First clinical trial with etomoxir in patients with chronic congestive heart failure

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ABSTRACT

In the failing human myocardium, both impaired calcium homoeostasis and alterations in the levels of contractile proteins have been observed, which may be responsible for reduced contractility as well as diastolic dysfunction. In addition, levels of a key protein in calcium cycling, i.e. the sarcoplasmic reticulum Ca$^{2+}$-ATPase, and of the $\alpha$-myosin heavy chain have been shown to be enhanced by treatment with etomoxir, a carnitine palmitoyltransferase inhibitor, in normal and pressure-overloaded rat myocardium. We therefore studied, for the first time, the influence of long-term oral application of etomoxir on cardiac function in patients with chronic heart failure. A dose of 80 mg of etomoxir was given once daily to 10 patients suffering from heart failure (NYHA functional class II–III; mean age 55±4 years; one patient with ischaemic heart disease and nine patients with dilated idiopathic cardiomyopathy; all male), in addition to standard therapy. The left ventricular ejection fraction was measured echocardiographically before and after a 3-month period of treatment. Central haemodynamics at rest and exercise (supine position bicycle) were defined by means of a pulmonary artery catheter and thermodilution. All 10 patients improved clinically; no patient had to stop taking the study medication because of side effects; and no patient died during the 3-month period. Maximum cardiac output during exercise increased from $9.72 \pm 1.25$ l/min before to $13.44 \pm 1.50$ l/min after treatment ($P < 0.01$); this increase was mainly due to an increased stroke volume [$84 \pm 7$ ml before and $109 \pm 9$ ml after treatment ($P < 0.01$)]. Resting heart rate was slightly reduced (not statistically significant). During exercise, for any given heart rate, stroke volume was significantly enhanced ($P < 0.05$). The left ventricular ejection fraction increased significantly from $21.5 \pm 2.6\%$ to $27.0 \pm 2.3\%$ ($P < 0.01$). In acute studies, etomoxir showed neither a positive inotropic effect nor vasodilatory properties. Thus, although the results of this small pilot study are not placebo-controlled, all patients seem to have benefitted from etomoxir treatment. Etomoxir, which has no acute inotropic or vasodilatory properties and is thought to increase gene expression of the sarcoplasmic reticulum Ca$^{2+}$-ATPase and the $\alpha$-myosin heavy chain, improved clinical status, central haemodynamics at rest and during exercise, and left ventricular ejection fraction.

Key words: congestive heart failure, etomoxir, phenotype, sarcoplasmic reticulum Ca$^{2+}$-ATPase.

Abbreviations: ACE, angiotensin-converting enzyme; CPT, carnitine palmitoyltransferase; SERCA2, sarcoplasmic reticulum Ca$^{2+}$-ATPase.

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INTRODUCTION

Chronic heart failure is generally understood as a reduced pumping function of the heart, which results in reflex activation of certain neuroendocrine compensatory mechanisms. In addition, distinct molecular alterations of the failing myocardium have been observed which may contribute to the pathological state. In animal models of heart failure and in failing human myocardium, decreased gene expression of the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA2) [1–7] and a shift from \(\alpha\)-myosin to \(\beta\)-myosin has been described. These molecular alterations may be associated with impairments of calcium homoeostasis [15–23] and of contractility of the failing myocardium [24–27]. Furthermore, alterations similar to the phenotype observed in cardiac hypertrophy and cardiac failure have also been observed on altering thyroid gland activity [28–31] and under conditions of metabolic derangement [32–34]. Reversal and even normalization of phenotype changes in cardiac hypertrophy and cardiac failure may therefore be achieved by specific pharmacological interventions with respect to the hormonal or metabolic state of the body.

