

CLINICAL TRIAL PROTOCOL

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Randomized double-blind placebo-controlled trial of perhexiline in heart failure with preserved ejection fraction syndrome

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ABSTRACT Recently heart failure with preserved ejection fraction (HFpEF) has emerged as a huge epidemic. Increasing evidence shows the role of energy deficiency in the pathophysiology of HFpEF. In the current study, we hypothesize that the use of metabolic modulator perhexiline would correct myocardial energy deficiency and improve exercise capacity and diastolic abnormalities in patients with this syndrome.

Background

Heart failure (HF) is a major public health problem with significant burden to patients, healthcare providers and society. It affects around 900,000 people in the UK today and is associated with a poor prognosis despite major therapeutic advances over the past two decades [1]. In the past, research has focused principally on patients with left ventricular systolic dysfunction, as indicated by a reduced left ventricular ejection fraction (LVEF) [2]. However, data from various epidemiological investigations and hospital-based reports have shown that up to half of patients with clinical features of HF have preserved LVEF. In those who are hospitalized for HF de-compensation, the length of hospital stay and readmission rates are similar to those of patients with HF with reduced left ventricular ejection fraction (HFrEF) [3]. Furthermore, the mortality rate is only slightly better than for patients who have HFrEF [4]. These patients are typically elderly women who are frequently hypertensive (usually systolic hypertension), diabetic and/or have coronary artery disease, and are often overweight. Importantly, the prevalence of HF with preserved ejection fraction (HFpEF) appears to be increasing [3–5]. HFpEF patients have often been referred to in the past as having ‘diastolic heart failure’, which makes the assumption that diastolic dysfunction is the underlying pathophysiology, but there has been considerable controversy about this. More recently, the descriptive term ‘heart failure with preserved ejection fraction’ has been favored as it avoids any presumptions [6]. Perhaps because the pathophysiology of HFpEF is poorly understood, there is correspondingly little evidence-based therapy [6].

Despite normal LVEF, HFpEF patients manifest subtle systolic dysfunction, involving impairment of long axis systolic function; there is, however, a reasonable (although not universal) consensus that the principal abnormality in HFpEF is of active relaxation and/or passive filling of the LV (except among those who argue that LV active relaxation is in fact part of systole) [6–9]. Nevertheless,

KEYWORDS

- cardiac spectroscopy
- diastole • ejection fraction • heart failure
- perhexiline

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resting measures of active relaxation and filling relate poorly to symptoms and exercise capacity, therefore no 'gold standard' diagnostic echocardiographic test exists for HFpEF. Effective ventricular filling results from a highly energy-dependent active relaxation process, from passive filling, which is dependent on loading conditions as well as the intrinsic (passive) properties of the LV [9], and from atrial systolic contribution. Since these parameters change markedly during exercise due to sympathetic activation, it is not surprising that at rest these parameters are poorly predictive of exercise capacity and symptoms [9].

Exercise normally increases the rate of active relaxation, ensuring adequate filling during the shortened diastole associated with high heart rates. This occurs as a result of a putative cascade of key protein phosphorylation by PKA, including troponin I, SERCA and titin [10,11]. We previously demonstrated a marked impairment of cardiac energetic status in patients with HFpEF, which appeared, together with ventriculo-arterial mismatching (due to increased large artery stiffness) to be responsible for an abnormal dynamic slowing of left ventricular active relaxation and a modest impairment of LV contractile function on exercise, together likely responsible for the exercise limitation [12]. In another study in patients with hypertrophic cardiomyopathy (HCM) we confirmed the previously reported impairment of cardiac energetics [13] and showed that, as in HFpEF, this was associated with a dynamic slowing of LV active relaxation on exercise. The metabolic modulator perhexiline corrected this energetic impairment and the diastolic abnormality on exercise and significantly improved exercise capacity (peak VO_2) [13]. Perhexiline is believed to improve cardiac energetics by shifting cardiac metabolism away from the use of free fatty acids as the dominant substrate towards carbohydrate oxidation, which results in increased mechanical efficiency (more work per unit oxygen). It has been shown to inhibit the enzymes CPT1 and 2, which are crucial for the uptake of long-chain fatty acids into the mitochondria [14]. Perhexiline was initially introduced in the 1970s as an antianginal but following reports of hepatotoxicity and neuropathy it was voluntarily withdrawn by the manufacturers [14]. Subsequently, this toxicity was shown to be related to long-term exposure to high plasma levels of the drug, predominantly in patients who were slow CYP2D6 metabolizers [14]. Monitoring of plasma levels with appropriate

dose titration was shown to eliminate these complications, resulting in renewed use of the drug particularly in Australasia [14].

