Multicentre double-blind randomized controlled trial of perhexiline as a metabolic modulator to augment myocardial protection in patients with left ventricular hypertrophy undergoing cardiac surgery

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Received 11 May 2014; received in revised form 12 September 2014; accepted 6 October 2014

Abstract

OBJECTIVES: Patients undergoing cardiac surgery require adequate myocardial protection. Manipulating myocardial metabolism may improve the extent of myocardial protection. Perhexiline has been shown to be an effective anti-anginal agent due to its metabolic modulation properties by inhibiting the uptake of free fatty acids into the mitochondrion, and thereby promoting a more efficient carbohydrate-driven myocardial metabolism. Metabolic modulation may augment myocardial protection, particularly in patients with left ventricular hypertrophy (LVH) known to have a deranged metabolic state and are at risk of poor postoperative outcomes. This study aimed to evaluate the role of perhexiline as an adjunct in myocardial protection in patients with LVH secondary to aortic stenosis (AS), undergoing an aortic valve replacement (AVR).

METHODS: In a multicentre double-blind randomized controlled trial of patients with AS undergoing AVR ± coronary artery bypass graft surgery, patients were randomized to preoperative oral therapy with either perhexiline or placebo. The primary end point was incidence of inotrope use to improve haemodynamic performance during the first 6 h of reperfusion, judged by a blinded end points committee. Secondary outcome measures included haemodynamic measurements, electrocardiographic and biochemical markers of new myocardial injury and clinical safety outcome measures.

RESULTS: The trial was halted early on the advice of the Data Safety and Monitoring Board. Sixty-two patients were randomized to perhexiline and 65 to placebo. Of these, 112 (54 perhexiline and 48 placebo) patients received the intervention, remained in the trial at the time of the operation and were analysed. Of these 112 patients who achieved the primary end point, 30 patients (16 perhexiline and 14 placebo) had inotropes started appropriately; there was no difference in the incidence of inotrope usage OR of 1.65 [confidence interval (CI): 0.67–4.06] \( P = 0.28 \). There was no difference in myocardial injury as evidenced by electrocardiogram odds ratio (OR) of 0.36 (CI: 0.07–1.97) \( P = 0.24 \) or postoperative troponin release. Gross secondary outcome measures were comparable between the groups.

CONCLUSIONS: Perhexiline as a metabolic modulator to enhance standard myocardial protection does not provide an additional benefit in haemodynamic performance or attenuate myocardial injury in the hypertrophied heart secondary to AS. The role of perhexiline in cardiac surgery is limited.

Keywords: Myocardial protection • Left ventricular hypertrophy • Perhexiline • Metabolic modulation • Aortic stenosis • Cardiac surgery

\textsuperscript{†}Presented at the Society of Cardiothoracic Surgery of Great Britain and Ireland annual meeting, Edinburgh, UK, held in March 2014.

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INTRODUCTION

Aortic stenosis (AS) is a degenerative condition primarily of the elderly population. The pathophysiological response to AS is left ventricular hypertrophy (LVH) [1]. If left untreated, median survival post-symptom onset is 2 years [2]. Therefore, aortic valve replacement (AVR) is indicated in symptomatic patients with AS to improve both symptoms and prognosis [3]. LVH is a well-known risk factor for increased morbidity and mortality particularly following cardiac surgery [4].

In the UK, the early mortality following AVR remains at 3% despite an increasing elderly population, which has a higher predicted risk profile [5]. A low cardiac output state (LCOS) following AVR has been identified as the commonest mode of death (36%) in patients with LVH following an AVR [6] and in patients undergoing isolated AVR, 38% of patients who had an LCOS died [7].

Standard techniques of myocardial protection may be inadequate in the presence of LVH due to an increased diffusion distance in the setting of a less dense capillary bed [8]. Moreover, LVH inherently has an impaired myocardial metabolism; uncoupling of glycolysis and glucose metabolism, shift away from free fatty acid use and a depressed energetic state [1, 9]. In patients with LVH, there is an associated increased mortality and morbidity including respiratory failure, renal failure, heart failure, arrhythmias and length of stay and increased left ventricular mass index has been implicated as an independent predictor of mortality [6, 10].

