

# Exercise Physiology

## Metabolic Modulator Perhexiline Corrects Energy Deficiency and Improves Exercise Capacity in Symptomatic Hypertrophic Cardiomyopathy

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**Background**—Hypertrophic cardiomyopathy patients exhibit myocardial energetic impairment, but a causative role for this energy deficiency in the pathophysiology of hypertrophic cardiomyopathy remains unproven. We hypothesized that the metabolic modulator perhexiline would ameliorate myocardial energy deficiency and thereby improve diastolic function and exercise capacity.

**Methods and Results**—Forty-six consecutive patients with symptomatic exercise limitation (peak  $\dot{V}O_2 < 75\%$  of predicted) caused by nonobstructive hypertrophic cardiomyopathy (mean age,  $55 \pm 0.26$  years) were randomized to perhexiline 100 mg ( $n=24$ ) or placebo ( $n=22$ ). Myocardial ratio of phosphocreatine to adenosine triphosphate, an established marker of cardiac energetic status, as measured by  $^{31}P$  magnetic resonance spectroscopy, left ventricular diastolic filling (heart rate normalized time to peak filling) at rest and during exercise using radionuclide ventriculography, peak  $\dot{V}O_2$ , symptoms, quality of life, and serum metabolites were assessed at baseline and study end ( $4.6 \pm 1.8$  months). Perhexiline improved myocardial ratios of phosphocreatine to adenosine triphosphate (from  $1.27 \pm 0.02$  to  $1.73 \pm 0.02$  versus  $1.29 \pm 0.01$  to  $1.23 \pm 0.01$ ;  $P=0.003$ ) and normalized the abnormal prolongation of heart rate normalized time to peak filling between rest and exercise ( $0.11 \pm 0.008$  to  $-0.01 \pm 0.005$  versus  $0.15 \pm 0.007$  to  $0.11 \pm 0.008$  second;  $P=0.03$ ). These changes were accompanied by an improvement in primary end point (peak  $\dot{V}O_2$ ) ( $22.2 \pm 0.2$  to  $24.3 \pm 0.2$  versus  $23.6 \pm 0.3$  to  $22.3 \pm 0.2$  mL  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ;  $P=0.003$ ) and New York Heart Association class ( $P < 0.001$ ) (all  $P$  values ANCOVA, perhexiline versus placebo).

**Conclusions**—In symptomatic hypertrophic cardiomyopathy, perhexiline, a modulator of substrate metabolism, ameliorates cardiac energetic impairment, corrects diastolic dysfunction, and increases exercise capacity. This study supports the hypothesis that energy deficiency contributes to the pathophysiology and provides a rationale for further consideration of metabolic therapies in hypertrophic cardiomyopathy.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00500552. (*Circulation*. 2010;122:1562-1569.)

**Key Words:** cardiomyopathy ■ exercise ■ hypertrophy ■ metabolism ■ spectroscopy

Hypertrophic cardiomyopathy (HCM) is the commonest inherited cardiac condition (prevalence,  $\approx 0.2\%$ ).<sup>1</sup> Symptoms arising from left ventricular (LV) outflow tract obstruction, present in  $\approx 30\%$  of HCM patients, are amenable to drug therapies and to interventions such as surgical septal myectomy or alcohol septal ablation.<sup>2</sup> However, treatment options in symptomatic patients without outflow tract obstruction are substantially less successful, mandating a more

comprehensive understanding of the mechanisms underlying symptoms in HCM with the intention of identifying and testing novel therapies.<sup>3,4</sup>

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**Clinical Perspective on p 1569**

More than 400 mutations in genes encoding cardiac contractile proteins have been implicated in HCM.<sup>5</sup> HCM-