Etomoxir is a blocker of the mitochondrial carnitine palmitoyltransferase (CPT) and has been developed primarily for treatment of diabetes mellitus (see Figure 1 in Wolf and Engel [36] and McGarry et al. [35]). The observed inhibition of mitochondrial CPT-1, which is common to a number of oxirane carboxylic acid derivatives, is irreversible and stereospecific [35–39]. Rupp and co-workers [40–42] have demonstrated that blockade of the lipolytic pathways by etomoxir may increase levels of SERCA2 in the rat myocardium, which was also associated with an increase in the \(\alpha\)-myosin heavy chain. Furthermore, the same authors demonstrated that etomoxir can prevent the shift in myosin isoenzymes from \(V_{\alpha}\) to \(V_{\beta}\) and reverse the decrease in gene expression and function of SERCA2 in rat cardiac hypertrophy induced by aortic constriction [43,44]. Because toxicological and clinical studies with etomoxir have already been performed in patients with diabetes mellitus [45,46], we were in a position to treat a small number of heart failure patients with etomoxir.

The goal of the present study was to test the effects of etomoxir given orally over a period of 3 months for treatment of heart failure. The following criteria for progression or improvement of heart failure were evaluated: (1) clinical status, (2) central haemodynamics at rest and during exercise, including cardiac output, stroke volume and filling pressures, and (3) echocardiographic left ventricular ejection fraction. Furthermore, because reduced levels of SERCA2 in the sarcoplasmic reticulum may be involved in the inverse force–frequency relationship observed in the failing human myocardium [21], special attention has been paid to the relationship between stroke volume and heart rate. Furthermore, in order to exclude a direct positive inotropic effect on the myocardium, additional acute in vivo and in vitro studies were performed.

METHODS

Chronic haemodynamic effects of etomoxir administered over a period of 3 months

Patients

A total of 10 patients were included in the study, suffering from chronic heart failure due to dilated cardiomyopathy (nine patients) or ischaemic cardiomyopathy (one patient). All patients were in sinus rhythm, had an ejection fraction of 40% or less (as assessed by two-dimensional echocardiography), and had shown stable haemodynamic conditions during the previous 3 months, including unaltered medication of standard therapy, which consisted of an angiotensin-converting enzyme (ACE) inhibitor, a diuretic and digoxin. In addition, three patients received \(\beta\)-adrenoceptor blockers, which were initiated at least 6 months prior to the beginning of etomoxir treatment. For details of individual treatment for all patients, see Table 1. Patients with any of the following diseases were excluded from the study: diabetes mellitus, acute or subacute myocarditis, chronic alcoholism and valvular heart disease. All 10 patients were in NYHA Class II–III. The study protocol was approved by the Ethics Committee of the University of Freiburg, and written informed consent was given by each patient.

Study protocol

All patients were studied invasively (see below) and echocardiographically before and after a 3-month period of treatment with etomoxir (80 mg/day, oral application). We chose this dosage because it has been shown to be effective with regard to metabolic parameters: 80 mg of etomoxir reduced serum glucose by 20%, decreased low-density lipoprotein cholesterol by 40–50% and increased high-density lipoprotein cholesterol by 10–15% in diabetes patients [36]. Standard triple or quadruple therapy was maintained throughout the whole study period. This standard background medication was not changed in dose and no new medications were added during the study period. Clinical examinations and blood tests were performed at baseline, after 1 week, after 4 weeks and at the end of the study.

Echocardiography, right-heart catheterization and physical exercise

M-mode, two-dimensional and Doppler echocardiographic measurements were performed using an ultra-
sonographic system (Toshiba Corp.; Model SSH-140A) with a 2.5–7.5 MHz transducer.

After the patient had fasted for 12 h, right-heart catheterization was performed. Patients had not taken any medication for 24 h before this procedure. A Swan–Ganz catheter was placed into the pulmonary artery via the right cubital vein or the right jugular vein. Right atrial, pulmonary artery and pulmonary capillary wedge pressures were measured, and cardiac output was determined by the thermodilution technique (in triplicate). In all patients, a stabilization period of 60 min was observed before resting haemodynamic measurements were taken. The patient was then exposed to a workload of 25 W for 3 min. Thereafter, the workload was increased stepwise by 25 W for a period of 3 min at each level. At the end of each workload level, measurements were taken.

