Response to Exercise Generates Lactate and Fluid Intake: Effects on Mitochondrial Function in Heart and Vascular Smooth Muscle

We thank Thornton and Hess for their comments on our article and its editorial commentary. We understand the possible effects of lactate on mitochondrial function. Indeed, recent data place lactate as an active metabolite capable of moving between cells, tissues, and organs, where it may be oxidized as a fuel or reconverted to form pyruvate or glucose. Lactate is also capable of entering cells via the monocarboxylate transporter protein shuttle system. However, our concern is that data on mitochondrial dysfunction acquired in patients with end-stage heart failure do not help us in understanding the involvement of mitochondria in the disease process.

Endurance exercise increases the size and number of mitochondria and increases monocarboxylate transporter 1 density in skeletal muscle. Increased monocarboxylate transporter 1 content with exercise is likely to increase cellular and mitochondrial lactate influx, but it remains unclear whether this lactate influx enhances mitochondrial function in patients with heart failure. A single bout of exercise is shown to induce a rapid increase in mitochondrial biogenesis that is mediated by activation of Akt and increased expression of a transcription coactivator, peroxisome proliferator-activated receptor-α coactivator 1α. A recent study reported that mammalian target of rapamycin (mTOR), a kinase that regulates cell growth, size, and survival, is necessary for the maintenance of mitochondrial oxidative function. Computational genomics identified the transcription factor yin-yang 1 as a common target of mTOR and peroxisome proliferator-activated receptor-γ coactivator 1α. It is, thus, possible that exercise-induced activation of phosphatidylinositol 3-kinase (p110α)-Akt-mTOR signaling may have upregulated mitochondrial gene expression in the cardiovascular system through the direct modulation of yin-yang 1-peroxisome proliferator-activated receptor-γ coactivator 1α activity. If mitochondrial dysfunction is found to play a primary role in the development of heart failure, targeting early events in mitochondrial dysfunction may help to design therapies to prevent the development of heart failure before reaching an end stage.

Changes in cell hydration are registered by osmosensing structures, which then trigger signals involved in the control of metabolism and gene expression. Hypovolemia could be linked to tissue hypoxia. Chronic hypoxia activates the hypoxia-inducible factor 1 system, leading to the decrease in mitochondrial use of oxygen and to the initiation of glycolytic pathways. In our study, the downregulation of hypoxia-inducible factor 1α and other angio-

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Disclosures
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