muscle pH, including recruitment thresholds, and ventilatory response has never been investigated. Of note, haemodynamic and ventilatory effects may be induced by two different afferent pathways, or just a single pathway.

Mechanoreflex is activated by mechanical stretching, beginning their discharge at the start of the exercise. Afferent stimuli are...
conveyed by group III ( thinly myelinated) fibres with free endings in the muscle interstitial space, which allows a faster response.13

Central pathways
Afferent fibres reach the dorsal horn of the spinal cord. The main effect of mechanosensitive afferent fibres involves the inhibition of vagal tone, leading to a swift increase in heart rate.16 The central pathways of the ergoreflex have been incompletely characterized. During metaboreflex stimulation, several regions of the central nervous system are activated, including the nucleus of the solitary tract, the rostral and ventral portions of the medulla, the caudal ventrolateral medulla, and the lateral segmental field.16 Several of these regions are activated also during chemoreflex stimulation.10 The chemoreflex is another feedback system regulating ventilation and haemodynamic function according to the partial pressures of carbon dioxide and oxygen in the arterial blood, and to arterial pH.10 Therefore, the integration of afferences of the ergoreflex, chemoreflex, as well as the baroreflex, might ensure an integrated response of cardiorespiratory feedbacks during physical activity, thanks to sympathetic and ventilatory stimulation.

Effects
Metaboreflex activation has been consistently reported to increase blood pressure by increasing sympathetic outflow.10 The mechanisms behind this phenomenon have been investigated in the experimental settings of exercise and post-exercise muscle ischaemia.17,18 While a flow-mediated mechanism could be pivotal in both cases, the effects on heart rate are small or absent in the setting of post-exercise muscle ischaemia, probably because they are counterbalanced by the withdrawal of the central command following the end of exercise, and by a baroreflex-mediated increase in parasympathetic tone.17 Less is known about the effects of metaboreflex activation on cardiac haemodynamics, i.e. myocardial contractility, stroke volume (SV), and cardiac output (CO). Although ventricular contractility and SV in humans can be increased during metaboreflex activation, sustaining CO despite the rise in afterload due to vasoconstriction,19–21 such contribution may be less significant than that of peripheral resistances in specific conditions (e.g. reduced cardiac reserve due to strenuous exercise).10,18 and the different experimental designs used so far (e.g. rhythmic vs. static exercise, uneven exercise workload and duration) have yielded controversial results.10 Finally, metaboreflex-mediated increase in cardiac filling pressures has been hypothesized, mediated by vasoconstriction in the splanchic circulation and increased blood return.10 Notably, in case of left ventricular dysfunction, a lack of CO increase was observed while the blood pressure response was sustained by systemic vasoconstriction: this abnormal response was detected in both HF with reduced ejection fraction21 and HF with preserved ejection fraction.23

In healthy subjects, metaboreflex activation is associated with a rise in ventilation to compensate the need for increased oxygenation to the exercising muscles.24 Mechanoreflex stimulation increases vascular resistances and heart rate and then ultimately blood pressure10; furthermore, passive limb movement was found to increase ventilation by 24% compared to baseline.25

Assessment of ergoreflex sensitivity
The methodology for evaluating metaboreflex sensitivity was first described by Alam and Smirk in 1937,8,9 as described above. Since then, the protocol for assessing the ergoreflex has changed, mainly to achieve total vascular occlusion only post-exercise with the scope of reducing the ischaemic time and hence pain, which is a possible confounding factor.16,27 The protocol has been standardized by Piepoli et al.1 Briefly, the subject is asked to exercise with the non-dominant arm by performing two 5 min handgrip manoeuvers reaching approximately 50% of pre-determined maximal contraction, in random order, separated by a 30 min interval: one bout with circulatory occlusion during the last 10 s of exercise and the all 3 min recovery phase (‘clamp session’). During the clamp session, forearm cuff inflation to 30 mmHg above systolic blood pressure from the last 10 s of exercise till the end of the 3 min recovery phase; after cuff inflation, the subject is instructed to relax. Ergoreceptor sensitivity is quantified as the percentage of the ventilatory and haemodynamic response to exercise maintained by circulatory occlusion during the third minute compared with the third minute of basal recovery, which can be calculated through the following equation:

\[
\left( \frac{\text{Rec/Ex clamp}}{\text{Rec/Ex no clamp}} \right) \times 100,
\]

where Ex is the mean ventilation (or blood pressure) during the last 30 s of exercise, Rec the mean ventilation during the last 30 s of the third minute of recovery, and all measures are performed during the clamp bout and the ‘no clamp’ bout.