Metabolic therapies have been proposed as a targeted therapy for improving the tolerance of the myocardium to the global ischaemia reperfusion injury, associated with cardiopilec arrest especially in the metabolically vulnerable hypertrophied myocardium. We have previously trialled glucose-insulin-potassium (GIK) as an adjunct to standard cardiopilec protection [11–13] in patients undergoing coronary artery bypass graft (CABG) surgery and/or AVR with LVH. The effects of GIK have been hypothesized to act through multiple pathways that include suppression of lipolysis, insulin-related glucose flux and anaerolysis.

GIK therapy in patients with LVH undergoing AVR has been shown to significantly reduce LCOS. In addition to the above modes of action, the pleotrophic signalling properties of insulin resulting in activation of the phosphatidylinositol three-kinase pathway with an increase in protein kinase B- and AMP-activated protein kinase activation, together with increase in O-GlcNAcylation have been shown to be cardioprotective [11].

Although GIK has been shown to be efficacious in this respect, its use is labour-intensive and the associated hyperglycaemia and vasoplegic ultimately have prevented its more widespread introduction. Perhexiline has been hypothesized to have many of the metabolic benefits of GIK without the documented side-effects or logistical pitfalls. Perhexiline is thought to promote carbohydrate metabolism by inhibiting carnitine palmitoyl transferase-1 (CPT-1), the enzyme responsible for the uptake of free fatty acids into the mitochondrion [14, 15]. By inhibiting CPT-1, substrate utilization is shifted towards a more efficient carbohydrate metabolism, reducing inefficient free fatty acid (FFA) metabolism in times of oxygen deprivation [16], with consequent improvement in cardiac energetic state. In addition to CPT-1 inhibition, perhexiline has shown to decrease thioderoids-interacting protein expression, in turn limiting oxidative stress via the anti-oxidant thioderoids system [17].

Perhexiline has shown to be an effective anti-anginal agent [15] and has been demonstrated to improve oxygen consumption, quality of life and ejection fraction in patients with chronic heart failure [18]. In recent studies, it has been shown to improve myocardial energetics in patients with heart failure secondary to hypertrophic cardiomyopathy [19]. We have evaluated the effects of perhexiline in patients with ischaemic heart disease undergoing isolated CABG surgery but demonstrated no added benefit of perhexiline [20]. In this study, the majority of patients had normal ventricular function and no hypertrophy. The effects of perhexiline have not been evaluated in patients with LVH secondary to AS.

Although the effects of GIK have been beneficial in patients with and without LVH, our group has shown that the magnitude of the benefit was greater in patients with LVH [11]. This could be due to the inherent derangement in metabolism and a reduced energetic state associated with LVH. We hypothesize that the energetically impaired hypertrophic myocardium may be more vulnerable to ischaemia/reperfusion injury and thus may derive greater benefit from an improved metabolism. Therefore, this study was designed to examine the role of perhexiline in myocardial protection, in patients with LVH secondary to AS undergoing cardiac surgery.

METHODS

Study design

We conducted a double-blind randomized placebo-controlled trial of oral perhexiline therapy in patients undergoing AVR or CABG with evidence of LVH. LVH was measured using echocardiography and defined by left ventricular mass index > 134 g/m² for men or 100 g/m² for women [21].

The study and all amendments were approved by the Cambridgeshire 1 Research Ethics Committee (08/H0304/48), the UK Medicines and Healthcare products Regulatory Authority (16719/0210/001-0004) and the Hospital Trust Board of Research (RRK3535). The trial was registered with clinicaltrials.gov (NCT00989508), the European Clinical Trials Database (2008-002376-95) and the UK Clinical Research Network (5886). All research was performed in accordance with the Declaration of Helsinki within a research governance framework.

Once written informed consent was obtained, the participants were randomly allocated on a 1:1 ratio to perhexiline or placebo using a blinded minimization procedure stratified for surgeon and need for concomitant CABG surgery. Patient inclusion and exclusion criteria are outlined in Table 1.