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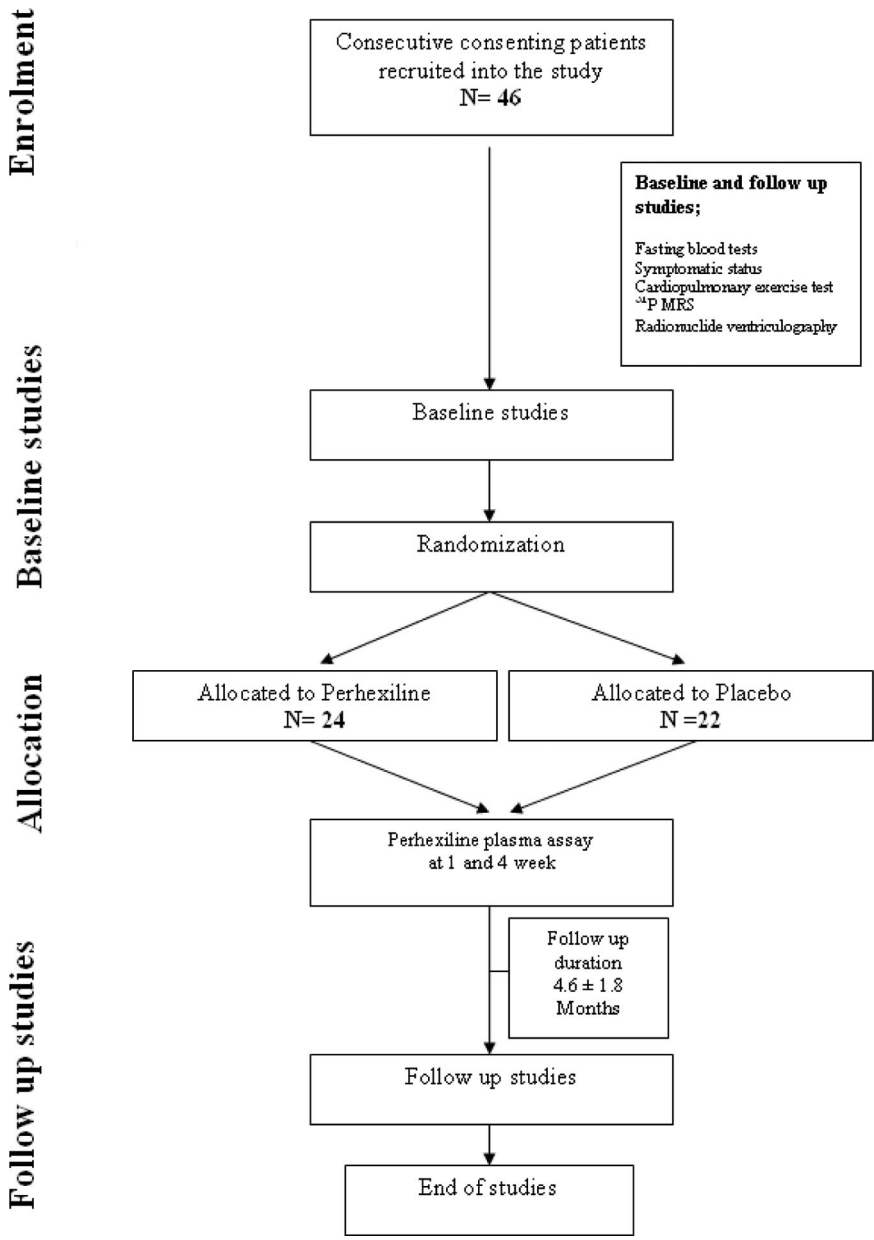
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**Figure 1.** Flow diagram of the study. MRS indicates magnetic resonance spectroscopy.

causing mutations increase sarcomeric  $Ca^{2+}$  sensitivity, ATPase activity, and the energetic cost of myocyte contraction.<sup>6-9</sup> These abnormalities led to the proposal that the pathophysiology of HCM is attributable, at least in part, to excessive sarcomeric energy use.<sup>10</sup> The resulting hypertrophy of HCM, exacerbated by mitochondrial dysfunction<sup>11</sup> and accompanied by microvascular dysfunction,<sup>12-14</sup> may limit myocyte oxygen delivery and further exacerbate the primary energy deficiency.<sup>15</sup> Consistent with a functional role for the observed energy deficiency of HCM,<sup>16,17</sup> LV relaxation (a highly energy-requiring process) paradoxically slows in HCM patients on exercise and is correlated with exercise limitation.<sup>18</sup> To assess a causative role for energy deficiency and to test a potentially novel therapeutic strategy for HCM, we evaluated whether perhexiline, an agent thought to improve cardiac energetics by shifting substrate use to more efficient carbohydrate metabolism,<sup>19-22</sup> would increase exercise capacity by improving cardiac energetics and LV relaxation (ie, diastolic filling).

**Methods**

An expanded Methods section appears in the online-only Data Supplement.

**Study Design**

The study was approved by the South Birmingham Research Ethics Committee and conforms to the Declaration of Helsinki. All participants provided written informed consent. The study was a randomized, double-blind, placebo-controlled, parallel-group design of 3 to 6 months' duration (mean,  $4.6 \pm 1.8$  months). The predefined primary end point was peak oxygen consumption (peak  $\dot{V}O_2$ ); secondary end points were symptomatic status, resting myocardial energetics (ratio of phosphocreatine to adenosine triphosphate [PCr/ATP ratio]), and diastolic function at rest and during exercise (heart rate normalized time to peak filling [nTTPF]). A flow diagram of the study is shown in Figure 1.

