

Review

Exercise Intolerance in Heart Failure: Did We Forget the Brain?

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Exercise tolerance is affected in patients with heart failure (HF). Although the inability of the heart to pump blood to the working muscle has been the conventional mechanism proposed to explain the lowered capacity of patients with HF to exercise, evidence suggests that the pathophysiological mechanisms associated with their exercise intolerance is more complex. Recent findings indicate that lowered cerebral blood flow (CBF) and oxygenation likely represent limiting factors for exercise capacity in patients with HF. After an overview of cardiac and peripheral responses during acute and chronic exercise in healthy individuals, we succinctly review cardiac and noncardiac mechanisms by which HF influences exercise tolerance. We then consider how HF, comorbidity, and HF treatment influence CBF and oxygenation at rest and during exercise. Finally, we provide suggestions for further research to improve our understanding of the role of the brain in exercise intolerance in HF.

RÉSUMÉ

Chez les patients en insuffisance cardiaque, la tolérance à l'exercice est limitée. Jusqu'ici, cette limitation était expliquée par l'incapacité du cœur à pomper suffisamment de sang pour irriguer convenablement les muscles du corps pendant l'exercice, mais de nouvelles données suggèrent que les mécanismes physiopathologiques sous-jacents pourraient être beaucoup plus complexes que prévu. En effet, ces nouvelles données donnent à penser qu'une réduction du débit sanguin et de l'oxygénation du cerveau constitue l'un des facteurs limitant la capacité des patients atteints d'insuffisance cardiaque à faire de l'exercice. Après un survol des réponses cardiaques et périphériques en cours d'exercice, tant court que prolongé, chez des sujets en bonne santé, nous examinons succinctement les mécanismes cardiaques et autres de l'insuffisance cardiaque qui influent sur la tolérance à l'exercice. Nous traitons ensuite de la manière dont l'insuffisance cardiaque, son traitement de même que les comorbidités qui y sont associées influent sur le débit sanguin et l'oxygénation du cerveau au repos et pendant l'exercice. Enfin, nous présentons des pistes de recherche susceptibles d'améliorer notre compréhension du rôle du cerveau dans l'intolérance à l'exercice chez les patients atteints d'insuffisance cardiaque.

Exercise limitation is a hallmark of heart failure (HF). Traditionally perceived as a direct consequence of the inability of the diseased heart to pump blood to the working muscle, a significant amount of research has established that the pathophysiological mechanisms underlying the inability to tolerate exercise in HF is more complex, and the role of cardiac and peripheral factors is still under debate.¹ Recent evidence suggests that lowered cerebral blood flow (CBF) and

oxygenation may be limiting factors for exercise capacity in patients with type 2 diabetes and HF.^{2,3}

It has traditionally been thought that CBF remains normal even in patients with moderate to severe HF because of blood flow redistribution from cutaneous, splanchnic, renal, and skeletal muscle vascular beds.^{4,5} Nonetheless, accumulating evidence suggests that CBF, whether estimated by the ¹³³Xe injection method,⁶ transcranial Doppler ultrasonography,⁷ Doppler ultrasonography of extracranial arteries,⁸ or measured by radionuclide angiography,⁹ is reduced in patients with mild to severe HF. Although the mechanisms involved in CBF reduction in HF remain unclear, they may be related to a low cardiac output (CO) or vasoconstriction of the cerebrovasculature induced by higher activity of brain sympathetic nervous activity (SNA) and the renin-angiotensin-aldosterone system.^{10–13} Furthermore, common HF comorbidities such as atrial fibrillation, obesity, hypertension, diabetes, and sleep apnea have also been associated with a reduction in cerebral

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perfusion,¹⁴⁻¹⁸ which could worsen CBF regulation in patients with HF. Accordingly, abnormal CBF regulation induced by HF, whether directly or indirectly through its comorbidities or treatment, could affect CBF and oxygenation and be a key player in exercise intolerance reported in these patients.

Normal Cardiac and Noncardiac Adaptations to Acute and Chronic Exercise

Cardiac factors

CO increases with exercise intensity until maximal oxygen consumption ($\dot{V}O_{2\max}$) is reached. This elevation in CO is the consequence of a progressive and linear increase in heart rate (HR) with exercise intensity until maximal effort and a curvilinear rise in stroke volume (SV), which occurs early after onset of exercise and up to $\sim 50\%$ $\dot{V}O_{2\max}$. The elevation in HR is a result of a reduction in parasympathetic stimulation of the cardiac pacemaker cells of the sinoatrial node combined with higher cardiac sympathetic activity (influencing HR at higher exercise intensities). The increase in SV results mainly from a greater force of contraction through an increase in left ventricular end-diastolic volume induced by an enhanced venous return, stretching cardiac muscle fibers (Frank-Starling mechanism), and increased ventricular contractility secondary to catecholamine-mediated sympathetic stimulation.¹⁹

