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Letters

TO THE EDITOR

Perhexiline, Cardiac Energetics, and Heart Failure

Lessons From the First Law of Thermodynamics

"The sum of the actual and potential energies in the universe is unchangeable."
—William J.M. Rankine, 1853 (1)

We read with interest the recent study by Beadle et al. (2), describing the improvement in cardiac energetics of patients with heart failure treated with perhexiline. One of the investigators' main conclusions is that perhexiline improves cardiac energetics without evidence of altered cardiac substrate utilization. On the basis of the First Law of Thermodynamics and on our experimental observations (3,4), we offer a different interpretation.

The heart is a self-renewing biological pump that converts chemical energy into mechanical energy, with some energy loss as heat and kinetic energy. As in any other system, energy transfer in the cardiovascular system obeys the First Law of Thermodynamics, which states that within a closed system, energy can only be converted from one form into another (4). This principle was first proposed by Helmholtz in his treatise "On the Conservation of Force" (1847) and summarized by William Rankin in 1853 as follows: "…The sum of the actual and potential energies in the universe is unchangeable" (1).

Based on this law, and assuming no change in cardiac power after treatment in either group (data not provided), the improvement in phosphocreatine (PCr)/ATP ratio observed in the hearts of patients treated with perhexiline (2) may be explained by either the switch from the predominant oxidation of one energy providing substrate to another; increased efficiency in energy provision from the oxidation of the same substrates by decreased energy loss as heat or kinetic energy; or a sum of these mechanisms.

The authors' conclusion is based on the fact that there were no differences between the 2 groups in cross-heart respiratory exchange ratio or cardiac metabolite extraction. However, these measurements were only performed after the intervention, at a point where there were already no differences in PCr/ATP between the groups. The authors comment that, despite this, one would have expected a difference in the transmyocardial substrate differences and/or the respiratory quotient if perhexiline worked through substrate switches. Without any pre-treatment data, this cannot be determined.

In addition, the authors comment that the lack of difference in blood substrate levels between the groups further supported their hypothesis. The reader appreciates the data on glucose, glycerol, lactate, NEFA, triglycerides, pyruvate, and insulin. However, neither amino acids nor ketone bodies have been taken into consideration, both of which can be used by the heart as fuel given its omnivorous nature (3,4). In addition, the heart's endogenous fuels, glycogen and triglycerides have been overlooked (4).

An interesting aspect would be to measure energy loss as heat production and, perhaps even more interesting, to measure differences in turbulent kinetic energy before and after drug treatment, because increased energy loss as turbulent flow occurs in patients with dilated cardiomyopathy (5).

In summary, the work by Beadle et al. (2) points to a promising metabolic approach to improve contractile efficiency in heart failure. However, when considering the results, the flow of energy and First Law of Thermodynamics are still valid.

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REPLY: Perhexiline, Cardiac Energetics, and Heart Failure

Lessons From the First Law of Thermodynamics

We thank Drs. Davogustto and Taegtmeyer for their interest in our recent work (1) and for stressing the importance of the First Law of Thermodynamics. We concur that our data do not completely exclude a shift in the dominant substrate use as a mechanism; however, when considered in light of the previous study by Unger et al. (2), we nevertheless contend that it raises the possibility of an alternative or additional mechanism of action of perhexiline. Several of these were discussed in the paper, but these may include an increase in the efficiency of generation of energy from the same substrates, for example through reduced mitochondrial uncoupling. In heart failure, a reduction in CK activity has previously been reported (3) that appears in part as a result of increased oxidative stress, and partially corrected acutely by allopurinol (4). Perhexiline has been reported to reduce NADPH oxidase activity and to reduce cardiac TxNIP levels. Either or both of these mechanisms might contribute to a shift in the ratio of PCr to ATP.

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Please note: Prof. Frenneaux is an inventor of a method of use patent for perhexiline in heart muscle disease. Dr. Beadle has reported that he has no relationships relevant to the contents of this paper to disclose.

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