**Patient Selection**

Patients were consecutively recruited from cardiomyopathy clinics at The Heart Hospital, University College London Hospitals (London,

UK) and Queen Elizabeth Hospital (Birmingham, UK) between 2006 and 2008. All patients fulfilled conventional echocardiographic criteria for the diagnosis of HCM (LV wall thickness,  $\geq 1.5$  cm in the absence of abnormal loading conditions).<sup>23,24</sup> Inclusion criteria were as follows: 18 to 80 years of age, exertional symptoms, sinus rhythm, peak  $\dot{V}O_2 < 75\%$  of predicted for age and gender, and the absence of resting or provokable LV outflow tract obstruction (peak gradient  $< 30$  mm Hg). Exclusion criteria were the presence of epicardial coronary artery disease, abnormal liver function tests, concomitant use of amiodarone or selective serotonin reuptake inhibitors (because of potential drug interactions with perhexiline), and peripheral neuropathy; women of childbearing potential also were excluded. Diabetic patients were excluded to maintain the blinding of the study because perhexiline may lead to a reduction in plasma glucose, necessitating a reduction in antidiabetic therapy.

### Control Selection

Thirty-three control subjects of similar age and gender distribution were recruited for comparison of baseline data. Control subjects were recruited via advertisements placed in the University Hospital of Birmingham, University of Birmingham, and local blood donor centers. Control subjects were asymptomatic and had normal ECGs/echocardiograms.

### Intervention

After baseline studies, patients were randomized in a double-blind fashion, with a block size of 4, to receive either perhexiline 100 mg OD (n=24) or placebo (n=22). Serum perhexiline levels were obtained at 1 and 4 weeks after initiation of the drug. Dose adjustments were advised by an unblinded physician according to serum level to achieve therapeutic level (therapeutic range, 0.15 to 0.6 mg/L) and to avoid drug toxicity. Identical dosage adjustments were made for randomly allocated placebo-treated patients by the unblinded observer to ensure that blinding of the investigators was maintained as previously described.<sup>21</sup>

### Statistical Analysis

Data were analyzed with SPSS 15.0 for Windows and Microsoft Office Excel 2007 and are expressed as mean  $\pm$  SEM. Comparisons of continuous variables between perhexiline and placebo baseline data were made by unpaired Student *t* test (2 tailed) if variables were normally distributed and the Mann-Whitney *U* test if the data were nonnormally distributed. Categorical variables were compared with the Pearson  $\chi^2$  test. ANCOVA with baseline values as covariates was performed to test for the significance of differences in the perhexiline versus placebo group after treatment. A value of  $P=0.05$  was taken to indicate statistical significance. For the primary end point of the overall study, 44 patients are required to detect a change in peak  $\dot{V}O_2$  of 3 mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> in the treatment versus the placebo group with a power of 90%, an SD of 3 mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>, and a value of  $P<0.05$ . Thirty patients are required to identify a 5% change in cardiac PCr/ATP ratio with a power of 90%, an SD of 4.1%, and a value of  $P<0.05$ . Forty patients are required to detect a change  $\geq 25\%$  in nTTPF with power of 0.99, an SD of 18%, and value of  $P<0.05$ .

## Results

### Baseline Data (HCM Patients Versus Control Subjects)

The clinical characteristics and cardiopulmonary exercise test results of the HCM patients and control subjects are shown in Table 1. The groups were similar with respect to age and gender. Heart rate was lower in the HCM group compared with the control subjects, probably because of medication use ( $\beta$ -blockers and/or calcium channel blockers).

Genomic DNA samples with consent for genetic analysis were available on 28 of the study HCM subjects. Thirteen

subjects were found to have either known pathogenic variants or variants considered to be pathogenic on the basis of their absence in normal control chromosomes (n>1000) and predicted impact on protein structure. Three missense mutations were identified in *MYH7* (1 previously reported and 2 novel); 9 pathogenic variants were identified in *MYBPC3* (1 novel truncation, 6 previously reported missense mutations, and 2 novel missense mutations); and 1 previously reported missense mutation was identified in *TNNT2*.

