Perhexiline and Hypertrophic Cardiomyopathy  
A New Horizon for Metabolic Modulation  

John D. Horowitz, MBBS, PhD; Yuliy Y. Chirkov, PhD

Despite the considerable morbidity and mortality associated with hypertrophic cardiomyopathy (HCM), proven therapeutic modalities for this disorder remain limited. The most feared complication, sudden death, usually due to ventricular tachyarrhythmias, can be averted by the use of implantable defibrillators, but patient selection for such procedures remains problematic. In recent years, evidence has accumulated that the presence of substantial outflow tract obstruction is associated with increased severity of symptoms and increased risk of sudden death, and interventions based on amelioration of outflow tract obstruction, via surgical myectomy or alcoholic septal ablation, appear to be relatively effective in improving systematic status.

Effective in improving systematic status.2,3

There is increasing evidence that impairment of myocardial energetics occurs in patients with HCM, and indeed that this energetic impairment may play a primary role in the pathophysiology of HCM. There is also evidence that HCM is associated with decreased efficiency of oxygen utilization, which may interact with and exacerbate the energetic impairment.

Perhexiline Improves Symptomatic Status in Nonobstructive HCM

In the current issue of Circulation, a study by Abozguia et al11 evaluated the effects of perhexiline on exercise performance in a cohort of patients with nonobstructive HCM who had remained symptomatic despite medical therapy. This double-blind, placebo-controlled study essentially represented an “add-on” medical therapeutic strategy, because almost all of the patients were already being treated with β-adrenoceptor or calcium antagonists. The primary end point of the study, peak VO2, was increased significantly by perhexiline therapy, with concomitant and marked amelioration of diastolic dysfunction during exercise. Furthermore, New York Heart Association functional class and Minnesota Living with Heart Failure Questionnaire score both improved substantially. The effects of perhexiline, therefore, constituted a clinically important symptomatic improvement, which was achieved with virtually no adverse effects from active medication.

A critically important aspect of the study was the determination of PCr:ATP ratios via magnetic resonance spectroscopy, to test the hypothesis that perhexiline might improve myocardial energetic status. Perhexiline substantially increased this ratio, with a mean change from 1.27±0.02 to 1.73±0.02. However, it must be noted that this did not constitute full normalization of myocardial energetic status. These results raise 2 fundamental questions: How exactly did perhexiline therapy effect this improvement, and what are the implications of these findings with regard to both the...
understanding of the pathogenesis of HCM and the development of new therapeutic options for its management? A particular issue raised by the study is whether it substantiates the hypothesis that energetic impairment is fundamental to the pathogenesis of HCM.

**Perhexiline: Carnitine Palmitoyltransferase-1 Inhibition and Beyond**

Perhexiline is a pharmacologically complex drug, with complex pharmacokinetics and considerable potential for toxicity. Its therapeutic use has been limited by these issues but has survived because of the perception that it is remarkably effective in relieving symptoms of otherwise refractory ischemia and because it is virtually free of negative inotropic effects and therefore can be used safely in patients with concomitant severe left ventricular systolic dysfunction. Appreciation of the relationship between plasma perhexiline concentrations and the potential for the development of neurotoxicity and hepatotoxicity during long-term therapy led to the development of routine plasma perhexiline monitoring, which virtually eliminated long-term toxicity.\(^1\)\(^2\),\(^1\)\(^3\)

The postulated mechanisms of the therapeutic effect of perhexiline have evolved markedly over the 40 years since the drug was first used clinically. Originally screened as a prophylactic antianginal agent because of its coronary vasodilator effects, perhexiline was later found to be a calcium antagonist. However, it rapidly became clear that its relatively weak calcium antagonist effects were unlikely to be relevant in most clinical circumstances and were not consistent with the lack of negative inotropic effects in the clinical context.

The finding that perhexiline was a potent inhibitor of carnitine palmitoyltransferase-1 \(\text{CPT}_1\)\(^1\)\(^4\) and, to a lesser extent, of \(\text{CPT}_2\), potentially explained both the anti-ischemic effects of the drug in the absence of negative inotropic activity and the potential for the long-term development of toxicity to liver and peripheral nerves on the basis of tissue phospholipidosis. It was on the basis of these findings that the postulated clinical utility of perhexiline has been extended beyond refractory myocardial ischemia to conditions characterized by impairment of myocardial energetics irrespective of the presence or absence of fixed epicardial coronary artery disease, such as inoperable aortic stenosis\(^1\)\(^5\) and congestive cardiomyopathy.\(^1\)\(^6\) Indeed, Lee et al\(^1\)\(^6\) have reported remarkable improvements in left ventricular systolic function and symptomatic status in patients with New York Heart Association class II to III heart failure, irrespective of the presence or absence of coronary artery disease. Inhibition of \(\text{CPT}_1/\text{CPT}_2\) by perhexiline would be likely to induce an increase of at least 13% in efficiency of myocardial oxygen utilization. In working rat hearts, perhexiline increased efficiency by approximately 30%,\(^1\)\(^7\) which suggests additional mechanisms of effect.

Perhexiline appears to exert important anti-inflammatory [in part via nicotinamide adenine dinucleotide phosphate-oxidase inhibition] and nitric oxide–potentiating effects that may occur independent of \(\text{CPT}\) inhibition. The nitric oxide-potentiating effect is manifest within platelets\(^1\)\(^8\) and neutrophils.\(^1\)\(^9\) This contributes to attenuation by perhexiline of the phenomenon of tissue nitric oxide resistance, and is relevant particularly to the potential utility of the agent in acute coronary syndromes. However, it is also possible that these effects may be of some relevance in the context of HCM, as summarized in the Figure.

Therefore, the results of the study by Abozguia et al\(^1\)\(^1\) might well result from improvement of myocardial energetic status by perhexiline. However, HCM has also been associ-
Implications for Future Therapeutics in HCM

The results of the present study by Abozguia et al.\(^4\) therefore, raise the issue of the potential efficacy of both perhexiline and other “metabolic” agents in the entire clinical spectrum of HCM. Other potential forms of pharmacotherapy directed at amelioration of energetic impairment in HCM are summarized in the Table. Of the agents listed, only amiodarone has been used widely in HCM; its efficacy may reflect its actions in inhibiting CPT\(_1\).\(^14\) However, there is also a case for the development of agents with less potential toxicity than amiodarone and perhexiline. Therefore, agents such as trimetazidine and metformin may merit evaluation. Such agents would be most suitable to test the hypothesis that energetic impairment in HCM is a “primary” problem;\(^10\) this would require long-term studies in genotype-positive, phenotype-negative individuals to evaluate effects on the rate of development of left ventricular hypertrophy.

Finally, it is obviously desirable that the present observations about perhexiline be subjected to more extensive clinically based scrutiny. Such a study not only should address the effects of perhexiline on clinical status, but should also encompass its potential utility in patients with “obstructive” or decompensated HCM, as well as evaluate the long-term safety of such therapy.

Disclosures

None.

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Table. Agents That Modulate Myocardial Metabolic Efficiency and Their Major Mechanism(s) for Potentially Improving Energetics

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NO indicates nitric oxide; PFOX, partial fatty acid oxidation; NAD(P)H, nicotinamide adenine dinucleotide phosphate-oxidase; and AMPK, AMP-activated protein kinase.

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