The effect of dietary creatine supplementation on skeletal muscle metabolism in congestive heart failure

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Aims To assess the effects of dietary creatine supplementation on skeletal muscle metabolism and endurance in patients with chronic heart failure.

Methods A forearm model of muscle metabolism was used, with a cannula inserted retrogradely into an antecubital vein of the dominant forearm. Maximum voluntary contraction was measured using handgrip dynamometry. Subjects performed handgrip exercise, 5 s contraction followed by 5 s rest for 5 min at 25%, 50%, and 75% of maximum voluntary contraction or until exhaustion. Blood was taken at rest and 0 and 2 min after exercise for measurement of lactate and ammonia. After 30 min the procedure was repeated with fixed workloads of 7 kg, 14 kg and 21 kg. Patients were assigned to creatine 20 g daily or matching placebo for 5 days and returned after 6 days for repeat study.

Results Contractions (median (25th, 75th interquartiles)) until exhaustion at 75% of maximum voluntary contraction increased after creatine treatment (8 (6, 14) vs 14 (8, 17), P = 0·025) with no significant placebo effect. Ammonia per contraction at 75% maximum voluntary contraction (11·6 μmol/l/contraction (8·3, 15·7) vs 8·9 μmol/l/contraction (5·9, 10·8), P = 0·037) and lactate per contraction at 75% maximum voluntary contraction (0·32 mmol/l/contraction (0·28, 0·61) vs 0·27 mmol/l/contraction (0·19, 0·49), P = 0·07) fell after creatine but not after placebo.

Conclusions Creatine supplementation in chronic heart failure augments skeletal muscle endurance and attenuates the abnormal skeletal muscle metabolic response to exercise.

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Key Words: Chronic heart failure, creatine, phosphocreatine, skeletal muscle metabolism.

Introduction

Exertional fatigue and dyspnoea are the dominant symptoms of chronic heart failure although the precise pathophysiology of these symptoms remains undetermined[1]. Certainly, the exercise capability of patients with chronic heart failure bears little relationship to the magnitude of the central haemodynamic disturbance[2]. Abnormalities of skeletal muscle in chronic heart failure are well described and there is increasing evidence that these may be an important determinant of symptoms in chronic heart failure[3–7]. The histology and biochemistry of skeletal muscle in chronic heart failure is abnormal at rest and on exercise magnetic resonance scanning indicates there is an early onset of anaerobic metabolism with a rapid fall in intracellular pH and a swift depletion of high energy phosphate bonds as determined by a fall in the ratio of phosphocreatine to inorganic phosphate[3–6].

Phosphocreatine and creatine have integral roles in energy metabolism in skeletal muscle via their part in the creatine kinase equilibrium reaction linked with adenosine triphosphate (ATP) and adenosine diphosphate (ADP) homeostasis (ADP + phosphocreatine ⇔ ATP + creatine)[8]. Phosphocreatine may act as a temporal buffer to maintain ATP concentrations at the myofibril via rephosphorylation of ADP[8]. Evidence also exists for a spatial buffering effect of phosphocreatine with phosphocreatine generated at the mitochondria via the creatine kinase reaction diffusing to the myofibril to buffer ADP[9]. The role of phosphocreatine is to deliver high-energy phosphate to the myofibril and to act as a store of high-energy phosphate to regenerate ATP via the creatine kinase reaction during intense
muscular contraction. At rest, phosphocreatine is then regenerated via the creatine kinase reaction. In addition to the exercising abnormalities of phosphocreatine/creatine, resting muscle biopsies in chronic heart failure have demonstrated a reduction in skeletal muscle creatine content and magnetic resonance studies have demonstrated a delay in the resynthesis of phosphocreatine post-exercise [10,11]. Creatine is ingested in a normal diet and is found in meat and fish [12]. Dietary supplementation with supraphysiological amounts of creatine in normal volunteers increases skeletal muscle creatine content, increases muscle work and delays the onset of fatigue during exercise and may augment the resynthesis of phosphocreatine after exercise [13–15]. Creatine supplementation also attenuates the accumulation of humoral markers of metabolic stress during exercise [13,16]. One study has suggested that creatine supplementation in chronic heart failure produces an increase in skeletal muscle total creatine and phosphocreatine with an improvement in skeletal muscle performance [17].