Table 1: Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>LVH secondary to AS awaiting AVR</td>
<td>Patient choice</td>
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<td>AVR ± CABG with LVH secondary to AS Elective and urgent cases</td>
<td>Pregnancy</td>
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<td>Renal impairment (creatinine &gt; 200 μmol/l)</td>
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<td>Diabetes mellitus</td>
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<td>Peripheral neuropathy</td>
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<td>Intention to perform any other cardiac procedure excluding salvage operations</td>
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<td>Severe aortic regurgitation</td>
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<td>Age &lt; 18 years</td>
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Trial therapy

The investigational medicinal products (IMPs) such as perhexiline and placebo tablets were manufactured by Sigma Pharmaceuticals (Baulkham Hills, Australia) and were provided with a certificate of analysis. They were ordered through UDG Ltd (South Normanton, UK). Bilcare GCS (Crickhowell, UK) provided the packaging, labeling and Qualified Person release on the perhexiline/placebo samples. The tablets were bottled into predefined bottle numbers according to the randomization sequence. All tablets were identical (white/off-white and 8.5 mm in diameter) and were labelled ‘PEXSIG’.

With our knowledge of the pharmokinetics of perhexiline, a pragmatic short loading regime followed by a maintenance regime was devised. Participants were dosed on a loading regime of 200 mg bd (twice daily) for 3 days and maintained on a fixed maintenance regime of 100 mg bd thereafter until their surgery. We have previously demonstrated that this regime was adequate to achieve therapeutic levels (0.16–0.6 mg/l) [20]. IMP therapy was administered for a minimum of 4 days prior to surgery and a maximum of 27 continuous days including the loading regime. Therapy was commenced from randomization to time of surgery. Patients were routinely followed up by telephone enquiry to assess compliance and side-effects. For in-patients, the IMP was prescribed and administered as outlined above.

Surgery, anaesthesia, cardiopulmonary bypass and myocardial protection

Anaesthesia, cardiopulmonary bypass and myocardial protection were all standardized as previously reported [13]. Anaesthesia was achieved with fentanyl, propofol and pancuronium/rocuronium and maintained with propofol and alfentanil; other volatile anaesthetic agents were not permitted. Standard myocardial protection was achieved using St Thomas’ solution buffered in cold blood given antegrade, intermittently (12 ml/kg for induction and 6 ml/kg for maintenance doses at 20 min intervals). In cases of AVR + CABG, distal coronary anastomoses were constructed using a single aortic cross-clamp period and proximal anastomoses during partial aortic occlusion.

End points

Primary end point. The primary end point was the incidence of appropriate inotrope use based on a comparison of cardiac index to baseline, to achieve an increase in cardiac index of > 0.3 l/min/m² within the first 6 h of reperfusion. A blinded end points committee was convened at predetermined recruitment targets. It was deemed appropriate to start an inotrope to treat a low cardiac output episode (LCOE). LCOE was defined as hypotension (mean arterial pressure <60 mmHg) with a cardiac index <2.2 l/min/m² in the presence of adequate filling pressures (central venous pressure (CVP): 8–12 mmHg and/or pulmonary artery wedge pressure (PAWP) of 12–16 mmHg) and adequate heart rate (80–110 bpm) ± an intra-aortic balloon pump required for >60 min to improve the haemodynamic status, within the first 6 h of reperfusion. Reperfusion was achieved when the aortic cross clamp was removed, re-establishing flow into the coronary arteries and time from reperfusion was calculated from this point. The primary end point and haemodynamic measurements were obtained by using a Swan–Ganz thermodilution pulmonary artery catheter placed within the pulmonary artery. Cardiac output studies were performed using the Swan–Ganz catheter based on the Fick principle of thermodilution [11].

Secondary outcome measures. Predefined secondary outcome measures included the total incidence and volume of inotrope and vasoconstrictor requirements. Electrocardiographic evidence of new myocardial injury was measured by comparing baseline electrocardiograms (ECGs) with ECGs on discharge by an independent blinded cardiologist. New myocardial injury was defined as the presence of new Q waves (≥2 mm in depth) in two or more contiguous leads, new bundle branch block or loss of R wave progression. The release of troponin in the first 6, 12 and 24 h of reperfusion was compared with baseline. Other outcome measures included postoperative intensive care unit (ITU) and total length of stay, wound infection and the incidence of systemic complications including arrhythmias.

Troponin analysis was performed using the Elecsys Troponin assay (Roche Diagnostics, Burgess Hill, UK). In March 2011, troponin analysis at the primary centre changed to using the high sensitivity troponin T analysis using the Cobas immunoassay and Elecsys analysers (Roche Diagnostics, Burgess Hill, UK).