HCM patients exhibited marked exercise limitation compared with control subjects (peak  $\dot{V}O_2$ , 23  $\pm$  0.1 versus 38  $\pm$  0.2 mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>;  $P<0.0001$ ; Table 1). This remained so after patients taking  $\beta$ -blockers were excluded ( $P<0.0001$ ). Resting cardiac PCr/ATP ratio was lower in HCM patients than in control subjects (1.28  $\pm$  0.01 versus 2.26  $\pm$  0.02;  $P<0.0001$ ; Table 1), and this remained so after the exclusion of patients taking  $\beta$ -blocker therapy ( $P<0.0001$ ). At rest, nTTPF, a sensitive marker of LV relaxation, was similar in HCM patients and control subjects (0.17  $\pm$  0.002 versus 0.18  $\pm$  0.003 seconds;  $P=0.44$ ). During submaximal exercise (at a workload that achieved 50% of heart rate reserve), it remained relatively constant in control subjects (from 0.18  $\pm$  0.003 to 0.16  $\pm$  0.002 seconds;  $\delta$ nTTPF = -0.01  $\pm$  0.004 seconds) but lengthened in patients (from 0.17  $\pm$  0.002 to 0.34  $\pm$  0.002 seconds;  $\delta$ nTTPF = 0.13  $\pm$  0.003 seconds;  $P<0.0001$ ; Table 1 and Figure 2). Transmitral Doppler measurements showed no significant difference in peak E, deceleration time, and E/A ratio in HCM patients versus control subjects (Table 1). However, pulse-wave tissue Doppler imaging measurements of S, E', and A' were significantly lower in HCM patients compared with control subjects (Table 1).

### Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

The perhexiline and placebo groups were well matched (Table 1). One patient (on placebo) did not complete the study because of poor compliance. Six patients were subtherapeutic and none were above the therapeutic range at the end of the study. Side effects were restricted to transient nausea (n=3) and dizziness (n=2) in the perhexiline group and transient nausea (n=2) and headache (n=1) in the placebo group. There were no instances of hepatotoxicity and no deaths or major adverse events during the study period.

### Exercise Capacity (Peak Oxygen Consumption)

At baseline, peak  $\dot{V}O_2$  was similar in both groups (Table 1). After treatment, peak  $\dot{V}O_2$  fell by 1.3 mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> in the placebo group (from 23.6  $\pm$  0.3 to 22.3  $\pm$  0.2 mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>) but increased by 2.1 mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> in the perhexiline group (from 22.2  $\pm$  0.2 to 24.3  $\pm$  0.2 mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>;  $P=0.003$ ; Table 2). There were no significant changes in  $\dot{V}O_2$  anaerobic threshold or  $\dot{V}E/\dot{V}CO_2$  slope between the groups.

### Symptomatic Status

Minnesota Living With Heart Failure Questionnaire score showed an improvement in the perhexiline group (from 36  $\pm$  0.94 to 28  $\pm$  0.75) but no change in the placebo group (from 37  $\pm$  1.21 to 34  $\pm$  1.25;  $P<0.001$  for difference in