Analysis of data
During exercise, invasive measurements were always taken at the end of a 3-min period of constant workload. Because the maximally measured parameters are not necessarily identical with the parameters measured during maximum exercise, we have presented peak values as well as values at maximum exercise (see Table 2).

Statistics
All values are given as means ± S. E. M. Differences in parameters before and after treatment were assessed by the two-tailed Student’s t-test for paired differences. A P value of ≤ 0.05 was accepted as statistically significant.

Acute effects of etomoxir on isolated human muscle preparations
Atrial muscle strips were prepared from right atrial muscle tissue, which was obtained from eight patients undergoing routine coronary bypass surgery. All of these patients were in sinus rhythm and had a normal left ventricular ejection fraction. After the right atrial appendix was cut and removed by the surgeon, the tissue was immediately submerged in Krebs–Ringer solution [47,48] containing 2,3-butanedione monoxime [49]. Muscle strips were carefully prepared under a microscope as described previously [47]. Thereafter, 2,3-butanedione monoxime was washed out and stimulation was started. The muscle was stretched to its optimum length (l_{max}), by using steps of 0.1 mm and 0.05 mm. The bath temperature was kept constant at 37 °C by an electronic feedback system. The stimulation frequency was chosen to be physiological, and therefore was kept constant at 60/min throughout the experiment. The average length and cross-sectional area of the right atrial preparations were 3.5 ± 0.4 mm and 0.32 ± 0.04 mm² respectively. Peak developed tension was 23.1 ± 2.9 mN/mm² under control conditions.

In the same way, left ventricular muscle preparations were prepared from six explanted hearts from patients suffering from dilated cardiomyopathy (NYHA class III–IV). The average left ventricular ejection fraction was 19 ± 6%. In the six left ventricular muscle preparations, muscle length and cross-sectional area were 3.4 ± 0.3 mm and 0.28 ± 0.06 mm² respectively; the peak developed tension was 22.6 ± 3.0 mN/mm² under control conditions.

Etomoxir was added at increasing concentrations starting at 1 nM. The final concentration was 10 µM. Etomoxir was kindly provided by Dr. H. P. O. Wolf (Projekt-Entwicklung GmbH, Allensbach, Germany).

Acute haemodynamic effects of etomoxir in patients with dilated cardiomyopathy
Central haemodynamics were measured in five patients (aged between 30 and 72 years old) in which dilated cardiomyopathy was diagnosed by coronary angiograms (ejection fraction 20 ± 5%) and left ventricular cardiography, by use of a Swan–Ganz catheter over a period of 5 h. Patients gave written informed consent the day before instrumentation, and stopped taking all medication, which consisted of ACE inhibitors (captopril, enalapril, lisinopril), diuretics, β-blockers and digitals, 12 h before the invasive procedure. The patients were in the fasting state for at least 12 h. In the morning, the patients were transferred to the coronary care unit. The Swan–Ganz catheter was advanced via the right atrium and the right ventricle into the pulmonary artery using the right cubital or right internal jugular vein approach. After 10 min of rest, initial measurements of pulmonary capillary wedge pressure, systolic and diastolic pulmonary artery pressures, right atrial pressure, cardiac output (cold injection), as well as arterial systolic and diastolic pressures (non-invasively), were recorded. An oral dose of 80 mg of etomoxir was then given to the patients. Invasive measurements were repeated at 1, 2, 3 and 4 h after the application of etomoxir. A period of 4 h was chosen because in animal experiments it has been demonstrated that the full biological action of etomoxir is reached after 30 min, irrespective of the route of application (oral or intravenous) [39].

