Perhexiline: Lessons for Heart Failure Therapeutics*

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In heart failure with reduced ejection fraction, mechanical work produced by the left ventricle to support the systemic circulation decreases over time despite relatively constant myocardial oxygen consumption. The resulting decrease in the ratio of mechanical work to oxygen consumed, or mechanical efficiency, is a cardinal feature of heart failure (1). Extensive research in experimental models and human subjects has shown that treatment with neurohormonal blockade and cardiac resynchronization induces secondary improvements in efficiency in patients with heart failure over time. As such, there has been a long-standing interest in understanding cardiac metabolism with the goal of improving efficiency as a primary therapeutic target (2).

Although myocytes can metabolize a variety of substrates to generate adenosine triphosphate (ATP), their principal energy source is fatty acids, which are metabolized in the presence of oxygen through beta-oxidation within mitochondria. Myocytes also produce ATP through glycolysis, and although slightly fewer molecules of ATP are produced per carbon-equivalent of fuel consumed, glycolysis is far more efficient in terms of oxygen cost. This provides a rationale to test whether agents that inhibit beta-oxidation, or that promote glycolysis, improve cardiac energetics and function in heart failure. Perhexiline, which has been investigated or used clinically since the 1970s, reduces fatty acid oxidation by inhibiting carnitine palmitoyltransferase-1 and -2 (CPT-1/2), transport proteins that shuttle fatty acids from the cytoplasm into mitochondria (3). After inhibition of CPT-1/2, beta-oxidation is reduced, shifting metabolism toward glycolysis and increasing mechanical efficiency. These mechanisms are believed to explain the antianginal effects of perhexiline in the setting of coronary disease and provide a rationale for therapeutic use in heart failure.

In this issue of JACC: Heart Failure, Beadle et al. (4) report the results of a phase 2 randomized, double-blinded, placebo-controlled study of whether inhibition of fatty acid oxidation with perhexiline improves myocardial energetics as assessed by the myocardial phosphocreatine (PCr)/ATP ratio detected by 31P cardiac magnetic resonance spectroscopy in subjects with nonischemic dilated cardiomyopathy. Prior studies have already suggested that perhexiline improves exercise capacity in heart failure after longer-term exposure (5). The unique contribution of the current study is that it sheds light on the earliest pharmacological effects of perhexiline using direct measures of energy metabolism in the human left ventricle. Additional strengths include careful attention to achieved drug levels, because metabolism of perhexiline is greatly affected by CYP2D6 genotype, and direct assessment of substrate utilization across the coronary circulation in a subset of participants. As expected, treatment with perhexiline substantially increased the PCr/ATP ratio after 1 month of therapy; however, there were no detectable changes in noninvasively assessed ventricular function and no detectable effects on substrate utilization. Reconciling these results sheds light on the clinical pharmacology of perhexiline and on more general questions regarding how best to evaluate novel heart failure therapeutics.

*Editorials published in JACC: Heart Failure reflect the views of the authors and do not necessarily represent the views of JACC: Heart Failure or the American College of Cardiology.

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As pointed out by the authors, the spectroscopic findings clearly show evidence of a biological effect on cardiac metabolism. The absence of changes in resting measures of contractile function could indicate that there was not yet sufficient time to affect ventricular function or that such changes were present but not detected due to insensitivity of echocardiography. Of note, the initial design paper (6) and ClinicalTrials.gov registration (NCT00841139) indicate that cardiac magnetic resonance imaging was planned to assess left ventricular structure and contractile function. If these data are available, they will be of interest to discern any small effect on function that might have been missed by echocardiography.

A more provocative result is the lack of any detectable change in substrate utilization with perhexiline despite clear changes in spectroscopic measures of energetics. Again, it is possible that insensitivity in the measurement techniques resulted in a failure to detect such changes. This seems unlikely on the basis of the assays used and points to the intriguing hypothesis that myocardial CPT-1/2 inhibition may not, in fact, be the relevant mechanism for a therapeutic effect of perhexiline in heart failure. One possibility suggested by the authors is that CPT-1/2 inhibition is the right mechanism but the relevant site of drug action is skeletal muscle. This is supported by earlier studies showing an improvement in exercise capacity with perhexiline.

Another possibility is that there may be an entirely different biochemical mechanism at work. In published reports, there are at least 4 other known pharmacological effects of perhexiline, including inhibition of calcium channels, inhibition of HERG and Kv1.5 potassium channels, potentiation of insulin release, and cyclic guanosine monophosphate- and nitric oxide-mediated reductions in platelet reactivity. Several of these could plausibly affect cardiovascular function in vivo. An informal search of high-throughput screening results available in PubChem (7) reveals a number of additional molecular targets that are potently affected by perhexiline, along with nearly 200 bioactivity assays that are altered by perhexiline. Despite many years of classic perhexiline pharmacology, it thus remains possible that relevant pharmacological mechanisms remain undiscovered. This is further complicated by modifiers of drug response present in human subjects with complex disease, including comorbidities, concomitant therapy, and genetic background, as nicely illustrated by the effects of CYP2D6 variation on metabolism of perhexiline. In summary, the totality of evidence suggests that perhexiline has promise as a heart failure therapy. However, the complex landscape of what perhexiline is actually doing in patients needs to be considered to inform its therapeutic advancement. The authors are wise to conclude that unanticipated mechanisms may be relevant.

It is worth noting that the insights described in the preceding text would have been entirely missed by a trial involving standard clinical endpoints such as cardiopulmonary exercise testing and echocardiography. The most interesting positive and negative findings were detected by “deep phenotyping” approaches, including magnetic resonance spectroscopy and invasive assessment of myocardial substrate utilization. Such approaches are expensive and complex for participants and investigators, but there is no better way to understand mechanisms of drug action in human subjects. Funding constraints and the promise of electronic medical records have shifted the trend in clinical investigation toward more pragmatic study designs using large populations (8). This is indeed a major advance that will accelerate the pace of drug development. However, the study by Beadle et al. (4) shows that there really is no shortcut to understanding how a drug works in human disease.

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References


Key Words heart failure, metabolism, perhexiline, therapy