THE HEART is the most energetically demanding organ in the human body, with mitochondrial oxidative phosphorylation turning over up to 6 kg of ATP each day to meet the requirements of contraction, via myosin-ATPase, and ion movements, via the Ca$^{2+}$ pumps and Na$^+${-}K$^+$-{ATPase. Chronic heart failure, which affects 2% of adults in the developed world, is characterized by impaired cardiac energy reserves (8), which correlate well with clinical symptoms, including breathlessness and fatigue, and predict mortality better than many measures of cardiac function including left ventricular ejection fraction. Underlying the poor energetics of the failing heart are persistent abnormalities in mitochondrial function, such as impaired oxidative capacity, excess reactive oxygen species (ROS) generation, and mitochondrial uncoupling (6, 7). These abnormalities in some ways epitomize the progressive nature of heart failure, as initially adaptive responses become maladaptive in the long-term contributing to further mitochondrial dysfunction and spiraling energetic decline (7). There is therefore great demand for novel therapeutic approaches that aim to redress the energetic defects of the failing heart, and different exercise training regimens have garnered attention as potentially efficacious treatment strategies.

Heart failure patients were once advised against engaging in any physical activity, yet the beneficial effects of training during rehabilitation are now firmly established, with improvements seen in quality of life and morbidity/mortality as well as decreased susceptibility to fatigue (2). Endurance training protocols promote dramatic improvements in skeletal muscle oxidative capacity in both patients with chronic heart failure and experimental animal models (9). Moreover, in rats with experimental heart failure, endurance training brought about ventricular remodeling, enhanced contraction, and improved Ca$^{2+}$ handling; yet in contrast to skeletal muscle, no modifications in cardiac mitochondrial function or energetics were found (9).

Recently, high intensity aerobic interval training (at 95% of peak heart rate) was found to have a substantially superior effect on cardiovascular function in patients with post-infarction heart failure when compared with isoclonic moderate continuous training (at 70% of peak heart rate), with improvements noted in maximal oxygen uptake, work economy, cardiac output, and diastolic function (10). Additionally, in the same study, protein levels of the mitochondrial biogenesis factor, PGC1$\alpha$, were elevated in the skeletal muscle of the high intensity trained group, alongside an enhanced antioxidant capacity (10). High intensity interval training (HIT) is therefore known to enhance oxygen consumption in skeletal muscle (1, 10), yet the effects on cardiac energy metabolism remained unclear.

In a study reported in the Journal of Applied Physiology, Hafstad and colleagues (3) set out to investigate the consequences of different training intensities for cardiac metabolism, by subjecting mice to 10 wk of treadmill running using HIT (10 bouts of 4 min at 85–90% $\dot{V}$O$_{2\max}$) or distance-matched moderate intensity continuous training (MIT; at 70% $\dot{V}$O$_{2\max}$). The authors carried out a comprehensive study of the effects of these two regimens, including measures of aerobic capacity, transcriptional changes, mitochondrial function, and citrate synthase activity (a marker of mitochondrial density), as well as detailed analysis of substrate utilization, contractile function, and oxygen consumption in the isolated perfused working heart.

Compared with sedentary controls, both training regimens elicited the same degree of cardiac hypertrophy and, interestingly, similar increases in skeletal muscle citrate synthase activity. Only HIT, however, resulted in an increase in cardiac citrate synthase activity, suggesting that a greater training intensity is required to stimulate mitochondrial biogenesis in the heart compared with skeletal muscle. Moreover, in support of this finding, the maximum rate of mitochondrial oxygen consumption in cardiac muscle fibers increased following HIT but not MIT, suggesting an elevated capacity to synthesize ATP. Meanwhile, a partial switch in myosin heavy chain (MHC) isoform, from βMHC to αMHC, occurred in HIT hearts, potentially increasing myosin-ATPase activity and thereby complementing the enhanced mitochondrial function.