Therapies focusing on the traditional neurohumoral blockade paradigm that has been so successful in HFrEF have been shown to be ineffective in HFpEF [15–17,24]. A recent study reported increased exercise capacity with the rate slowing agent ivabradine [18]. However, given the central role of energetic impairment in patients with HFpEF, we propose that therapy aimed at correcting this may be effective in the condition.

Hypothesis

We postulate that perhexiline will improve cardiac energetics, leading to augmented diastolic function on exercise, and in turn to increased exercise capacity and improved quality of life in HFpEF patients.

• Objectives

To assess the effects of perhexiline in patients with HFpEF syndrome. The study is a randomized, double-blind, placebo-controlled trial. The outcomes of the study will be:

Primary

- Peak oxygen consumption (peak VO_2) by cardiopulmonary exercise testing.

Secondary

- Symptomatic status (Modified Minnesota Living with Heart Failure Questionnaire) and 6MWT;
- Resting myocardial energetics, assessed by ^{31}P cardiac MR spectroscopy (MRS);
- Resting and exercise diastolic function (nuclear studies);
- Indirect measures of LVEDP (resting and peak exercise plasma BNP, resting tissue Doppler E/Ea);
- Global LV ejection fraction (MRI).

Methods

A total of 72 patients who meet the selection criteria will be recruited from NHS Grampian and University Hospitals Birmingham NHS trust. Informed consent will be obtained from each patient. Since the primary end point for this study is peak VO_2 , we will include only patients who had objective evidence of exercise limitation in whom the limitation was cardiac in origin.

• Study design

This is a multicenter, prospective, randomized, double-blind, placebo-controlled trial of 72 patients with HFpEF syndrome (as defined below in the inclusion criteria).

Inclusion criteria

HFpEF will be defined as:

- Clinical symptoms and signs consistent with HF;
- LVEF $\geq 50\%$, with no evidence of significant valvular disease, no hypertrophic cardiomyopathy and no evidence of pericardial constriction;
- A peak VO_2 $< 80\%$ predicted, with RER > 1 and with a pattern of gas exchange on metabolic exercise testing indicating a cardiac cause for limitation;
- All patients recruited will be in sinus rhythm.

Exclusion criteria

- BMI > 35 kg/m²;
- Objective evidence of lung disease on formal lung function testing (defined as desaturation on exercise, obstructive pattern on flow volume loops, FEV₁/FVC ratio of < 70);
- History of active angina and/or evidence of reversible ischemia on exercise ECG;
- Impaired hepatic function (defined as more than twice upper range of normal value);
- Known hypersensitivity to perhexiline;
- Concomitant use of amiodarone, quinidine, haloperidol, fluoxetine, paroxetine;
- Patients with impaired renal function (creatinine > 250 $\mu\text{mol/l}$ OR eGFR < 24).

Investigations

• Baseline evaluation

Subjects will be interviewed, examined and asked to provide written consent. At first consultation, FBC, BNP, U&Es and LFTs will be taken. BP and ECG including corrected QT interval will be measured. They will also complete a Minnesota Living with Heart Failure Questionnaire and perform standard pulmonary function tests (PFTs). Subjects taking β -blockers will be required to have the same inclusion criteria.

• Cardiopulmonary exercise test

Subjects will perform symptom-limited erect treadmill exercise using a standard ramp protocol with simultaneous respiratory gas analysis. Sampling of expired gases will be performed continuously, and data will be expressed as 30-s means. Minute ventilation, oxygen consumption (peak VO_2), carbon dioxide production and respiratory exchange ratio will be obtained. Blood pressure will be monitored throughout.