**Table 1. Clinical Characteristics of HCM Patients and Control Subjects**

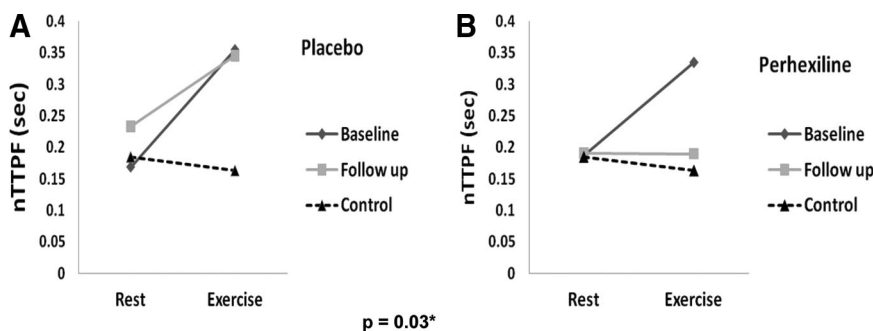
	HCM Patients	Control Subjects	<i>P</i>	HCM (Perhexiline)	HCM (Placebo)	<i>P</i>
Age, y	55±0.26	52±0.46	0.2	56±0.46	54±0.64	0.42
Men, n (%)	46 (34)	33 (20)	0.64	24 (19)	22 (17)	0.69
Heart rate, bpm	69±0.27	82±0.47	<0.001*	69±0.53	69±0.52	0.97
Systolic BP, mm Hg	126±0.64	126±0.44	0.93	123±0.84	130±0.92	0.2
Diastolic BP, mm Hg	76±0.25	78±0.34	0.33	74±0.45	78±0.57	0.24
Peak $\dot{V}O_2$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	23±0.1	38±0.2	<0.0001*	22.2±0.2	23.6±0.3	0.42
Resting nTTPF, s	0.17±0.002	0.18±0.003	0.44	0.19±0.003	0.17±0.004	0.52
Pcr/ATP ratio	1.28±0.01	2.26±0.02	<0.0001*	1.27±0.02	1.29±0.01	0.86
<b>Echocardiography</b>						
LVEF, %	65±0.2	63±0.2	0.24	66±0.35	63±0.34	0.24
LVEDV index, mL/m <sup>2</sup>	46±0.26	41±0.4	0.1	44±0.58	44±0.31	0.32
LVESV index, mL/m <sup>2</sup>	16±0.15	15±0.14	0.26	15±0.28	16±0.16	0.18
LAV index, mL/m <sup>2</sup>	35.37±0.33	14.68±0.39	<0.0001*	35.9±0.38	39.45±0.77	0.4
Mitral E velocity, m/s	0.69±0.003	0.66±0.005	0.33	0.66±0.01	0.67±0.004	0.12
Mitral A velocity, m/s	0.7±0.005	0.59±0.004	0.01*	0.76±0.01	0.68±0.01	0.13
Mitral E/A ratio	1.1±0.01	1.17±0.01	0.28	1±0.01	1.03±0.01	0.1
Mitral DCT, ms	238±1.66	259±2.14	0.26	246±2.39	227±1.86	0.52
TDI S velocity, cm/s	0.06±0.001	0.08±0.001	<0.0001*	0.06±0.001	0.06±0.001	0.65
TDI E' velocity, cm/s	0.06±0.001	0.09±0.001	0.002*	0.06±0.001	0.06±0.001	0.6
TDI A' velocity, m/s	0.07±0.001	0.09±0.001	<0.0001*	0.07±0.001	0.06±0.001	0.62
E/E' ratio	12±0.1	8±0.1	<0.0001*	12±0.2	12±0.1	0.6
MWT [cm]	2.31±0.01	...	...	2.32±0.02	2.25±0.01	0.58
F H/O HCM, n	19	0	...	11	8	0.51
F H/O SCD, n	9	0	...	4	5	0.52
<b>Drug therapy, n</b>						
β-blocker	17	0	...	10	7	0.21
Calcium channel blocker	24	0	...	11	8	0.53
Diuretic	10	0	...	4	5	0.49
ACE inhibitor	6	0	...	3	2	0.84
ARB	4	0	...	3	1	0.41
Warfarin	5	0	...	2	3	0.48
Statin	15	0	...	7	7	0.9

BP indicates blood pressure; LVEF, LV ejection fraction; LVEDV index, LV end-diastolic volume indexed to body surface area; LVESV, LV end-systolic volume indexed to body surface area; LAV, left atrial volume; DCT, deceleration time; TDI, tissue Doppler imaging; MWT, minimal wall thickness; F H/O, family history of; SCD, sudden cardiac death; ACE, angiotensin-converting enzyme; and ARB, angiotensin II receptor blockers. TDI measurements were averaged from basal anterolateral and basal inferoseptum in apical 4-chamber view.

response between placebo and perhexiline). New York Heart Association classification improved in more patients in the perhexiline than the placebo group (67% versus 30%); fewer worsened (8% versus 20%; *P*<0.001).

**Myocardial Energetics**

Typical cardiac <sup>31</sup>P magnetic resonance spectroscopy spectra from a patient with HCM is shown in Figure 3. The mean Cramer-Rao ratios for Pcr and ATP for the entire group were



**Figure 2.** The effects of placebo and perhexiline on diastolic filling. A and B, nTTPF changes in the placebo and perhexiline groups, respectively. nTTPF changes in healthy control subjects (dotted lines) are shown for comparison. \**P*=0.03 for the difference between the perhexiline and placebo responses.

**Table 2. Effects of Placebo and Perhexiline on Metabolic Exercise Parameters, Myocardial Energetic, Symptomatic Status, and LV Systolic Function at Rest and During Exercise**

Parameter	Perhexiline Group		Placebo Group		P, ANCOVA
	Baseline	Follow-Up	Baseline	Follow-Up	
Metabolic exercise parameters					
Peak $\dot{V}O_2$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	22.2±0.2	24.3±0.2	23.6±0.3	22.3±0.2	0.003*
$\dot{V}O_2$ -AT, mL · kg <sup>-1</sup> · min <sup>-1</sup>	16±0.11	15±0.1	17±0.23	16±0.15	0.85
$\dot{V}E/\dot{V}CO_2$ slope	30±0.12	32±0.12	30±0.23	32±0.3	0.99
Myocardial energetic status					
PCr/ATP ratio	1.27±0.02	1.73±0.02	1.29±0.01	1.23±0.01	0.003*
Symptomatic status					
MLHFQ score	36±0.94	28±0.75	37±1.21	34±1.25	<0.001*
LV systolic function (at rest and during exercise), %†					
Resting EF	68±0.51	67±0.49	66±0.46	65±0.42	0.22
Exercise EF	72±0.75	69±0.45	73±0.56	75±0.39	0.07