We have previously shown resting and exercising abnormalities of skeletal muscle metabolism and their relationship to symptoms in chronic heart failure using a forearm model of muscle metabolism [18]. The purpose of this study was to investigate the effects of dietary creatine supplementation on the metabolic response of the forearm to exercise in patients with chronic heart failure.

Methods

Patients

We recruited 20 male patients (mean (SEM) 63·5 (1·4) years) from outpatient clinics. All had stable chronic heart failure of at least 3 months duration. The patient demography is detailed in Table 1. There were no significant differences in baseline demographic variables between creatine and placebo treated groups. All patients had radiographic cardiomegaly and echocardiographic confirmation of left ventricular dilatation and dysfunction (left ventricular end-diastolic dimension >5·5 cm, fractional shortening <25%). Local ethical approval was obtained and all patients gave written informed consent.

Table 1 Patient demography in creatine and placebo treated groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Creatine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/Female)</td>
<td>10/0</td>
<td>10/0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64·9 ± 5·7</td>
<td>62 ± 6·5</td>
</tr>
<tr>
<td>Aetiology of CHF</td>
<td>IHD 7, DCM 3</td>
<td>IHD 7, DCM 2, AVR 1</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2·80 ± 0·42</td>
<td>3·00 ± 0·47</td>
</tr>
<tr>
<td>Frusemide dose (mg)</td>
<td>271 ± 169</td>
<td>244 ± 130</td>
</tr>
</tbody>
</table>

IHD = ischaemic heart disease; DCM = dilated cardiomyopathy; AVR = aortic valve replacement.

Creatine administration

Patients were then randomly allocated in a double-blind design to receive creatine 5 g four times a day or matching placebo for 5 days. On the 6th day patients were restudied in an identical manner to the baseline study.
Biochemical analysis

Lactate
Blood lactate was determined from 1 ml samples of blood which were immediately deproteinized in 3 ml of 10% cold perchloric acid and centrifuged. The supernatant was stored at -20 °C until later analysis. The intra-assay coefficient of variation for lactate in our laboratory is 1.0% (n=10) and the inter-assay coefficient of variation for lactate is 3.5% (n=10).

Ammonia
Three ml samples of blood were mixed with lithium heparin and centrifuged, the serum was stored at -80 °C until analysis within 36 h of the sampling. The intra-assay coefficient of variation for ammonia in our laboratory is 2.5% (n=10) and the inter-assay coefficient of variation for ammonia is 2.9% (n=10).

Oxygen extraction
Skeletal muscle oxygen extraction was calculated as the ratio of arteriovenous oxygen difference and arterial oxygen content, multiplied by 100%. Arterial oxygen content is calculated as haemoglobin concentration/dl × 1.34 × % arterial oxygen saturation.

Results

There were no adverse effects reported after creatine or placebo ingestion and all patients completed the 5 day course of treatment.

Muscle endurance
There was a significant increase after creatine ingestion in the number of contractions performed before exhaustion at the 75% maximum voluntary contraction workload (8 (6, 14) vs 14 (8, 17), P=0.025) (Fig. 1). Eight of 10 creatine treated patients demonstrated an improvement. No significant effect was found in placebo-treated patients (12 (6, 21) vs 13.5 (8.5, 20), P=0.44). There was no effect of creatine or placebo on the number of contractions performed at the 21 kg workload in the fixed protocol, although 9/10 patients in each treatment group completed the protocol before and after randomization.

Metabolic response
There was no significant change in the overall lactate or ammonia response to exercise as assessed by area under the curve after creatine or placebo ingestion at either the

![Figure 1](image-url)
the fixed workload protocol. However, there was a significant fall in ammonia production after creatine ingestion at the 75% maximum voluntary contraction (volitional exhaustion) workload with the results expressed as ammonia per contraction (6·5 μmol/l/contraction (4·4, 8·3) vs 4·9 μmol/l/contraction (4·4, 14·7), P = 0·221) at the 75% maximum voluntary contraction workload.

Oxygen extraction
There was no significant effect of either creatine or placebo on oxygen extraction (Table 2).