Statistical analysis

An estimated sample size of 196 patients was required based on a power of 90% with a α of 0.05 randomizing 1:1 between treatment and control groups. This was estimated based on the incidence of inotrope use observed on an earlier trial conducted within the department (myocardial protection with GIK); incidence of inotrope use in placebo was 40% and in the GIK group was 19% [13]. Assuming perhexiline therapy may show a similar reduction in inotrope usage, we intended to recruit 220 patients to provide an adequate power to analyse all the secondary end points.

A statistical analysis plan was developed prior to database locking. The main outcome measures were analysed on an intention-to-treat basis. Analysis was performed using SAS (version 9.2, SAS Institute, Inc., Cary, NC, USA). Continuous data were assessed for normal distribution and presented as mean ± standard deviation (SD) of the mean or median [interquartile range (IQR)]. Student’s t-test was used to analyse normally distributed data. Skewed data were analysed by Mann–Whitney U-test. Categorical data were analysed by Fisher’s exact test. Statistical significance was defined as a P < 0.05. The primary analysis was conducted using non-linear mixed models, including baseline status and randomized group as fixed effects and operating surgeons as random effects. The analysis as per the analysis plan was intended to stratify for baseline ventricular function and priority (elective/urgent) status, accounting for surgeon as a random effect. However, due to the small number of patients in these groups, stratification by ventricular function and priority was not performed but surgeons were used as random effects. Missing data for outcomes were not imputed.

All errors including errors to treatment and data entry errors were treated as measurement errors and therefore the locked database was analysed on an intention-to-treat basis for the primary and secondary outcomes. Hence if any error was found during the analysis, no further new analyses were conducted on the locked database. Further analyses would have been performed only if any supportive analyses would have led to qualitatively different results. The assessment for futility was conducted using the
O’Brien Fleming alpha spending function plan, performed to examine the effect of primary outcome including futility; benefits are based upon Lan–DeMets plan and harm based upon the power family spending function.

**Data safety monitoring and futility analysis**

An independent data safety monitoring board (DSMB) was appointed and a DSMB meeting was held once a predetermined target of 45% recruitment (99 patients) had been operated on and discharged (allowing for all outcome measures to be collected). The DSMB were requested to assess the trial for safety and efficacy and also assess the trial for futility based on the results of a preceding trial, evaluating the role of perhexiline, as an adjunct to myocardial protection in patients undergoing CABG [20]. Futility was assessed using the O’Brien Fleming Spending approach.

**RESULTS**

**Study population**

The participant flow is illustrated in the CONSORT flow diagram (Fig. 1). Sixty-two and 65 patients were randomized to perhexiline and placebo, respectively. Five patients withdrew consent; 4 and 1 from the perhexiline and placebo groups, respectively. Of these, 3 had started trial therapy before they withdrew consent (prior to surgery), from any further participation; 2 and 1 in the perhexiline and placebo groups, respectively; hence although these patients were followed up as per the trial protocol, they have been excluded from all analyses. Three patients were withdrawn from the trial; 2 were randomized, but did not receive the intervention but met the exclusion criteria; 1 had atrial fibrillation and the other post-randomization was scheduled for a transcatheter aortic valve implantation. The third was withdrawn due to pre-existing renal impairment (creatinine > 200), but had inadvertently started the trial therapy; hence although followed up as per the trial protocol, they have been excluded from all analyses. Therefore 112 patients, 54 and 58 in the perhexiline and placebo groups respectively, were randomized, received the intervention and protocol, they have been excluded from all analyses. Three patients were withdrawn from the trial; 2 were randomized, but did not receive the intervention but met the exclusion criteria; 1 had atrial fibrillation and the other post-randomization was scheduled for a transcatheter aortic valve implantation. The third was withdrawn due to pre-existing renal impairment (creatinine > 200), but had inadvertently started the trial therapy; hence although followed up as per the trial protocol, they have been excluded from all analyses. Therefore 112 patients, 54 and 58 in the perhexiline and placebo groups respectively, were randomized, received the intervention and underwent an operation. A further 2 patients from the perhexiline group and placebo group were excluded from the primary outcome analysis only, as they did not have a pulmonary artery flotation catheter; inserted post anaesthetic induction.

Preoperative and operative demographics are outlined in Tables 2 and 3, respectively. The echocardiographic demographics are outlined in Table 4. There were no significant differences in operative or echocardiographic variables between groups.