AT indicates anaerobic threshold;  $\dot{V}E/\dot{V}CO_2$  slope, minute ventilation–carbon dioxide production relationship; MLHFQ, Minnesota Living With Heart Failure Questionnaire; and EF, ejection fraction. ANCOVA P values represent the significant difference between perhexiline and placebo responses.

\*Statistically significant.

†Measured with radionuclide ventriculography.

7.5% and 10.8%, respectively, indicating satisfactory signal-to-noise ratio. Three patients were excluded from the initial analysis because of poor signal-to-noise ratio (Cramer-Rao ratios >20%). The PCr/ATP ratio increased with perhexiline (1.27±0.02 to 1.73±0.02) compared with placebo (1.29±0.01 to 1.23±0.01;  $P=0.003$ ; Table 2). The effect of perhexiline on PCr/ATP ratio remained significant with the inclusion of the 3 patients with poor signal-to-noise ratio ( $P=0.02$ ).

### Serum Metabolite Profiles

Perhexiline induced significant changes in serum glucose (5.39±0.14 to 4.96±0.20 mmol/L,  $P=0.003$ , versus 5.36±0.26 to 5.32±0.19 mmol/L,  $P=0.7$ ) and free fatty acid levels (381.61±33.56 to 297.39±31.00 mmol/L,  $P=0.04$ , versus 353.11±34.74 to 329.00±32.62 mmol/L,  $P=0.61$ ) in the perhexiline versus placebo groups, respectively (Table 3).

### Exercise Radionuclide Measurements

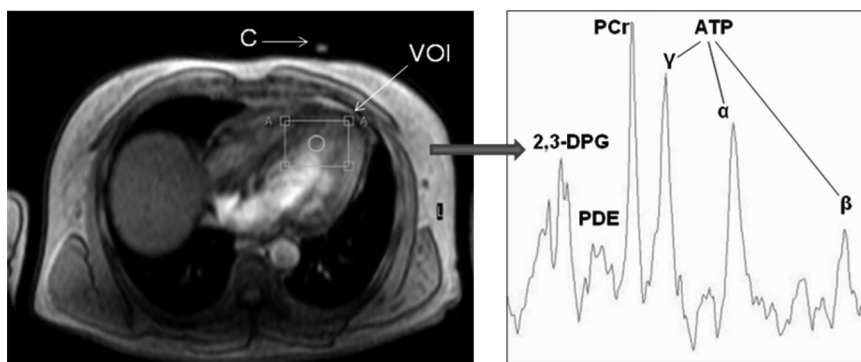
Whereas the placebo group showed prolongation of nTTPF during exercise before and after therapy (by 0.15±0.007 and 0.11±0.008 seconds, respectively), in the perhexiline group,

nTTPF lengthened at baseline (by 0.11±0.008 seconds) but shortened on treatment (by -0.01±0.005 seconds;  $P=0.03$  for difference between the perhexiline and placebo response; Figure 2A and 2B). There were no significant changes in ejection fraction at rest or during exercise (Table 2). Ejection fraction decreased <50% on exercise in 3 patients (2 in the perhexiline group and 1 in the placebo group).

Although our study was not designed (and hence not powered) to relate genetic status to drug response, there was no statistical heterogeneity in baseline characteristics or response to therapy as judged from the perspective of genotype status (data not shown).

### Discussion

This study confirms that patients with symptomatic nonobstructive HCM manifest a cardiac energy defect (reduced PCr/ATP ratio) accompanied by a slowing of the energy-dependent early diastolic LV active relaxation during exercise (prolongation of nTTPF). Consistent with the hypothesis that impaired myocardial energy status contributes to the pathophysiology of HCM, perhexiline augmented myocardial PCr/ATP ratio, corrected the abnormal prolongation of nTTPF on



**Figure 3.** A typical example of <sup>31</sup>P cardiac spectra of an HCM patient. C indicates center of phosphorus coil; VOI, voxel of interest; 2,3-DPG, 2,3-diphosphoglycerate; PDE, phosphodiesterases; and  $\alpha$ ,  $\beta$ , and  $\gamma$ , the 3 phosphorus nuclei of ATP.

