Heart failure is the major cause of morbidity and mortality in the developed world, with over 5 million people afflicted in the U.S. alone (1). From 30% to 40% of patients die within the first year after receiving the diagnosis of heart failure (1). Further, heart failure consumes a significant amount of resources, and this is only likely to increase as the population ages. Consequently, the development of therapeutic strategies to improve outcomes and slow or halt the progression of heart failure is a major goal of clinical cardiovascular investigation. Development of successful therapeutic strategies is predicated on a clear understanding of the pathophysiology of heart failure. Although heart failure is a diverse group of diseases with numerous etiologies, one common pathophysiological abnormality is perturbation of myocardial energetics, also known as the “energy-depletion” hypothesis (2). The alterations in cardiac energy metabolism in patients with heart failure are extensive and include initially increased glucose utilization followed by reduced glucose and fatty acid utilization, decreased production of high energy phosphates, reduced oxygen consumption and respiratory chain function as well as diminished amounts of creatine kinase, phosphocreatine, and creatine kinase transfer activity (2–11). In contrast, free adenosine diphosphate (ADP) concentration and uncoupling protein activity increase, both of which inhibit cardiac function (2,12). These changes can be detected using phosphorus-31 magnetic resonance spectroscopy, which shows reduced levels of phosphocreatine (PCr), adenosine triphosphate (ATP), and the PCr/ATP ratio in patients with heart failure (2,13,14). Numer-
myocyte myofibrils (2). Myocardial ATP levels remain stable until the very late stages of heart failure (13,33,34). In order to maintain ATP levels when ATP consumption exceeds ATP synthesis, PCr levels fall as high-energy phosphates are transferred to ADP to form ATP, thus resulting in a reduction in the PCr/ATP ratio (13,35). In addition, the creatine transporter in the mitochondria is down-regulated in patients with chronic heart failure, resulting in a decline in creatine levels, and this further depresses the PCr/ATP ratio (36,37). Energy-consumptive therapies such as positive inotropic agents increase ADP concentrations, which inhibit myocardial contractility (12). The extent of reduction in PCr/ATP ratios correlates with New York Heart Association functional class, with greater reductions in the ratios with more severe classes of heart failure (which are defined by the extent of limitations in exercise tolerance) (32) and with systolic (38) and diastolic function (39). A small study of 39 patients with heart failure and idiopathic dilated cardiomyopathy showed that the PCr/ATP ratio as assessed by phosphorus-31 magnetic resonance spectroscopy may be a more robust predictor of cardiovascular and all-cause mortality and may be superior to other predictors of outcomes such as exercise capacity (40).

With this background, the idea of determining the effect of exercise training on high-energy phosphate concentrations as assessed by phosphorus-31 magnetic resonance spectroscopy is very timely. In the study by Beer et al. (19), 24 sedentary patients with nonischemic dilated cardiomyopathies were randomized to an exercise training group or a control group. All patients underwent baseline maximal exercise stress testing, magnetic resonance imaging, and phosphorus-31 magnetic resonance spectroscopy as well as follow-up studies 2 and 8 months later. The exercise training group underwent 5 45-min training sessions per week for 2 months and were then encouraged to continue exercise from 2 to 8 months. The control group received no such training. For the exercise group, there was a 17% increase in maximal VO_2 and a 13% increase in exercise time. No such improvement was seen in the control group. Further, the (LV) ejection fraction was improved and LV dimensions were also seen in the exercise training group but not the control group after long-term (8 month) but not short-term exercise training. This observation confirmed the results of other studies (27). Thus, exercise training had a beneficial effect on exercise tolerance, LV function, and dimensions. With regard to myocardial energetics, there was no significant change in the PCr concentration in patients in the exercise and in the control groups. Thus, exercise training did not decrease myocardial energy consumption. In fact, there was some evidence that exercise training improved LV work power, LV work power/gram and LV work power, and forward work efficiency, though these differences were not statistically significant. This was not seen in the control group. Thus, as with ACE inhibitors and beta-blockers, exercise training can produce improvements in exercise tolerance and cardiac structure and function.

There are issues not addressed by the study of Beer et al. (19). The exact doses of heart failure therapies taken by the patients was not well defined, so we do not know if these patients were receiving maximal medical therapy in terms of ACE inhibitor and beta-blocker doses. Whether maximal therapeutic doses of these agents would improve myocardial work efficiency is therefore unknown. Additionally, the patients enrolled in this study were Weber class A and B (New York Heart Association functional class II) in terms of their symptoms and thus had relatively preferred exercise tolerance for heart failure patients. Whether the benefits seen in these patients with mild-moderate heart failure in terms of preserved myocardial energetics can be extrapolated to patients with more severe heart failure (Weber class C and D) is not clear. Not only is it unclear whether these patients will have improvements in exercise tolerance and ventricular function as a result of exercise training but the effect on myocardial energetics in these patients, whose pre-training PCr/ATP ratios are more perturbed than those enrolled in this study, is also not clear.

The study by Beer et al. (19) provides preliminary evidence that exercise training in a small group of patients with mild to moderate systolic heart failure as defined by Weber class, in addition to its benefits for improving exercise capacity and LV function, is energy sparing as are other therapies associated with improved outcomes such as ACE inhibitors and beta-blockers (4,6,7,15,20). Further investigations in larger groups of patients will be required to further clarify the effects of exercise training on myocardial energetics. The study by Beer et al. (19) does not appear to be powered to demonstrate whether exercise training improves forward work efficiency and LV work power, and a larger study will need to be performed to demonstrate if exercise training translates into a fundamental improvement in myocardial work and efficiency. The patient population was one with well preserved exercise tolerance as they were Weber class A and B. These patients tend to have a better prognosis. What will be even more crucial will be to determine if patients who are Weber class C and D, and thus have greater limitations to exercise tolerance and worse outcomes, have similar benefits from exercise training, including improved exercise tolerance and LV function with either no deleterious effect on myocardial energetics or even improvement in myocardial work and efficiency. This may be more easily demonstrated in this patient population as they have greater perturbation of high-energy phosphate concentrations, including a reduction in myocardial ATP concentration in some patients (32). It also may be more likely to demonstrate a survival benefit from exercise training in patients with heart failure who have more severe functional limitations and thus have worse outcomes and more clinical events. In particular, a larger study involving patients with more advanced heart failure would be necessary to determine if exercise training has a beneficial effect.
on survival as well as whether assessments of myocardial energetics such as PCr/ATP ratios can predict outcomes in these patients. Such a study might also include more long-term supervised exercise training beyond the 2-month period in the study by Beer et al. (19). This might more successfully demonstrate a survival benefit for exercise as well as improvement in myocardial work and efficiency. As to whether a larger study might demonstrate salutary effects on right ventricular function from exercise training, this may be more difficult to predict and to accomplish.

In summary, Beer et al. (19) have provided evidence that exercise training in patients with Weber class A and B heart failure improves exercise performance and ventricular function without adverse effects on myocardial energetics. This provides further justification for exercise training as adjunctive therapy in these patients.

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