**Perhexiline therapy**

The median duration of trial therapy was 8.5 days [interquartile range (IQR): 5–17.5] for all trial participants in the final analysis, and was 8 days (IQR: 5–11) and 8 days (IQR: 6–14) in the perhexiline and placebo groups, respectively (P = 0.41). Of the 112 patients that received trial therapy, 10 patients were not on trial therapy at the time of their operation; 4 ran out of tablets before their operation and 6 stopped therapy due to side-effects; of the 6, 5 were in the treatment group. Of the 4 that ran out of tablets, 3 were on placebo and 1 on perhexiline.

Serum for perhexiline concentration analysis was available in 106 patients, 51/54 (94%) in the perhexiline group and 55/58 (95%) in the placebo group and were analysed for perhexiline and hydroxy-perhexiline concentrations. All but one patient in the placebo group had a serum perhexiline concentration of zero; in this patient, perhexiline and hydroxy-perhexiline concentrations were 0.09 and 0.74, respectively. This patient had been wrongly allocated into the placebo group as a data entry error prior to locking the database; was analysed within the placebo group on an intention-to-treat basis without any further analyses thereafter and therefore treated as an unbiased measurement error.

In the treatment group, median perhexiline concentration was 0.22 mg/l (IQR: 0.09–0.43). Twenty-four patients (47%) were within the therapeutic range, with 7 above the therapeutic range and 20 (39%) below the therapeutic range. Of those that were sub-therapeutic, 2 patients had no detectable perhexiline concentration in the serum; 1 stopped therapy due to side-effects after 1 day of therapy and the other ran out of tablets 1 month prior to the operation.

**Primary outcome**

Of 110 patients, the blinded end points committee judged that 38 patients had inotropes started appropriately. Of the 30, 16/52 were in the perhexiline group and 14/58 in the placebo group; there was no statistical significance in the incidence of appropriate inotrope usage odds ratio (OR) of 1.65 [confidence interval (CI) 0.67–4.06] P = 0.28.

**Secondary outcomes**

**Haemodynamic measurement.** Heart rate, filling pressures (CVP and PAWP) and mean arterial pressures did not differ significantly between the two groups. Baseline cardiac index was similar between the groups. Mean cardiac index was not significant at each time point until at 12 h of reperfusion (Table 5) when the perhexiline group had a lower cardiac index.

**Inotrope and vasoconstrictor use.** The use of all inotropes was assessed between removals of the aortic cross clamp for 6 h and then from 6 to 12 h of reperfusion. There was no difference in the usage of inotropes between groups during the first 6 h of reperfusion, with 22 (40%) and 15 (26%) patients in the perhexiline and placebo groups respectively OR of 2.31 (0.99–5.74), P = 0.053. There was a statistically significant difference in inotrope usage within 6–12 h, with 26 (48%) and 15 (26%) of patients in the perhexiline and placebo groups respectively; requiring inotropes, OR of 3.11 (1.34–7.23), P = 0.009.

Within the first 6 h of reperfusion, overall (phenylephrine and/or noradrenaline) constrictor use was 91% in the placebo group and 89% in the perhexiline group (P = 0.76). Within 6–12 h of reperfusion, overall vasoconstrictor use was 64% in the placebo group and 80% in the perhexiline group (P = 0.09). The use of phenylephrine and noradrenaline individually at each time point was not significant between the groups.

**Myocardial injury**

**Electrocardiogram evidence.** Myocardial injury as defined by electrocardiographic evidence of myocardial infarction was not different between the groups. New myocardial injury was identified in 2 (4%) patients in the perhexiline group and 6 (10%)
patients in the placebo group and showed no statistical significant difference OR of 0.36 (CI: 0.07–1.97) \( P = 0.24 \).

**Biomarker evidence.** In March 2011, the method of troponin analysis changed. Therefore, the analysis of troponin between perhexiline and placebo was sub-divided into those that had the older version of troponin analysis (\( n = 46, 23 \) in each group) and those that had the newer high sensitivity troponin analysis (\( n = 55, 24 \) in the perhexiline group and 31 in the placebo group). Analysis of troponin at baseline and at 6, 12 and 24 h showed no statistical difference between the groups with either method of troponin analysis. With the old method, mean troponin (SD) was 0.78 ng/ml (0.37) and 0.85 ng/ml (0.38) for perhexiline and placebo groups, respectively OR of \(-0.08 \) (–0.30 to 0.15) \( P = 0.5 \). With the new method, mean troponin (SD) was 1431.3 ng/l (709.3) and 1114.6 ng/l (1137.4) for perhexiline and placebo groups, respectively OR of 334.4 (–446.9 to 1115.6) \( P = 0.39 \).