RESULTS
Etomoxir treatment over 3 months
Ten patients with chronic congestive heart failure each received 80 mg of etomoxir daily, given once in the evening, for 3 months. All patients were male; nine had idiopathic dilated cardiomyopathy and one had ischaemic cardiomyopathy. Individual data on age and left ventricular ejection fraction are given in Table 1. All patients were on standard medical therapy, with digitalis, ACE inhibitors and a diuretic. Four patients were additionally

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Table 1  Characteristics of patients included in the 3-month study
Disease: ICM, ischaemic cardiomyopathy; DCM, dilated cardiomyopathy. Medication: ACEI, ACE inhibitors; Dig, digoxin; Diu, diuretics; Beta, β-blockers; A, amiodarone; C, coumarin; N, nitrates; ASS, acetylsalicylic acid (aspirin). EF, left ventricular ejection fraction.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Disease</th>
<th>Medication</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>ICM</td>
<td>ACEI, Diu, Beta, N, ASS</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>DCM</td>
<td>ACEI, Dig, Diu</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>DCM</td>
<td>ACEI, Dig, Diu, C</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>DCM</td>
<td>ACEI, Dig, Diu, C</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>DCM</td>
<td>ACEI, Dig, Diu, Beta, C</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
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<td>ACEI, Dig, Diu</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>DCM</td>
<td>ACEI, Dig, Diu, Beta</td>
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<tr>
<td>8</td>
<td>56</td>
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<td>ACEI, Dig, Diu, Beta</td>
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</tr>
<tr>
<td>9</td>
<td>60</td>
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</tr>
<tr>
<td>10</td>
<td>63</td>
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<td>ACEI, Dig, Diu, A, C</td>
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<tr>
<td>Mean</td>
<td>55</td>
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<td>S.E.M.</td>
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<td>2.6</td>
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Table 2  Haemodynamic data from the 3-month study
Significance of differences compared with value before treatment: *P < 0.05.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>76.00 ± 3.7</td>
<td>68.90 ± 3.3</td>
</tr>
<tr>
<td>Peak</td>
<td>122.90 ± 9.0</td>
<td>135.60 ± 6.7</td>
</tr>
<tr>
<td>During maximal exercise</td>
<td>122.90 ± 9.0</td>
<td>135.40 ± 6.9</td>
</tr>
<tr>
<td>Cardiac output (litres/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>5.20 ± 0.32</td>
<td>5.95 ± 0.41</td>
</tr>
<tr>
<td>Peak</td>
<td>9.72 ± 1.25</td>
<td>13.44 ± 1.50*</td>
</tr>
<tr>
<td>During maximal exercise</td>
<td>9.94 ± 1.09</td>
<td>13.35 ± 1.53*</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td>69.4 ± 4.0</td>
<td>92.6 ± 8.8*</td>
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<tr>
<td>Peak</td>
<td>84.4 ± 7.3</td>
<td>108.60 ± 8.7*</td>
</tr>
<tr>
<td>During maximal exercise</td>
<td>80.1 ± 6.8</td>
<td>98.10 ± 8.7*</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>14.9 ± 3.3</td>
<td>11.0 ± 1.89</td>
</tr>
<tr>
<td>Peak</td>
<td>35.3 ± 2.8</td>
<td>25.0 ± 2.28</td>
</tr>
<tr>
<td>During maximal exercise</td>
<td>34.3 ± 3.1</td>
<td>24.4 ± 2.21*</td>
</tr>
<tr>
<td>Mean pulmonary pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>25.3 ± 4.0</td>
<td>19.2 ± 1.8</td>
</tr>
<tr>
<td>Peak</td>
<td>52.4 ± 3.3</td>
<td>42.3 ± 3.7*</td>
</tr>
<tr>
<td>During maximal exercise</td>
<td>51.8 ± 3.0</td>
<td>40.9 ± 3.6*</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>21.5 ± 2.6</td>
<td>27.0 ± 2.3*</td>
</tr>
</tbody>
</table>

Clinical course
No patient stopped taking the study medication, deteriorated or died. All patients improved clinically, and no side effects were observed.