• Assessment of resting & exercise diastolic function

Left ventricular ejection fraction and diastolic filling will be assessed by equilibrium R-wave gated blood pool scintigraphy using a standard technique at rest and during graded semi-erect exercise on a cycle ergometer, as previously described by us. 10 min after an intravenous injection of ≈ 1.7 mg stannous pyrophosphate, 5 ml of blood will be drawn into a heparinized syringe and incubated for 20 min with 925 MBq (25 mCi) of $^{99\text{m}}\text{Tc}$ pertechnetate before reinjection. Studies will be acquired on a small-field-of-view gamma camera fitted with a low-energy, general-purpose, parallel-hole collimator and interfaced to a dedicated minicomputer. With the patient on the cycle ergometer, the detector will be adjusted for the left anterior oblique view with the best ventricular separation and 10–15° of caudal tilt. A 20% tolerance window will be set about the patient's heart rate, and each RR interval will be divided into 28 equal frames throughout. A constant number of frames per RR interval ensure constant temporal resolution during diastole at all heart rates. Data from each beat will be acquired into a memory buffer in a 64 \times 64 'word' matrix and, if accepted, will be reformatted with two-thirds forward, one-third backward gating. 3 min of data will be acquired at rest and at each level of exercise after a 1-min period for stabilization of heart rate at the commencement of each stage. The initial workload will be 25 W and will be increased by 25-W increments. Exercise will terminate if the patient develops fatigue, breathlessness, arrhythmia, heart rate > 200 beats/min or hypotension (systolic blood pressure less than baseline). The rest and exercise-gated bloodpool scintigraphs will be analyzed by a single operator who will be blinded to the patient's history and exercise performance. The composite cycle derived from each stage will be spatially and temporally filtered. Left ventricular counts in each frame will be determined by a semi-automated edge-detection algorithm. Left ventricular ejection fraction will

be calculated from the background-corrected left ventricular activity–time curve. Stroke counts are calculated as the product of background-corrected end-diastolic counts (corrected for number of cycles accepted and cycle duration) and left ventricular ejection fraction. Peak left ventricular filling rate in terms of end-diastolic volumes per second (EDV/s) and time to peak filling in milliseconds after end systole will be calculated from the second derivative of the diastolic activity–time curve. The validity of these radionuclide measures of diastolic filling at high heart rates has been established previously [19].

• Echocardiography

Echocardiography will be performed with patients in the left lateral decubitus position. Images will be stored digitally and all measurements will be averaged over 3 beats. Standard echocardiographic views will be obtained from parasternal and apical windows on held expiration. Transmitral flow profiles, pulmonary vein flows and tissue doppler assessment of mitral annulus velocities (as a measure of long axis systolic and diastolic function) will be performed. The E/Ea ratio will be calculated as an indirect measure of LVEDP. Radial, circumferential and longitudinal strain will be assessed using speckle tracking.

MRI & ³¹P MRS

• Cardiac MRI: cardiac

Cardiac MRI will be performed on a 3 T Phillips MR system to assess LV systolic function, LV volumes and LV mass, resting regional myocardial perfusion (first pass imaging following GdDTPA contrast injection); the degree of fibrosis (GdDTPA late enhancement).

• ³¹P MRS: cardiac

This will be performed on a Philips Achieva 3 T scanner using a 14-cm diameter transmit/receive ³¹P surface coil. Subjects are examined supine with the coil centered on the precordium and positioned at the isocentre of the magnet. A non-water-suppressed ¹H point resolved spectroscopy acquisition is used to monitor resonance frequency determination and B₀ shimming over the ³¹P-CMRS volume of interest, which is carefully positioned to cover the entire inter-ventricular septum. The ³¹P-CMRS acquisition consists of an ECG-gated image selected *in vivo* spectroscopy sequence (ISIS), triggered to mid–late diastole, with a repetition time of at least 10 s, an echo time of 0.1 ms, 128 averages and 512 samples,

as previously shown by us at 3 T [20]. The total spectroscopic scan duration is 20 min. Java magnetic resonance user interface (jMRUI version 3.0) [21] is used to post-process the data with a 15-Hz Gaussian filter and Fourier transformation. Phase correction is performed with the PCr peak as the reference peak. Quantification is performed with AMARES using prior knowledge to preselect the peaks. The concentrations of PCr, γ -ATP and 2,3-diphosphoglycerate (2,3-DPG) are calculated as area under the peaks. Cramér-Rao standard deviations of all peaks are calculated and only those <20% will be accepted. In all spectra, γ -ATP will be corrected for blood contamination and PCr/ATP ratios are saturation corrected [20,22,23].

• Intervention

After the investigations have been performed, the subjects will be randomized to receive either 100 mg twice a day of perhexiline a day or placebo (see **Appendix 1** online at <http://www.futuremedicine.com/doi/full/10.2217/FCA.14.62>). Blood samples for serum perhexiline levels will be checked at 7 days, then at 4 weeks, and the patients will be contacted by phone after each blood test to recommend the dose adjustments depending on the levels and to discuss any concerns that they might have (see **Appendix 2 & Appendix 3**). If the level reaches a steady state (between 0.15 and 0.60 mg/l) then they will be checked at 3 months (end of study), if not they will be checked every 2 weeks until they reach a steady state. The laboratory undertaking the plasma perhexiline measurements (Cardiff toxicology laboratories) will advise on appropriate dose titrations and also dummy dose titrations in the placebo group to ensure double blinding (the investigators will be blind to allocation and plasma levels). The target serum perhexiline level will be 0.15–0.60 mcg/ml (150–600 ng/ml). After 3 months all baseline investigations will be performed again.