**Side-effects.** Of 127 patients that received trial therapy, 11 (9%) patients reported side-effects. The majority of side-effects were reported by patients in the perhexiline group (\( n = 10 \)) and consisted of dizziness with a combination of nausea. Other side-effects reported included diarrhoea and itching. One patient in the placebo group reported a tingling sensation down the arm. Of the 11 (9%) with side-effects, 6 (5%) patients stopped trial therapy (1 had no detectable perhexiline concentrations and 1 was sub-therapeutic at the time of surgery). The other 5 (4%) continued on a reduced dose of trial therapy or had resolution of side effects after the loading regime.

**Safety outcomes and complications.** There was no difference between the groups for the incidence of reperfusion or post-operative arrhythmias, extubation times, length of ITU stay, length of hospital stay or in-hospital mortality. There was no significant difference of any of the postoperative complications (Table 6).
except for renal impairment (Creatinine > 200) with 6 patients developing renal impairment in the perhexiline group and none in the placebo group (P = 0.01), 2 requiring haemofiltration and 1 requiring dialysis.

**Futility analysis.** The DSMB recommended that the trial should be halted based on the futility of achieving the scientific objective; there was no evidence of clinical benefit associated with the investigational treatment and therefore it was deemed futile to continue recruiting into the trial. Based on these recommendations, the trial steering committee halted the recruitment into the trial. The O’Brien Fleming alpha spending plan for the primary outcome illustrated the efficacy, futility and harm as outlined in Fig. 2 (standard errors vs number of patients who completed the trial).
At a planned observation at 45% recruitment (99 patients), analysis of the primary outcome showed a significance of 0.823, which fell below the line of futility and above the line of harm, demonstrating futility of the trial.

DISCUSSION

This study evaluated the role of perhexiline as a metabolic modulating agent to improve myocardial protection in patients with LVH secondary to AS undergoing surgical AVR (HYPER trial). There was no overall benefit in perhexiline therapy as an adjunct to standard myocardial protection in patients undergoing AVR ± CABG. The primary end point of incidence of inotrope use to treat a LCOS appropriately was the same between groups. However, the overall incidence of inotrope use was higher in the perhexiline group during the first 12 hours following reperfusion and was statistically significant in the 6- to 12-h period post-reperfusion. There was no benefit of perhexiline therapy in reducing postoperative myocardial injury.

This study was the first to evaluate the role of perhexiline in patients with LVH secondary to AS undergoing cardiac surgery. Perhexiline has been shown to be an inhibitor of FFA utilization [14, 15]. Although FFA metabolism produces higher energy per gram mole of substrate than glucose, carbohydrate metabolism is more metabolically efficient, requiring less oxygen to generate an equivalent amount of ATP [9]. Therefore, it was hypothesized that promoting carbohydrate metabolism prior to cardiac surgery, should prime the cardiomyocyte to deal with the stressors of ischaemia and reperfusion. This study has demonstrated that oral perhexiline therapy does not augment standard myocardial protection in patients with LVH undergoing cardiac surgery. The role of perhexiline in the setting of cardiac surgery has only been