Resting and submaximal CO remain unchanged after endurance exercise training, which is a consequence of opposite effects of exercise training on HR and SV. Indeed, although resting and submaximal HR is lowered after endurance training, SV is increased at rest and submaximal exercise. An increase in plasma volume induced by endurance training, leading to augmented venous return and left ventricular end-diastolic volume, are factors contributing to increased SV. Training also influences the structure of the heart. Important adaptations include ventricular dilation (short-term) and hypertrophy of cardiac muscle fibers (long-term). These adaptations also contribute to increased SV with endurance training. At maximal exercise, CO is increased after endurance training, secondary to an elevated SV, because training does not change or might slightly reduce maximal HR.²⁰

Noncardiac factors

Blood vessels regulate their own flow according to the metabolic demand of surrounding tissues. During exercise, there is an increase in blood flow (85%-90% of CO) to working muscles, which is shunted away from the skin and renal, splanchnic, and hepatic beds. This redistribution of blood flow in response to exercise is accomplished by nervous and hormonal regulation. Vasoconstriction is necessary not only for an efficient redistribution of blood flow to meet the metabolic demand of working muscles but also to maintain blood pressure that would otherwise be threatened by the important vasodilatory capacity of the peripheral circulation.²¹ Notwithstanding the vasoconstriction taking place in the skin and viscera, total peripheral resistance decreases during exercise (functional sympatholysis), highly influenced by the presence of vasodilation in working muscles induced by local metabolic factors.

Endurance training is associated with improved capacity for blood flow toward working muscles induced by a higher number of capillaries in skeletal muscles. The higher capacity for blood flow with endurance training is associated with lowered total peripheral resistance. Consequently, increased left ventricular contractility may occur against a lower afterload.²² Endurance training also leads to significant metabolic adaptations in skeletal muscle, such as increases in both the size and number of mitochondria as well as in the activity of oxidative enzymes.²³

Exercise and the Failing Heart: Cardiac and Noncardiac Adaptations

Cardiac factors

Patients with HF and reduced ejection fraction (HFrEF) have attenuated CO during maximal exercise when compared with healthy controls, and the decrease in CO during exercise correlates with HF severity.^{24,25} The decreased CO during exercise is driven by a reduction in maximal HR and a lower HR reserve, amplified by the fact that patients with HF have higher resting HRs.²⁶ Also, the increase in SV normally occurring during exercise is attenuated in patients with HF, contributing to the decreased CO during exercise.²⁷ The correlation between maximal exercise CO and peak oxygen consumption ($\dot{V}O_{2\text{peak}}$) is excellent (cf. the Fick equation),²⁵ rationalizing the use of $\dot{V}O_{2\text{peak}}$ to select patients for advanced HF therapy, such as implantable left ventricular assist devices (LVADs) or cardiac transplantation. Of note, a recent study suggested that oxygen uptake kinetics during recovery from cardiopulmonary exercise testing may also represent an important prognostic marker of death, mechanical heart implantation, and cardiac transplantation.²⁸ In contrast, there is poor correlation between measures of cardiac function at rest and $\dot{V}O_{2\text{peak}}$, including CO or left-sided filling pressures.²⁵ In HF, left ventricular ejection fraction (LVEF) at rest does not correlate with $\dot{V}O_{2\text{peak}}$ and correlates moderately, at best, during exercise.^{1,26,29} Interestingly, right ventricular ejection fraction has been reported to correlate better with exercise capacity,^{30,31} although this finding has not been reproduced in all studies.³²

In patients with HF and preserved ejection fraction (HFpEF), primarily caused by left ventricular diastolic dysfunction, $\dot{V}O_{2\text{peak}}$ is closely correlated to exercise CO,³³ but there are significant hemodynamic differences between the response to exercise in patients with HFrEF compared with patients with HFpEF. Despite similar symptoms (New York Heart Association class), $\dot{V}O_{2\text{peak}}$ (and consequently exercise CO) is preserved to a greater extent in patients with HFpEF than in patients with HFrEF.³⁴ Exercise CO in HFpEF is limited to some degree by an inadequate increase in SV owing to limited left ventricular end-diastolic reserve, but recent studies have shown that inadequate chronotropic response is a more important determinant of exercise CO in these patients.³⁵ Exercise in patients with HFpEF is characterized by an abrupt and often prominent increase in left ventricular filling pressures (typically estimated by pulmonary capillary wedge pressure [PCWP]) with very early onset, which has been shown to be associated with dyspnea.³⁶⁻³⁸ Inadequate reduction in afterload during exercise, likely

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