To determine whether these bioenergetic alterations affected ventricular function and efficiency the authors measured cardiac work and metabolism in electrically paced isolated working hearts. Although absolute measures of aortic flow and stroke volume increased following HIT, this was found to scale with the increased heart size. Cardiac efficiency, however, assessed from the relationship between hydraulic work and cardiac output, was improved by HIT, though not MIT, due to a decreased oxygen demand from basal metabolic processes. Two further findings suggested possible mechanisms for this. First, HIT induced a myocardial substrate switch toward glucose oxidation and away from relatively inefficient fatty acid oxidation, accounting for some of the decreased oxygen demand. Notably, however, the actual improvement in efficiency in the HIT hearts exceeded the amount permissible by even a 100% switch to glucose use, hence an additional fall in oxygen demand remained unaccounted for. Second, expression of the antioxidant enzymes catalase and superoxide dismutase was elevated in hearts following HIT but not MIT. These enzymes decrease levels of ROS, which are known to activate the mitochondrial uncoupling proteins (UCPs), themselves possible agents of decreased cardiac efficiency. Interestingly, plasma levels of free fatty acids, also known to activate UCP expression and activity, fell following HIT, but were also decreased in MIT mice. As might be expected, aerobic capacity improved following both training regimens, as shown by enhanced $\dot{V}$O$_{2\max}$ alongside an increased running speed at $\dot{V}$O$_{2\max}$, however, a more pronounced...
improvement was noted with HIT than MIT. It is tempting, therefore, to suggest that the enhanced cardiac training effect of the former regimen, increasing oxidative capacity, myosin-ATPase activity, and cardiac efficiency might underlie this additional gain in performance.

Increased glucose oxidation, enhanced antioxidant enzyme expression, and an MHC isoform switch all point strongly toward hypoxia-driven transcriptional changes in the HIT heart, since similar alterations occur in hypoxic cells and skeletal muscle (5). The major cellular effector of such transcriptional changes in hypoxia is HIF-1α, and there are signs of its activation in the HIT heart, most notably the upregulation of the HIF target genes, vegf, ldh, and the glycolytic enzyme hk. Moreover, HIF activation is associated with downregulation of ppara expression in some tissues (5), and in the HIT heart this probably drives the observed decrease in fatty acid oxidation. Transient muscle hypoxia during exercise is thought to stimulate some beneficial training effects such as mitochondrial biogenesis, yet the findings in this study suggest that while moderate exercise can stimulate this in skeletal muscle, oxygen tension is only decreased in the myocardium at the high workloads associated with HIT.

A possible contradiction remains, however, in that sustained hypoxia is known to promote a loss of mitochondria in cultured cells and skeletal muscle (5) and also results in decreased cardiac energy reserves (4), so how might an hypoxic stimulus drive improvements in oxidative capacity? A resolution probably lies in the transient nature of the hypoxic stimulus during intense training, which would expedite the short-term loss of ATP reserves, activating the cellular energy sensor AMPK and in turn promoting mitochondrial biogenesis (via PGC1α), but without stimulating mitochondrial autophagy. The time dependency of the mitochondrial response to hypoxia, however, needs clarification, not least because of the widespread use of hypoxia as a supplementary stimulus in a variety of as yet incompletely understood training regimens.

This important work of Hafstad and colleagues has shed much light on the significance of training intensity for eliciting metabolic improvements in the myocardium and hence the therapeutic potential of HIT for heart failure patients. Improvements in oxidative capacity, antioxidant reserve, and cardiac efficiency would directly address many of the contributing factors thought to underlie the energetic abnormalities of the failing heart. Future studies to determine the cardiometabolic and mechanoenergetic effects of HIT in experimental models of heart failure should now be carried out. It clear, however, that when it comes to the myocardium, not all exercise training is equally beneficial, and high intensity training could prove to be a vital therapeutic strategy for treating those patients who were once prescribed bed rest.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

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