Piepoli et al.1 assessed metaboreflex sensitivity mostly in terms of ventilatory response to circulatory occlusion. However, they also evaluated two haemodynamic parameters, namely diastolic blood pressure and vascular resistance in the lower limbs (see below).

Mechanoreflex sensitivity has been evaluated mostly through low-level rhythmic exercise,28 passive muscle stretch,29,30 or passive limb movement.31,32 The different studies employed heterogeneous protocols, none of which is likely to elicit a selective mechanoreflex activation. Indeed, ‘low level rhythmic exercise also engages central command and perhaps even metaboreceptors, involuntary contraction can be painful and recruitment patterns are not physiologic, and passive exercise may evoke an arousal response’.26

Ergoreflex in heart failure: the ‘muscle hypothesis’
Heart failure patients often develop skeletal muscle depletion, manifesting as sarcopenia or cachexia, which predicts a poor prognosis.33 Muscle depletion can be explained by several mechanisms: release of pro-inflammatory cytokines; altered
mitochondrial function, with reduced adenosine triphosphate synthesis and increased synthesis of reactive oxygen species; reduction of physical activity because of lower exercise tolerance; hypo-anorexia, with reduced caloric intake; intestinal congestion and reduced intestinal absorption; resistance to several pro-anabolic hormones (insulin, growth hormone), and reduced levels of other pro-anabolic hormones (testosterone, dehydroepiandrosterone); increased circulating levels of myostatin, a protein which reduces the muscle mass; tissue hypoperfusion. Muscle damage may contribute to HF symptoms, and even to the progression of myocardial damage. According to the ‘muscle hypothesis’, skeletal myopathy would increase ergoreflex sensitivity, leading to exertional dyspnoea and autonomic imbalance with adrenergic activation and vagal withdrawal. Chronic adrenergic overactivity would result in abnormalities of myocardial structure and function; furthermore, peripheral vasconstriction would increase myocardial afterload and also reduce the perfusion of the skeletal muscle, thus worsening muscle damage. The ‘muscle hypothesis’ was proposed in 1994 to explain dyspnoea on effort in patients with HF. This hypothesis was corroborated by the detection, 2 years later, of ergoreflex overactivity in HF patients. Compared to 10 healthy and sedentary controls, HF patients (n = 12) displayed higher ergoreflex sensitivity, in terms of higher ventilatory rate (87% vs. 55%), diastolic blood pressure (98% vs. 54%), and vascular resistance in the lower limbs (108% vs. 49%) during the recovery with circulatory occlusion, compared with basal recovery. These responses could be the direct consequences of ergoreflex overactivity, but also partially derive from depressed baroreflex sensitivity and increased central chemoreflex sensitivity, which have been associated with ergoreflex overactivity in HF.

**Ergoreflex sensitivity and response to exercise**

Cardiopulmonary exercise test (CPET) evaluates patient’s aerobic capacity with breath-by-breath expired gas parameters. CPET provides information on the patient’s functional efficiency with peak oxygen uptake (VO₂), and ventilatory efficiency, expressed as ventilation per unit of carbon dioxide production (i.e. VE/VCO₂ slope). While determinants of reduced VO₂ in HF are better known, those...
of increased VE/VCO₂ slope have not yet been fully elucidated, but might include an overactive ergoreceptor and chemoreceptor response. Piepoli et al. assessed exercise tolerance and ergoreflex activity in 92 stable patients with heart failure (34 in New York Heart Association class I, 27 in class II, and 31 in class III) and 28 age-matched normal controls. In this study, increased ergoreflex was correlated both with functional capacity and the ventilatory response to exercise (i.e. peak VO₂, VE/VCO₂ slope), especially in patients with worse symptoms, while CPET key parameters weakly correlated with left ventricular ejection fraction. Therefore, increased ergoreflex sensitivity could limit exercise tolerance by both causing a greater sensitivity to muscle fatigue and an early onset of dyspnoea. Indeed, ergoreceptor overactivity was shown to be the only independent predictor of peak VO₂ and VE/VCO₂ slope in patients with HF, especially in patients with cardiac cachexia. Nevertheless, very few studies so far have investigated the role of ergoreflex sensitivity in promoting the early fatigability and poor exercise tolerance characterizing HF patients, and a paradoxical reduction in muscle perfusion (secondary to an exaggerated vasoconstriction response) has been proposed as a possible mechanism. In addition, ergoreflex overactivation may also act centrally, by lowering cerebral perfusion, with an increased perception of fatigue and impaired motor drive, but future research should confirm such assumptions and their potential clinical implications.