Haemodynamic data
Stroke volume increased significantly during the treatment period (P < 0.01), by 33% at rest and by 23% during maximum exercise (Table 2, Figure 1). Because resting heart rate was lowered during the treatment period, the increase in cardiac output at rest was only 15%, and not statistically significant (Table 2, Figure 1).
Etomoxir in human congestive heart failure

Figure 1 Effects of a 3-month period of etomoxir treatment on haemodynamic parameters

Etomoxir treatment consisted of a daily 80 mg dose. Effects are shown on stroke volume, cardiac output and pulmonary capillary wedge pressure (PCWP), as measured using a Swan–Ganz catheter, at rest and during maximal exercise. Significance of differences compared with before treatment: * P < 0.05.

However, peak cardiac output and cardiac output during maximum exercise were increased, from 9.7±1.3 to 13.4±1.5 l/min and from 9.9±1.1 to 13.4±1.5 l/min respectively (P < 0.01; Table 2, Figure 1). Pulmonary capillary wedge pressure was reduced by 27% at rest (not significant) and by 29% during maximum exercise (P < 0.01; Table 2, Figure 1). Mean pulmonary pressure at rest, mean pulmonary pressure at maximum exercise and peak mean pulmonary pressure were decreased by 24% (P < 0.05), 19% (P < 0.01) and 21% (P < 0.01) respectively (Table 2). Heart rate at rest decreased from 76±4 to 69±3 beats/min (not significant), and heart rate during maximum exercise increased from 123±9 to 136±7 beats/min (not significant; Table 2).

In Figure 2, stroke volume is plotted as a function of heart rate. For any given heart rate, stroke volume was always higher after the 3-month period of treatment with etomoxir. Thereby the maximum workload was increased from 504±117 to 660±135 W·min (P < 0.05).

Echocardiographic data

The mean left ventricular ejection fraction increased from 21.5±3.1% to 27.0±2.3% (P < 0.01). Despite a tendency for a decrease in the end-diastolic left ventricular diameter (not significant), wall thickness did not change during the treatment period. From these data it can be concluded that etomoxir has no influence on left ventricular muscle mass.

Acute studies with etomoxir

In order to exclude acute effects of etomoxir on myocardial function (positive inotropism) or on peripheral resistance (vasodilation), two additional studies were performed: an in vitro study in which the acute effect of etomoxir on isolated human myocardium was tested, and an in vivo study in which the acute influence of etomoxir on central haemodynamics was investigated.

Acute effects of etomoxir on isolated human muscle preparations

This study was performed using right atrial muscle preparations (n = 8) and left ventricular muscle preparations (n = 6) which contracted isometrically at 37 °C at a stimulation frequency of 60/min. Etomoxir...
S. Schmidt-Schweda and Ch. Holubarsch

Figure 3 Influence of etomoxir on peak developed force of isolated right atrial human myocardium (upper panel) and left ventricular human myocardium (lower panel)

Etomoxir was added at concentrations between 1 nM and 10 μM; isoprenaline (ISO) was added at 0.1 nM. C, control (no additions). In contrast with isoprenaline, etomoxir has no acute inotropic effect on the human myocardium.

was added stepwise starting with a concentration of 1 nM. The highest dose used was 10 μM. In neither atrial nor ventricular human myocardium was any influence on peak force development observed (Figure 3). In order to demonstrate the contractile reserve of the preparations, isoprenaline (isoproterenol) at a concentration of 0.1 μM was given at the end of the study protocol; isoprenaline increased peak force development of non-failing atrial muscle by 130% and that of failing left ventricular muscle by 32% (Figure 3).