Discussion
We have shown that dietary creatine supplementation in patients with chronic heart failure produces an improvement in skeletal muscle endurance and an attenuation of the derangement of the metabolic response to exercise observed in chronic heart failure. Previous studies have demonstrated a reduction in total creatine content in skeletal muscle in patients with severe chronic heart failure and that dietary creatine supplementation in chronic heart failure produces a significant increase in skeletal muscle creatine and phosphocreatine content[10,17]. The mechanism of the favourable changes in the present study is therefore likely to be an increase in pre-exercise skeletal muscle phosphocreatine and creatine content, and/or an enhanced resynthesis of phosphocreatine between exercise bouts[14].

The finding that dietary creatine supplementation in chronic heart failure appeared only to have a significant metabolic effect at workloads close to volitional exhaustion should not be surprising. During submaximal exercise there is little dependence on phosphocreatine availability and intracellular levels of ATP are maintained. The availability of phosphocreatine is one of the most important limitations to muscle performance during intense, fatiguing muscular exercise.

Figure 2 Blood ammonia concentration per contraction performed until volitional exhaustion at 75% of maximum voluntary contraction (MVC) workload pre (■) and post-treatment (□) with creatine or placebo. Results are displayed as median and 75th interquartile. *P = 0·037 post-creatine vs pre-creatine.

Figure 3 Blood lactate concentration per contraction performed until volitional exhaustion at 75% of maximum voluntary contraction (MVC) workload pre (■) and post-treatment (□) with creatine or placebo. Results are displayed as median and 75th interquartile. *P = 0·07 post-creatine vs pre-creatine.
Therefore it is not unexpected that during the relatively low intensity fixed workload protocol and at workloads of 50% maximum voluntary contraction or less where subjects are working submaximally that dietary creatine supplementation had no effect.

The improvements in skeletal muscle endurance and the metabolic response to exercise after creatine supplementation in chronic heart failure we have described are relatively small and it is uncertain whether they would result in a meaningful improvement in Symptoms or conventional treadmill exercise tolerance. However, relatively small increases in skeletal muscle metabolites at rest and on exercise in chronic heart failure are associated with important changes in Symptomatic status.

It is possible that a small improvement in abnormalities of skeletal muscle metabolism may result in substantial symptomatic improvement. There is an increasing body of evidence suggesting a pivotal role for abnormalities of skeletal muscle metabolism in the pathogenesis of symptoms in chronic heart failure and any intervention which can favourably affect these mechanisms is potentially important. However, it is arguable if the majority of patients with chronic heart failure in their customary activity ever exercise to a truly maximal level where creatine supplementation is most likely to be effective.

We may have underestimated the possible metabolic effects of creatine supplementation in chronic heart failure. In normal volunteers, there is a large interindividual variation in skeletal muscle creatine uptake after creatine supplementation, and it is probable that some of our creatine treated patients did not increase their skeletal muscle creatine content. Recent work suggests that the uptake of creatine into the skeletal muscle of normal subjects is enhanced by concomitant carbohydrate loading. The improvement in skeletal muscle endurance after creatine loading in normal volunteers muscle creatine remains elevated for several weeks after dietary creatine supplementation with 20 g daily for 5 days demonstrates that creatine is “trapped” within skeletal muscle once absorbed and would suggest that the favourable effect of creatine may be relatively long-lived.

We have demonstrated an improvement in the metabolic response and endurance of skeletal muscle in chronic heart failure as determined within 12 h of the completion of dietary creatine supplementation. We have not determined the duration of these favourable effects. However, the observation that in normal volunteers muscle creatine remains elevated for several weeks after dietary creatine supplementation with 20 g daily for 5 days demonstrates that creatine is “trapped” within skeletal muscle once absorbed and would suggest that the favourable effect of creatine may be relatively long-lived.

The most important limitation to the present study was the use of volitional exercise rather than electrical stimulation of skeletal muscle. We studied a group of severely symptomatic patients and chose to use volitional exercise to avoid the significant discomfort associated with electrical stimulation. Although subjects exercised only to volitional exhaustion they were given verbal encouragement to ensure optimum performance. The design of the study was double-blind and so no patient or physician bias could be introduced.

We have demonstrated that dietary creatine supplementation in chronic heart failure produces favourable effects on skeletal muscle endurance and metabolism. The potential for dietary creatine supplementation in chronic heart failure to produce significant longer term improvements in symptoms and exercise performance requires further study.

**References**