• Significance of the study

If positive, this study would provide a novel treatment strategy for this large group of patients with currently very limited treatment options.

• Statistical plan

n = 29 (perhexiline) and n = 29 (placebo) subjects would be required to detect a mean difference in peak VO₂ (the primary end point of the study) of 3 ml/kg/min and SD of 4.5 with a power of 80% and a p < 0.05 (using a one-tailed

t-test in which the hypothesis is that perhexiline increases peak VO_2). Data will be analyzed using analysis of covariance with baseline measures as covariates. A sample size of 24 per group would be required to identify a 25% increase in PCr/ATP ratio (assuming an SD of 0.53 and a ratio of 1.56 in the placebo group; using a one-tailed t-test in which the hypothesis is that perhexiline improves the cardiac energetics [PCr/ATP ratio]). We intend to study 36 (perhexiline) and 36 (placebo) subjects to allow for potential dropouts, and for those unwilling to undergo the cardiac MRS component of the study.

• **Trials management group**

A data monitoring committee will assess the progress, safety and feasibility of the study every 6 months from the onset of recruitment. Care will be taken so that data are not un-blinded to those directly involved in acquiring and analyzing data.

• **Indications for discontinuing perhexiline therapy & withdrawing participants from the study**

In accordance with the current revision of the Declaration of Helsinki (amended October 2000, with additional footnotes amended 2002 and 2004) and any other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason, without prejudice to his or her future medical care by the physician or at the institution, and is not obliged to give his or her reasons for doing so. The investigator may withdraw the patient/subject at any time in the interests of the patient/subject's health and well-being. In addition, the patient/subject may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the investigator;
- Pregnancy;
- Ineligibility (either arising during the study or retrospective having been overlooked at screening);
- Significant protocol deviation;
- Patient/subject noncompliance with treatment regimen or study requirements;
- Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures;

- An adverse event that requires discontinuation of the study medication or results in inability to continue to comply with study procedures. These include:

- Appearance of peripheral neuropathy;
- Appearance of clinical signs of hepatic disease;
- Persistent elevations in serum enzymes or abnormalities of specific liver function tests;
- Persistent or marked hypoglycemia.

• **Expected adverse drug reactions**

- Short term (occurring after as little as 24 h of therapy): nausea, dizziness (usually transient) and hypoglycemia in diabetic patients;
- Long term (usually occurring after >3 months of continuous treatment): peripheral neuropathy, hepatitis/cirrhosis, extrapyramidal dysfunction, muscle weakness and ataxia.

Discussion

HFpEF is a major and growing clinical problem associated with high morbidity and mortality. Blockade of neurohumoral activation, a strategy that has been very successful in systolic HF, has proved ineffective in HFpEF. There is an urgent need for effective therapy. Recent evidence has suggested a crucial role of cardiac energetic impairment in the pathophysiology of the disorder. The study targets this cardiac energetic impairment by investigating the effects of the metabolic modulator Perhexiline.

Other information

Eudra CT number: 2006-001109-28

Trial registration: ClinicalTrials.gov: NCT00839228

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Financial & competing interests disclosure

The authors thank the British Heart Foundation for funding this study through a grant. Frenneaux is inventor on method of use patents for perhexiline in heart muscle diseases. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical disclosure

The protocol has been approved by south Birmingham research ethics committee and has received clinical

authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Executive summary

- Heart failure with normal ejection fraction (HFNEF) is a common problem. Therapies that are effective in systolic heart failure have been shown to be ineffective in HFNEF.
- We previously demonstrated that impaired cardiac energetic status in these patients results in a profound dynamic disturbance of diastolic and contractile performance of the left ventricle during exercise in these patients.
- Perhexiline, a metabolic modulator was shown by us to abrogate cardiac energetic impairment in patients with symptomatic hypertrophic cardiomyopathy, correcting the exercise related diastolic and contractile dysfunction seen in these patients and thereby increasing exercise capacity and improving symptoms.
- In the present study we will test the hypothesis that perhexiline has similar beneficial effects in patients with HFNEF.

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