Acute haemodynamic effects of etomoxir in patients with idiopathic dilated cardiomyopathy

Haemodynamic measurements were performed in five patients with idiopathic dilated cardiomyopathy over a period of 4 h. Measurements were taken every 1 h. A dose of 80 mg of etomoxir was administered to the patients orally 1 h after the placement of a pulmonary artery catheter. No effects of etomoxir could be detected, either on heart rate and cardiac output or on systemic vascular resistance (Table 3).

DISCUSSION

Cardiac hypertrophy is thought to be an important mechanism by which the heart adapts to increased left ventricular wall stress. This adaptation involves not only a quantitative increase in muscle mass, but also some distinct qualitative changes in the myocardium which may have functional consequences. Four major phenotypic changes have been described: (1) increased expression of atrial natriuretic peptide and brain natriuretic peptide, (2) a shift in the myosin heavy chain from the α2 to the ββ dimers in rodents, (3) up-regulation of the gene encoding the sodium–calcium exchanger, and (4) down-regulation of gene expression for SERCA2.

Some of these phenotypic changes may be judged to be beneficial, in as far as they compensate for the increased wall stress. The synthesis and release of atrial natriuretic peptide and brain natriuretic peptide appear to ameliorate increased workload through the vasodilating and diuretic properties of these peptides [50–54]. The shift of myosin heavy chains from the V$^\alpha$- to the V$^\beta$-isoenzyme leads to slower cross-bridge cycling rates and thereby improved economy of force generation [55–59]. On the other hand, the reduced velocity of myocardial contraction associated with such a myosin isoenzyme shift results in reduced power output. In contrast with earlier work, more recent studies have provided evidence that α-myosin heavy chains are present in non-failing human myocardium, but not in failing myocardium [61–64]. Furthermore, depressed expression of SERCA2 may be associated with decreased calcium pump activity, and thereby impairment of diastolic relaxation and systolic contraction failure [8–16]. This view is supported by two observations: (1) the transition from cardiac hypertrophy to cardiac failure was accompanied by a decrease in SERCA2 levels in an animal model [60]; and (2) the reversed force–frequency relationship, as found in isolated human myocardium from failing hearts, was correlated with the decrease in SERCA2 protein [14]. Furthermore, using gene transfer technology, adreno-

Table 3 Haemodynamic data from the acute study with etomoxir

<table>
<thead>
<tr>
<th></th>
<th>0 h (beats/min)</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>85 ± 6</td>
<td>85 ± 5</td>
<td>86 ± 6</td>
<td>85 ± 5</td>
<td>86 ± 6</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>5.1 ± 0.4</td>
<td>5.1 ± 0.4</td>
<td>5.1 ± 0.3</td>
<td>5.1 ± 0.4</td>
<td>5.1 ± 0.4</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn·s·cm$^{-2}$)</td>
<td>1333 ± 158</td>
<td>1280 ± 142</td>
<td>1429 ± 190</td>
<td>1390 ± 166</td>
<td>1390 ± 161</td>
</tr>
<tr>
<td>Systolic arterial blood pressure (mmHg)</td>
<td>130 ± 16</td>
<td>133 ± 19</td>
<td>133 ± 16</td>
<td>132 ± 15</td>
<td>129 ± 17</td>
</tr>
<tr>
<td>Diastolic arterial blood pressure (mmHg)</td>
<td>70 ± 13</td>
<td>70 ± 12</td>
<td>71 ± 13</td>
<td>69 ± 14</td>
<td>70 ± 14</td>
</tr>
</tbody>
</table>

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virally mediated SERCA2 overexpression was shown to increase and accelerate calcium transients in myocytes [61,62]. In addition, overexpression of SERCA2 in a transgenic model accelerated calcium transients and myocardial relaxation [63]. Taken together, these findings support attempts to normalize gene expression of SERCA2 in patients with heart failure by pharmacological (or other) tools.