<table>
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<th>Table 5: Mean cardiac index comparisons at each time point</th>
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<td><strong>Measured cardiac index time point</strong></td>
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<td>Pre-CPB</td>
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<th>Table 6: Safety outcome measures and postoperative complications</th>
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<td><strong>Placebo</strong></td>
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<td>Haemofiltration (%)</td>
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<td>Neurological</td>
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<tr>
<td>Difficulty waking (%)</td>
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<td>Focal CVA (%)</td>
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Figure 2: The futility analysis using the alpha spending plan shows the bounds for efficacy, futility and harm for the primary outcome at each planned look at 45 (99 patients), 73 (160 patients) and 100% (220 patients) recruitment. It depicts the standard errors on the Y-axis and for each boundary (efficacy, futility and harm) vs the number of patients that would complete the trial at 45, 73 and 100% recruitment on the X-axis. At a planned look at 45% recruitment, analysis of the primary outcome showed a significance of 0.823, which fell below the line of futility and above the line of harm, demonstrating futility of the trial. If the significance at 45% fell below the line of efficacy and above the line of futility, then the trial was on target to achieve a positive outcome. Similarly, if the significance fell below the line of harm, then the trial would be halted early for the risk of harm or be modified to reduce harm for the patients. Alternatively if the significance fell above the line of efficacy, the trial would be halted early for efficacy.
evaluated in one other study, conducted by our group. This study randomly assigned oral perhexiline to patients with coronary artery disease undergoing CABG surgery (CASPER), and showed no cardioprotective or clinical benefits [20]. This CASPER trial recruited patients with ischemic heart disease that required CABG surgery only and the majority of these patients had good ventricular function and no hypertrophy. The HYPER trial evaluated patients with hypertrophic ventricles secondary to AS, irrespective of coronary artery disease. Due to this fundamental difference in patient cohort, it was plausible to run the trials in parallel. CASPER started recruitment 2 years and 8 months before HYPER, and the overlap between the two was 6 months.

Despite our findings, there have been studies advocating perhexiline as a clinically useful metabolic therapy. In a study by Abozguia et al. [19], perhexiline was shown to improve high-energy phosphate ratios, improve oxygen consumption and New York Heart Association symptoms in patients with hypertrophic cardiomyopathy. In an earlier study, Lee et al. [18] showed an improvement in oxygen consumption, quality of life and left ventricular ejection fraction in patients with chronic heart failure. In a review of perhexiline, clinical applications in ischaemic heart disease, AS and heart failure have been explored and supported [15]. One study supporting the use of perhexiline in the medical management of symptomatic AS, evaluated its role in 15 elderly patients, where 13 showed symptomatic improvement when followed up for 30 months [22]; this trial is limited by the small number of participants and its non-randomized nature. In addition, none of the patients were suitable for surgical intervention and did not undergo cardiac surgery. A common theme throughout all the studies that support perhexiline, as a metabolic agent is one where therapy is prolonged, monitored and optimized over months. This was not logistically possible in the real-world practice of cardiac surgery, reflected by this study.

In this study, the percentage of patients needing on-going vasoressor infusion in the first 6 h of reperfusion was high in both groups (91 vs 89%, placebo vs perhexiline, $P = 0.76$), and within the perhexiline group, was higher during the 6–12 h reperfusion period (64 vs 80%, placebo vs perhexiline, $P = 0.09$).

Furthermore, this study showed a statistically significant increase in overall inotrope usage within the perhexiline group in the 6–12 h reperfusion period, with no difference in serial measurements of other haemodynamic parameters, that is, filling pressures, heart rate and mean arterial pressures. In this study, inotrope use was used as a surrogate marker for myocardial protection based on its need to improve haemodynamic performance during an LCOS. A lower cardiac index would prompt the institution of inotropic support. Increased inotrope requirements during the 6–12 h period of reperfusion in this study, are consist with a significantly reduced cardiac performance measured by cardiac index at 12 h of reperfusion. These findings reflect similar findings from our previous trial (perhexiline in coronary artery surgery), where there was a significant reduction in cardiac index at 6 h albeit insignificant when corrected for baseline cardiac index (reduced in the perhexiline group) [20]. The reasons for reduced cardiac function at baseline associated with perhexiline are unclear and given the nominal nature of the statistical test for this analysis, the play of chance remains a plausible explanation of the result notwithstanding the apparently low $P$-value.

An alarming unexpected finding from this study is that perhexiline therapy has been associated with increased renal impairment (creatinine > 200) in 6 (11%) patients, with 2 (3%) requiring haemofiltration and 1 needing permanent dialysis. Baseline renal function was similar between the groups, with a marginally higher median serum creatinine level in the perhexiline group (not significant). Perhexiline is metabolized in the liver and its metabolites are excreted in the urine [15]. The variability of perhexiline metabolism among individuals and the associated risk of hepatotoxicity and neurological complications strongly contraindicate the use of perhexiline in patients with renal impairment. To our knowledge, there are no other reports implicating renal impairment with perhexiline therapy.