Finally, ergoreflex activity might also contribute to the development of periodic breathing during exercise or exertional oscillatory ventilation, which is, similarly to peak VO₂ and VE/VCO₂ slope, a powerful predictor of poor prognosis. The main evidence of this link is the demonstration that ET might lead to a significant decrease in exertional oscillatory ventilation, reason-ably by decreasing ergoreflex sensitivity. Even the close relationship between cachexia and abnormalities in cardiopulmonary reflex control supports this hypothesis.

**Which component of the ergoreflex is overactive in heart failure patients?**

Between the end of the 1990s and the early 2000s, several studies confirmed the 'muscle hypothesis', mostly assessing the trend of ventilation during selective metaboreflex stimulation in HF patients. By using a 'softer' protocol than the one by Piepoli et al. (2 min of rhythmic handgrip instead of 5, 30% of maximal voluntary contraction instead of 40%) to assess metaboreflex sensitivity, Sterns et al. evaluated muscle sympathetic nerve activity (MSNA) during metaboreflex activation in 9 HF patients and 8 age-matched control subjects. MSNA can be defined as the relative contribution of stimulation of skeletal muscle metaboreceptors to overall exercise-dependant sympathoexcitation. While resting MSNA bursts per minute were higher in HF patients compared with healthy subjects, no difference in MSNA response was identified during static exercise. However, upon post-handgrip regional circulatory occlusion, MSNA response was significantly lower in HF patients than in controls. These observations prompted these Authors to propose that metaboreflex is blunted in HF, and the abnormal cardio-respiratory response to exercise may derive from an overactive mechanoreflex.

In the following years, Middlekauff and Sinoway evaluated extensively mechanoreflex sensitivity in patients with HF. The response to mechanoreflex stimulation was studied in terms of blood pressure and MSNA; the results suggest a mechanoreflex overactivity in HF patients. For example, MSNA increased significantly in HF patients during passive exercise, but not in healthy controls; low-level rhythmic handgrip and involuntary biceps contractions were associated with greater increases in renal vascular resistances in HF patients than controls.

During a debate between Piepoli et al. and Sterns et al., the two groups recapitulated the evidence of overactive metabo- or mechanoreflex in HF patients. As noted by Middlekauff and Sinoway and, ’the increased metaboreceptor sensitivity position largely depends on measurement of the ventilation, while the increased mechanoreceptor sensitivity position largely depends on neurovascular measurements’. We may hypothesize that muscle wasting increases the sensitivity of both metabo- and mechanoreflex. The mechanoreflex may be particularly important during the early phase of exercise, and, having a greater impact on blood pressure and MSNA, might be explored by measuring them; conversely, the metaboreflex may be mainly involved in the later phases, around or after the anaerobic threshold, and could be optimally assessed by measuring ventilation.