**Table 3. The Impact of Perhexiline and Placebo on Serum Metabolites in HCM Patients. HOMA, Homeostasis Model of Assessment. Data Are Presented as Mean±SEM**

Parameter	Perhexiline Group		Placebo Group	
	Baseline	Follow-Up	Baseline	Follow-Up
Free fatty acids [umol/l]	382±34	297±31*	353±35	329±33
Glucose [mmol/l]	5.39±0.14	4.96±0.2**	5.36±0.26	5.32±0.19
Insulin [mU/l]	16.3±4.8	10.2±1.6	10.9±2.1	7.9±1.3
Insulin resistance [HOMA index]	0.32±0.1	0.19±0.03	0.22±0.05	0.16±0.03
GLYCEROL [umol/l]	96±11	107±8	83±8.06	106±12

\* $P < 0.05$  vs baseline. \*\* $P < 0.005$  vs baseline.

exercise, improved symptoms, and increased the functional capacity of patients in the perhexiline group.

The observation that patients with HCM manifest impaired myocardial PCr/ATP (Table 1), at least those with sarcomeric mutations, is an expected and likely direct consequence of the biophysical properties of the mutations and accords with previous animal and human studies.<sup>16,17,25–27</sup> Thus, although the pathogenesis of sarcomeric HCM has been varyingly attributed to increased sarcomeric  $\text{Ca}^{2+}$  sensitivity, ATPase activity, and aberrant cross-bridge dynamics<sup>6,8</sup> with complications such as oxidative stress<sup>28</sup> and altered sarcomeric phosphorylation,<sup>29,30</sup> a common feature of such studies is the excessive energetic cost of tension generation by sarcomeric mutations.<sup>7,9</sup> In addition to these biophysical considerations, further evidence that the energy deficiency in HCM is a primary event and not a secondary feature of cardiac remodeling (either LV hypertrophy or heart failure) derives from the observation that myocardial high-energy phosphates are even compromised in asymptomatic HCM<sup>16</sup> and prehypertrophic cardiomyopathy.<sup>10,17</sup> The resulting final common path of energy deficiency, rather than sarcomeric mutations per se, may specifically contribute to the HCM phenotype, as seen in other primary disorders of myocardial energy deficiency (eg, mitochondrial disorders and Friedreich ataxia).<sup>31</sup>

Because the heart has a high energy requirement,<sup>32</sup> cardiac energy deficiency would be expected to translate into characteristic physiological defects such as slowing of energy-dependent<sup>33</sup> early diastolic relaxation. Thus, although the nTTPF in control subjects remained approximately constant between rest and exercise, nTTPF paradoxically lengthened in HCM patients (Figure 2). This slower filling in the context of the reduced diastolic filling time reduces cardiac output and limits exercise capacity.<sup>18</sup>

It has been proposed that perhexiline inhibits the metabolism of free fatty acids and thereby enhances myocardial carbohydrate use (in effect improving insulin resistance<sup>34</sup>) by suppressing carnitine palmitoyl transferase I and II, transporters that are crucial for the uptake of long-chain free fatty acids into mitochondria.<sup>19,20,35</sup> The present study supports this proposal by observing that perhexiline, in common with other metabolic modulators,<sup>36</sup> improved the systemic metabolic milieu by significantly decreasing serum glucose and free fatty acids. Thus, although the mechanisms of action of

perhexiline are likely to be complex, its capacity to divert myocardial metabolism toward carbohydrates, especially in the context of myocardial oxygen limitation (eg, resulting from microvascular dysfunction),<sup>12,14</sup> is predicted to enhance the efficiency of myocardial energy generation.<sup>22,36,37</sup> Exploiting this effect, there is evidence that agents modifying substrate use (eg, trimetazidine and perhexiline) enhance myocardial energetics and are efficacious in the energy-starved state of heart failure.<sup>21,32,38</sup> The corresponding improvements in symptoms (the principal feature of HCM in these patients) and in peak  $\dot{V}\text{O}_2$  ( $\approx 2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  absolute,  $3.3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  placebo corrected) with perhexiline are clinically meaningful, and to the best of our knowledge, improvements of this magnitude have not been reported for other therapies in nonobstructive HCM. To put these benefits into context, they are comparable to the benefits noted with gradient reduction in obstructive HCM ( $\approx 3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ).<sup>39,40</sup> Importantly, this encouraging efficacy was achieved with few side effects; perhexiline plasma monitoring and dose titration prevent the hepatotoxicity and neuropathy that may occur in slow drug metabolizers.<sup>22</sup>

When genetic analysis was possible, the proportion (46%) and range of sarcomeric mutations were typical of other HCM cohorts. Although our study was not designed to relate genetic status to drug response, our patients (regardless of mutation status) responded to perhexiline. Sarcomeric mutations, by virtue of their well-characterized energy-profligate biophysical properties, provide a mechanistic rationale to treat HCM with energy-modulating therapies. Our data extend this argument by suggesting that, regardless of mutation status, the energy deficiency that characterizes HCM and its physiological sequelae renders most HCM patients amenable to metabolic therapy.

