

OPINION ARTICLE

Heart Failure as a Limitation of Cardiac Power Output

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There is perhaps no more poorly defined, yet widely impactful, pathological condition as heart failure.

Lilly et al. offer the following definition¹:

Heart failure is present when the heart is unable to pump blood forward at a sufficient rate to meet the metabolic demands of the body or is able to do so only if cardiac filling pressures are abnormally high.

This succinct definition averts the common misconception that heart failure always involves an impairment of baseline resting cardiac output. The definition also places necessary emphasis on the systemic, whole-body nature of the condition, with elevated preloads indicative of a volume-compensated or volume-overloaded state. Recent investigations place an even greater emphasis on contributing peripheral factors and identify an impairment of recruitable reserve oxygen delivery as a defining feature of heart failure. Despite the high degree of variability in the etiology and diagnosis of heart failure, exercise intolerance may be the unifying feature of this complex syndrome. Certainly, exercise intolerance—manifest, for example, as fatigue or dyspnea—represents a primary clinical complaint. Exercise intolerance, which may be assessed as diminished maximal aerobic capacity (MAC, or VO₂max), is among the strongest predictors of cardiovascular and all-cause mortality². Considering the pathway of oxygen from air to mitochondrion, illustrated in [Figure 1](#), we note that defects in physiological processes underlying each transport step in this pathway are implicated in the etiologies of heart failure³.

The delivery of oxygen via the circulatory blood to the periphery is centrally important in the pathway for oxygen transport. Thus it is not surprising that, similar and related to exercise capacity, the cardiopulmonary system's reserve capacity to generate mechanical power to deliver cardiac output is strongly predictive of mortality in heart failure⁴. In fact, a 2021 study

by Anand et al.⁵ demonstrates the strong prognostic value of cardiac power reserve in patients with normal ejection fraction. Moreover, computational analysis of clinically obtained data demonstrates clear systolic dysfunction in a substantial subset of heart failure patients with normal ejection fraction⁶. These findings suggest that ejection fraction is not an ideal metric of systolic function and that, like exercise intolerance, an impaired ability to recruit reserve cardiac power is a fundamental defining feature of heart failure regardless of ejection fraction. Of course, maximal voluntary cardiac power output occurs at VO₂max. And thus an impairment to reserve cardiac power output implies an impairment in VO₂max and exercise capacity. Cardiac power output capacity is not solely an intrinsic property of the heart. Physiologically, recruitment of cardiac power and output in exercise is elicited via four major mechanisms acting through the autonomic nervous system and the peripheral vasculature ([Figure 1](#)): positive inotropy; positive chronotropy; systemic vasoconstriction; and local metabolic-mediated vasodilation. Each of these four mechanisms is necessary, and none sufficient, for the physiological recruitment of cardiac output in exercise⁷. Indeed, deficiencies in both peripheral vasoregulatory mechanisms and central pump function are found to contribute to the exercise intolerance phenotype in heart failure³.

Focusing specifically on the myocardium, it has been long understood that mechanical pumping dysfunction in heart failure is associated with metabolic energetic dysfunction. This relationship is not surprising since myocardial mechanical work is driven by hydrolysis of ATP, which must be synthesized at free energy levels needed to drive excitation-contraction coupling⁸. In fact, myocardial energetic dysfunction is similarly observed in heart failure with reduced and preserved ejection fraction⁹, again suggesting a unifying abnormality in myocardial (metabolic and mechanic) *power capacity* as a driver of heart failure. Adopting this view of impaired power capacity as a criti-

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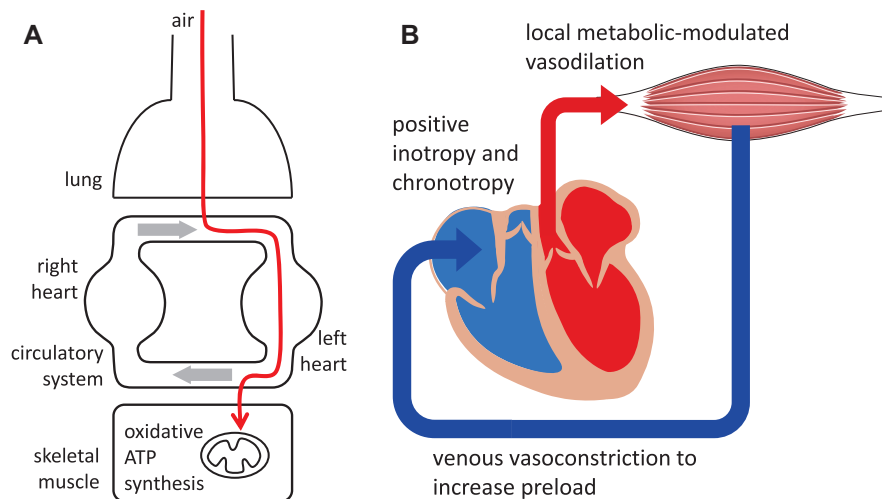


Figure 1. Factors governing whole-body oxygen transport. **A.** The pathway for oxygen from air to mitochondrial in peripheral skeletal muscle is illustrated. **B.** Diagram illustrates the four main physiological mechanisms driving recruitment of cardiac power and output in exercise: positive inotropy; positive chronotropy; systemic vasoconstriction; and local metabolic-mediated vasodilation. Diagram in Panel A adapted from Weibel¹⁰.

cal defining feature of heart failure, the following revision to the Lilly definition of heart failure may be suggested:

Heart failure is present when the heart is unable to generate sufficient cardiac power to meet the metabolic demands of the body at rest or exercise, or is able to meet metabolic demands only if cardiac filling pressures are abnormally high.

This definition supports a perspective on how numerous factors (including peripheral vascular, autonomic, and myocardial mechanical and metabolic mechanisms) work together in the recruitment of cardiac power reserve, and how dysfunction of multiple mechanisms and on multiple levels can drive impairment of cardiac power.

Finally, mechanisms underlying the recruitment of cardiac power may be fully understood only in terms of how they work together in the integrated system of the heart and the periphery. For example, recruitment of reserve cardiac power requires recruitment of oxidative ATP synthesis in the myocardium. Recruitment of ATP synthesis capacity relies on increased myocardial perfusion, while myocardial perfusion depends on local metabolic signaling and is driven by the systolic and diastolic mechanics of the myocardium. A perturbation to any of these processes (systolic and diastolic mechanics, myocardial perfusion, and myocardial metabolism) will necessarily affect all the others. Thus, furthering our understanding of the mechanisms governing cardiac mechanical and metabolic power capacity in health and disease calls for integrative multi-scale multi-systems research approaches.

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Conflict of Interest Declaration

DAB holds the position of Editorial Board Member for *Function* and is blinded from reviewing or making decisions for the manuscript.

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