Changes in phenotype similar to those described in pressure overload and heart failure are also seen with hormonal alterations and metabolic derangements [17–23]. It was shown for etomoxir, a blocker of the lipolytic pathway, that the expression and function of SERCA2 can be enhanced in normal as well as pressure-overloaded rats [32,33]. We therefore, for the first time, studied etomoxir, which was originally developed as an anti-diabetic drug, in ten patients with heart failure.

Our preliminary data showed significant improvements in all patients with regard to clinical symptoms, haemodynamic measurements and echocardiographic data. Furthermore, none of the patients, who were in moderate to severe heart failure, decompensated or died during the 3-month period. Because this pilot study was neither placebo-controlled nor blinded, one might argue that standard therapy, the spontaneous course of the disease or a bias of the investigators may be responsible for the final results. In this regard, it is important to state that all patients were in a stable phase of heart failure and had been treated with constant standard medication for at least 3 months before entering this study. Furthermore, the observation that cardiac output during maximum exercise was significantly increased, and also the fact that the stroke volume was significantly augmented at any given heart rate (Figure 2), proves the validity of the data.

Furthermore, one could argue that improvements in left ventricular function during exercise may be a consequence of differences in exercise capacity before and after treatment, especially because the maximum workload was significantly increased (from 504±117 to 660±135 W min) during the course of the trial. There are three arguments against this hypothesis. (1) We analysed not only cardiac output at maximum exercise, but also peak cardiac output, which was obtained at sub-maximal exercise. Both peak cardiac output and peak stroke volume were significantly increased after treatment (Table 2). (2) Left ventricular function was improved not only during exercise, but also at rest (left ventricular ejection fraction; Table 2). (3) To analyse further the pumping function of the left ventricle during exercise, stroke volume was plotted as a function of heart rate: Figure 2 demonstrates that stroke volume was significantly increased at the lowest (rest) and highest (maximum exercise) heart rate. Therefore the increase in cardiac output is unlikely to be due to an increase in heart rate related to a high exercise capacity, but rather reflects improved emptying of the left ventricle.

From the data presented we cannot reach conclusions about the mechanism of action of etomoxir in these heart failure patients. However, we can exclude three well known actions of pharmacological substances that may improve cardiac performance: positive inotropism, vasodilation and cardiac hypertrophy. First, one might argue that etomoxir has acute effects on the myocardial contractility of the failing heart, or may exert some vasodilatory effect like, for example, phosphodiesterase inhibitors. Therefore two additional types of acute studies were performed. Etomoxir at increasing concentrations had no inotropic effect on physiologically contracting human atrial muscle preparations or on preparations obtained from failing human left ventricles. In addition, central haemodynamics did not change acutely after oral intake of 80 mg of etomoxir.

Secondly, in contrast with a report on growth hormone application to patients with heart failure [64], etomoxir treatment in our patients did not result in cardiac hypertrophy, which might also result in improved cardiac performance. Therefore the hypothesis that etomoxir modulates the metabolic pathways of the heart (from lipolytic to glycolytic), and thereby may enhance the gene expression and function of SERCA2 and other functionally important proteins in the failing myocardium, is the most likely explanation for our results [40–44,65].

Although in the present study no patient suffered from myocardial ischaemia, the potential anti-ischaemic effect of etomoxir [66] has to be considered in cardiac patients. Furthermore, it is known that other agents, such as amiodarone, which is widely used in heart failure patients, may be able to inhibit CPT-1 [67]. Even if the potency of amiodarone is much lower than that of etomoxir, this effect may contribute to the beneficial actions of amiodarone. Therefore blocking CPT-1 activity may become a new therapeutic principle, not only in ischaemic heart disease but also in chronic heart failure.

To further evaluate the efficacy and the mechanism of action of etomoxir, two further studies are in preparation: a large randomized, placebo-controlled and double-blinded trial with clinical end-points, and a second smaller trial in which SERCA2 mRNA analysis will be performed using repeat myocardial biopsies from patients under treatment with etomoxir.

ACKNOWLEDGMENTS

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