In this study, perhexiline (or placebo) was added to standard medical therapy. Such therapy (eg,  $\beta$ -blockers) might have affected the cardiovascular response of participants to exercise. To account for this potential confounder, all pertinent physiological parameters were corrected for heart rate. In addition, the statistical significance of the results remained unchanged regardless of whether patients on  $\beta$ -blockers were included or excluded from analysis. Similarly, patients with flow-limiting coronary disease and diabetes mellitus were excluded to avoid the confounding influence of impaired cardiac energetic status associated with these disorders.<sup>41</sup> Multiple objective and independent parameters (ie, PCr/ATP, nTTPF, and  $\dot{V}\text{O}_2$ ) were assessed to obviate the biases that may confound interpretation of phase 2 trials. The PCr/ATP ratio was measured at rest; we speculate that the impact of perhexiline on PCr/ATP would be more striking in exercise, but current technology does not permit dynamic magnetic resonance spectroscopy measurements. To substantiate the <sup>31</sup>P magnetic resonance spectroscopy findings, analyses were performed both including and excluding studies with unacceptable signal-to-noise ratios (Cramer-Rao >20%); the results remained statistically similar under both circumstances. Although we do not present definitive evidence that perhexiline shifts myocardial substrate use toward carbohydrate metabolism, the combination of extensive biochemical evidence of the capacity of perhexi-

line to inhibit carnitine palmitoyl transferase and our demonstration of consistent changes in serum free fatty acids and glucose supports the hypothesis that perhexiline augments myocardial PCr/ATP, at least in part through metabolic modulation.

### Conclusions

The present study supports the hypothesis that HCM is, at least in part, a disease of energy deficiency. Metabolic modulation, myocardial PCr/ATP augmentation, and normalized diastolic ventricular filling by perhexiline translated into significant and clinically meaningful subjective and objective clinical improvement in patients with symptomatic nonobstructive HCM. Thus, this proof-of-concept study suggests that perhexiline has the capacity to make substantial impacts on the quality of life of this highly symptomatic population for whom alternative evidence-based therapeutic strategies are limited. We propose that longer-term studies are now needed to evaluate the impact of metabolic modulation both for symptom control and as potentially disease-modifying therapy that may improve prognosis and/or lead to LV hypertrophy regression in HCM.

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### Disclosures

Drs Ashrafian and Frenneaux have successfully applied for method-of-use patents for the use of perhexiline in heart failure and cardiomyopathies. The other authors report no conflicts.

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### CLINICAL PERSPECTIVE

Cardiac energy impairment is a consistent feature of hypertrophic cardiomyopathy and precedes the development of hypertrophy. We hypothesized that this energy deficiency plays a key role in the pathophysiology of exercise limitation via impairment of the highly energy-dependent process of left ventricular active relaxation on exercise. To test this hypothesis, we assessed whether the metabolic modulator perhexiline augmented myocardial energetics in hypertrophic cardiomyopathy and whether this translated into improved physiological and clinical outcomes in a randomized, double-blind, placebo-controlled study. In accordance with previous studies, the hypertrophic cardiomyopathy patients in the present study, who were symptomatic but manifested no left ventricular outflow tract obstruction, had a significantly decreased myocardial energy charge as assessed by  $^{31}\text{P}$  magnetic resonance spectroscopy; this was accompanied by a paradoxical dynamic slowing of myocardial relaxation during exercise. Perhexiline improved myocardial energetics, normalized the impairment of dynamic myocardial relaxation, and improved both patient symptoms and exercise capacity. The results of the present study support the hypothesis that energy deficiency contributes to the pathophysiology of exercise limitation in hypertrophic cardiomyopathy and that augmenting myocardial energetics through metabolic modulation may be a novel and potentially effective therapy for the management of symptomatic hypertrophic cardiomyopathy in patients without left ventricular outflow tract obstruction, although this requires confirmation in a larger study. The therapeutic potential is especially important in this group of patients in whom treatment options are limited.