The significant secondary outcomes in favour of placebo therapy highlighted in this study need cautious interpretation; they are secondary end points and given the neutral primary end point, the secondary end points have to be interpreted as exploratory [23]. Further studies to evaluate these secondary end points in greater detail will be restrained due to the neutral clinical implications of perhexiline in this setting.

Although there are a number of studies showing that perhexiline inhibits CPT action, it is also thought to be a competitive inhibitor [19], competing with the endogenous enzyme malonyl-CoA. Hence, this inhibitory pathway is further tested in a patient who has been starved overnight in preparation for cardiac surgery. In these patients, CPT-1 inhibition may be overwhelmed by the amount of FFAs in the circulation and may not be effective during the ischaemia/reperfusion phase when metabolic support is most required. Therefore, there is no quantification as to how much CPT-1 inhibition takes place throughout the human myocardium during ischaemia/reperfusion. In contrast, metabolic support with GIK is known to improve haemodynamic performance when administered inotropically, due to substrate availability with glucose and the multifactorial cardioprotective benefits of insulin, including up-regulation of pro-survival pathways [11].

A limitation of this study is that 39% of patients were below the therapeutic range of serum perhexiline concentration. A minimum of 4 days therapy prior to surgery (a threshold that was adapted to optimize recruitment) could have contributed to this. However, from our previous trial with perhexiline in CABG, a propensity-matched analysis of patients in the therapeutic range only, again showed no difference in the myocardial benefits [20]. Furthermore, it has been implicated that despite high concentrations of perhexiline being found in the human atria and ventricular myocardium, compared with serum [24], this high concentration may not be adequately at steady-state to exert the maximum effects of CPT inhibition required to promote carbohydrate metabolism. Moreover, in a novel metabolomic study assessing the metabolites of myocardial ventricular tissue, there was no change in metabolism towards a carbohydrate system and no effect on the myocardial metabolism with exposure to perhexiline [20]. In this trial, very few urgent patients were included; due to the minimum duration of trial therapy required before surgery. This latter limitation disallows any assessment of perhexiline therapy on urgent cases, however given there is no overall clinical benefit, this evaluation is less pertinent.

This study was halted early due to futility, affirming the limited clinical benefit of perhexiline in cardiac surgery. The futility analysis was conducted in light of the results from our earlier trial with perhexiline in CABG (CASPER) showing no benefit. At the time of the futility analysis (2 years and 8 months after commencing recruitment into HYPER), 99 patients had completed follow-up and were suitable for analysis. The CASPER trial closed 4 months before the futility analysis of HYPER and therefore the CASPER trial results informed the futility analysis. The O’Brien Fleming alpha spending plan analysis for the primary outcome (Fig. 2) shows the futility in trying to achieve complete recruitment to the
trial, therefore the recommendation of the DSMB to halt the trial was executed.

Through the trials of GIK in cardiac surgery, it is evident that some metabolic therapies are associated with improved myocardial protection. Future research should aim to identify and evaluate a metabolic modulating agent that is potent, easily administered and monitored and one that is applicable in real-world cardiac surgery. Despite the clinical findings reported here, a recent novel study employing a combined proteomics, metabolomics and computational modelling approach, in a small rat heart model has shown activation of the pyruvate dehydrogenase complex with perhexiline therapy and suggests that perhexiline may have yet unknown complex systemic effects [25]. Such complex experimental studies may help elucidate the specific actions of metabolic therapies, yet clinical application may not replicate laboratory findings.

In conclusion, oral perhexiline therapy as an adjunct to standard myocardial protection in patients with LVH secondary to AS does not show additive myocardial protective or clinical benefits. Association with reduced haemodynamic performance during late reperfusion and postoperative renal impairment should be treated with caution. Its use as a metabolic modulator may remain restricted to patients who are not cardiac surgical candidates and are refractory to maximal medical therapy.

ACKNOWLEDGEMENTS

The anaesthetists in the study group were David Riddington; Harjot Singh; Peter Townsend; Deborah Turfery; Mark Wilkes and Craig McGrath. The surgeons in the study group were Jonathan Hyde and Uday Dandekar.

Funding

This work was supported by the British Heart Foundation (BHF PG/08/040).

Conflict of interest: Michael Frenneaux is the inventor of the method of use patents for Perhexiline in heart muscle diseases.

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