**Modulating ergoreflex sensitivity to treat heart failure: exercise training and beyond**

Exercise training was traditionally contraindicated in HF patients for fear of a further deterioration of left ventricular function. In the 1990s, many small trials have documented that ET increases peak VO₂, restores the autonomic balance under resting conditions, improves central haemodynamics during rest and exercise, possibly even prolonging survival. Many positive effects of ET on the skeletal muscle have been reported, with improved morphology, function, perfusion, metabolism, and ultrastructure. Additionally, ET is expected to increase exercise tolerance by reducing ergoreflex sensitivity. In fact, ET has been reported to prevent the sensitization of muscle afferents in rats with HF. In a study by Piepoli et al., 6 weeks of forearm training reduced metaboreceptor contribution to the cardio-respiratory response to exercise, more in HF patients than in control subjects (ventilation: −58% vs. −25%; diastolic pressure: −33% vs. −5%; leg vascular resistance: −60% vs. −8%), and 6 weeks of detraining nullified the benefits of ET. Notably, the recent observation that the beneficial effect of ET in patients with HF may be mediated, at least in part, by a reduction in the exaggerated sympathetic response to exercise seems to support the role of overactive ergoreflex in this context, both as a mediator of poor physical tolerance and as a target of exercise-therapy.
On a speculative note, sildenafil, a type 5 phosphodiesterase selective inhibitor, may modulate overactive ergoreflex signalling in HF, likely thanks to improved muscle perfusion, endothelial activity, and ventilatory efficiency. Prostaglandins and bradykinin may represent other interesting therapeutical targets for hyperactive ergoreflex in HF, since they are associated with muscle training and ergoreflex sensitivity. Another intervention that may have an indirect effect on the ergoreflex in HF is cardiac resynchronization therapy. Indeed, cardiac resynchronization therapy may postpone the anaerobic threshold and reduce ergoreflex hyperactivity, possibly by increasing muscular oxidative metabolism and reducing CO₂ chemosensitivity. Further studies, combining muscle biopsy and molecular analysis may help in the future to select promising targets associated with ergoreflex related pathways to be then pharmacologically or electrically modulated.

A ‘muscle hypothesis’ in neuromuscular disorders

Besides patients with chronic HF, the pathophysiological relevance of muscle wasting and ergoreflex deregulation has been reported in heart transplant recipients, whose exercise capacity is often impaired for a long time despite the restored cardiac function and seems to improve in parallel with a progressive resetting in the cardiovascular response to metaboreflex. Neuromuscular disease is another setting where characterizing ergoreflex sensitivity is highly relevant. Patients with neuromuscular disorders often show cardiac involvement, but they also frequently display exertional dyspnoea, adrenergic activation and vagal withdrawal, together with a progressive muscle wasting. While pathophysiological mechanisms are different between HF and neuromuscular disorders patients, it is reasonable to hypothesize that ergoreflex sensitivity is enhanced in both these conditions. In particular, the increased sympathetic tone demonstrated in patients with muscle dystrophies and mitochondrial myopathy has been ascribed to mechanoreflex overactivity, probably based on the studies by Middlekauff and Sinoway on neurovascular function during mechanoreflex stimulation. By contrast, Taivassalo et al. postulated a metaboreflex overactivity in patients with mitochondrial myopathy to explain their abnormal cardio-respiratory response to exercise.

By using the protocol defined by Piepoli et al. (see above), we demonstrated a metaboreflex overactivity in a 30-year-old woman.
Conclusions and future perspectives

The ergoreflex is a neural mechanism coupling ventilation and haemodynamic function to exercise intensity, which is crucial for respiratory and cardiovascular homeostasis, and is altered in HF contributing to HF symptoms and disease evolution (Graphical Abstract). Our comprehension of the physiologic roles of the ergoreflex is still incomplete. Some possible reasons are (i) the interaction between the two components (i.e. the metaboreflex and the mechanoreflex), (ii) the difficulty in eliciting a selective mechanoreflex response, (iii) the difficulty of a simultaneous evaluation of ventilation or neurovascular function, and (iv) the use of different protocols to assess the metaboreflex. These factors are also hindering our evaluation of the ergoreflex in disease conditions. We may add that most of the studies performed so far in HF patients investigated the metaboreflex contribution to cardiorespiratory responses of small mass muscles (i.e. handgrip) that are less relevant than large muscle masses to the development of exercise intolerance and dyspnoea. Indeed, cardiovascular and ventilatory responses to exercise are affected, in addition to intensity, also by the size of active muscle mass; this could affect both the magnitude of the responses and the relative contribution provided by the muscle metaboreflex. In the setting of HF, it would be particularly important to verify whether increased ergoreflex sensitivity predicts a worse prognosis, and whether its overactivity can be relieved by ET. Additionally, preliminary results point to increased ergoreflex sensitivity (and specifically the metaboreflex) in neuromuscular disorders. The presence of ergoreflex overactivity in diseases other than HF, such as neuromuscular disorders and the beneficial effects of ET should be verified to provide better care to these patients.

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