I was particularly interested in the paper published in Cardiovascular Research (30, 413–418) by Gordon and co-workers entitled: Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. One of the objectives of their study was to evaluate the effects of creatine supplementation (20 g daily for 10 days) on ejection fraction in patients with congestive heart failure. A number of pointers have appeared in the literature which suggests the rational behind such an approach to increase ejection fraction is flawed.

As pointed out by Gordon and co-workers, intracellular creatine is decreased in cardiac hypertrophy and failure [1]. On the basis of work showing that creatine loading of skeletal muscle can increase skeletal muscle performance during high-intensity exercise [2], Gordon and co-workers imply that creatine loading of myocytes may aid their contractile function. However, it would be incorrect to assume that creatine has the same importance in high-energy phosphate transduction and muscle performance in the two muscle types. The creatine kinase system is thought to act primarily as a temporal high-energy phosphate buffer in skeletal muscle during high-intensity exercise [3]. As such, the system is central in maintaining the cellular ATP concentration during the first few seconds of exercise prior to activation of glycogen phosphorylase and consequently in maintaining muscle force development. It follows that increasing intracellular creatine and its phosphorylated form will attenuate the rapid depletion of this high-energy phosphate reserve during the first few seconds of exercise and thus increase muscle performance. The creatine kinase system in cardiac tissue is thought to act primarily as a spatial high-energy phosphate buffer [3]. During the normal contractile cycle, over a wide range of cardiac output, the phosphocreatine concentration changes little if at all [4]. Thus, during normal physiology, phosphocreatine is not depleted to the same extent of that in skeletal muscle. The relatively minor changes in phosphocreatine during a wide range of cardiac output suggest that loading the heart with creatine will not improve contractile function and ejection fraction. The obvious exception to the impunity of cardiac function with respect to the intracellular creatine and phosphocreatine concentration is if these metabolites fall below the $K_m$ values for their various cellular functions. The two most important functions of the creatine kinase system to examine are those at the inner mitochondrial membrane and the cellular contractile machinery [5]. Mitochondrial creatine kinase is co-localised with the adenine nucleotide translocator at the inner mitochondrial membrane. Through the law of local mass action, creatine pushes the local creatine kinase reaction towards production of ADP, thus amplifying the local ADP concentration and stimulating respiration [6]. Valdur Saks [7] has estimated the $K_m$ for creatine with respect to stimulation of mitochondrial respiration in saponin-skinned fibres to be 6.25 (0.21) mM. The physiological concentration of creatine is approximately 15–20 mM [8], at least double the value of the $K_m$. As suggested by Gordon and co-workers, the intracellular creatine concentration is decreased by approximately 20% during cardiac hypertrophy and failure (approximately down to 12–16 mM). This allows one to suggest that since creatine is in excess of the $K_m$ value for this metabolite even during cardiac failure, one would not expect to see any effect from creatine loading. A similar conclusion may be drawn when examining the creatine kinase system localised at the cellular contractile machinery. Phosphocreatine is thought to act to buffer the local ATP/ADP ratio in the vicinity of the myosin ATPase, thus maintaining the Gibbs free energy of ATP hydrolysis [5]. The $K_m$ of phosphocreatine with respect to this activity is 1.67 mM [9]. I am aware of no reports in the literature showing that phosphocreatine is reduced below this value during cardiac hypertrophy or failure. Thus our present understanding of the creatine kinase system in the myocardium allows us to predict the lack of efficacy of creatine supplementation in treating the failing myocardium.

This view does not detract from the very interesting
findings reported by Gordon and co-workers with regard to the beneficial effects of creatine supplementation on exercise performance. As the authors point out, a 10–20% improvement in exercise performance may be of considerable help to such patients. It would be remiss not to mention the current interest in supplementary phosphocreatine as a treatment for acute myocardial infarction. Its cardioprotective effect in this respect is primarily, but not exclusively, extracellular (see review [10]).

References


