Influence of central inhibition of sympathetic nervous activity on myocardial metabolism in chronic heart failure: acute effects of the imidazoline I1-receptor agonist moxonidine

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ABSTRACT

Although β-adrenergic blockade is beneficial in heart failure, inhibition of central sympathetic outflow using moxonidine has been associated with increased mortality. In the present study, we studied the acute effects of the imidazoline-receptor agonist moxonidine on haemodynamics, NA (noradrenaline) kinetics and myocardial metabolism. Fifteen patients with CHF (chronic heart failure) were randomized to a single dose of 0.6 mg of sustained-release moxonidine or matching placebo. Haemodynamics, NA kinetics and myocardial metabolism were studied over a 2.5 h time period. There was a significant reduction in pulmonary and systemic arterial pressures, together with a decrease in cardiac index in the moxonidine group. Furthermore, there was a simultaneous reduction in systemic and cardiac net spillover of NA in the moxonidine group. Analysis of myocardial consumption of substrates in the moxonidine group showed a significant increase in non-esterified fatty acid consumption and a possible trend towards an increase in myocardial oxygen consumption compared with the placebo group (P = 0.16). We conclude that a single dose of moxonidine (0.6 mg) in patients already treated with a β-blocker reduced cardiac and overall sympathetic activity. The finding of increased lipid consumption without decreased myocardial oxygen consumption indicates a lack of positive effects on myocardial metabolism under these conditions. We suggest this might be a reason for the failure of moxonidine to prevent deaths in long-term studies in CHF.

INTRODUCTION

Counteraction or suppression of the different neurohormonal systems that are activated in CHF (chronic heart failure) constitutes the key concept for treatment of this condition. Blockade of the renin-angiotensin–aldosterone system and the sympathetic nervous system is standard therapy today. Continuous development of other treatment strategies has stimulated the testing of antagonists to other neurohormones. Although results with some of these newer substances have been encouraging [1], others have failed to achieve additional positive long-term results compared with standard therapy [2–5]. β-Blockers are effective in large patient groups with CHF.

Key words: haemodynamics, heart failure, myocardial metabolism, noradrenaline, sympathetic nervous system, ventricular function.

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; AUC, area under the curve; CHF, chronic heart failure; CSF, coronary sinus flow; HR, heart rate; LVEF, left ventricular ejection fraction; MOXCON, MOXonidine CONgestive Heart Failure; MVO2, myocardial oxygen consumption; NA, noradrenaline; NEFA, non-esterified fatty acid; NYHA, New York Heart Association.

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but are less active in the selected patients for unclear reasons. To inhibit the deleterious increase in sympathetic nerve activity further, a selective blockade of sympathetic outflow from the central nervous system could offer an alternative approach for treatment of CHF. Moxonidine, a central imidazoline-receptor agonist, selectively blocks sympathetic outflow from the central nervous system [5]. Moxonidine lowers plasma NA (noradrenaline) following both acute and long-term administration [6,7]. Clinical studies initially showed promising results [8,9], but a long-term study [MOXCON (MOXonidine CONGestive Heart Failure)] was unable to confirm the benefit of this treatment [10]. The reason for this lack of effect is unclear. One possibility that has been considered is that a more complete blockade of the sympathetic nervous system than offered by β-receptor blockade alone might be deleterious, as most patients in the MOXCON study had background therapy with β-blockers. Alternatively, a too rapid dose titration might have been used in the MOXCON survival study [10].

The present study was started and conducted before the results of the MOXCON study were available. The aim of the present study was to evaluate cardiac and systemic NA effects of central sympathetic blockade in addition to standard therapy, including β-blockers, and to relate these effects to cardiac carbohydrate and lipid metabolism. It was hypothesized that moxonidine would reduce cardiac and systemic NA spillover, and that beneficial effects would be achieved on myocardial metabolism.

**Methods**

**Patients and treatment**

Sixteen patients with stable CHF, in NYHA (New York Heart Association) class II and III, caused by idiopathic dilated cardiomyopathy or ischaemic cardiomyopathy were included in the study. Inclusion criteria were LVEF (left ventricular ejection fraction) < 0.40, LVEDD (left ventricular end-diastolic diameter) > 60 mm and venous plasma NA ≥ 180 pg/ml. Patients were excluded if they had a history of recent myocardial infarction, active myocarditis, unstable angina pectoris, heart failure due to other known aetiologies (e.g. primary valvular disease) or if they suffered from active infectious diseases, cancer, renal artery stenosis, renal insufficiency (serum creatinine > 240 μmol/l), significant primary liver disease or chronic alcoholism. The patients were randomized to a double-blind treatment with a single oral dose of sustained-release moxonidine (0.6 mg) or matching placebo.

The study was approved by the Ethics Committee of the Medical Faculty, University of Göteborg, Göteborg, Sweden. Informed consent was obtained from each patient before inclusion in the study. One patient in the moxonidine group who developed sinus tachycardia caused by catheter manipulation was excluded and is not part of the present study. Baseline characteristics of the patients are given in Table 1. It may be noted that 80% of the patients in each group were taking β-blockers and diuretics, and all were taking ACEIs (angiotensin-converting-enzyme inhibitors).

**Haemodynamic study**

Because of the risk of potentiating the hypotensive effect of moxonidine, the morning dose of ACEIs was withheld on the study day. Upon arrival at the catheterization laboratory, the patient received an intravenous infusion of 3H-labelled NA (0.70 μCi/min at steady state) during the investigation, starting 60 min prior to baseline registration and continuing throughout the study period. During cardiac catheterization, a triple-lumen SwanGanz pulmonary artery catheter for haemodynamic measurements and a Wilton-Webster coronary sinus catheter were inserted percutaneously through the right internal jugular vein. Both catheters were left in place during the entire procedure and flushed continuously with heparinized saline. The correct position of the coronary sinus catheter was checked by fluoroscopic injection of radiopaque medium. An arterial line was established in the radial artery of the forearm. Right atrial pressure, pulmonary artery pressure, systemic arterial pressure, HR (heart rate) and ECG were monitored continuously throughout the study. Cardiac output was measured by the thermodilution technique from a minimum of three injections of 10 ml of ice-cold saline into the right atrium with the thermodilutor placed in the pulmonary artery, and data were calculated by computer (Siemens Micor). The coronary sinus catheter was attached to a Wheatstone bridge, and changes in thermodilutor resistance caused by temperature changes were recorded. Coronary sinus blood flow was calculated with a standard formula, as described...
previously [11]. After equilibration of baseline haemodynamics and immediately prior to drug administration, blood samples were obtained to provide baseline levels of oxygen content and plasma levels of lactate, glucose, NEFAs (non-esterified fatty acids), NA and $^3$H-labelled NA respectively. After baseline measurements had been obtained, the study drug or placebo was administered and measurements were repeated after 60, 90 and 120 min after administration. Concomitant with each haemodynamic recording, blood samples were drawn from the artery and coronary sinus.

**Determination of endogenous plasma catecholamines and myocardial substrates**

Plasma catecholamines were purified and concentrated by extraction with acid-washed aluminium oxide [12]. Catecholamines were extracted from 200 µl of plasma and were stored at −20°C. A linear standard curve was accomplished by preparation of four different external standard concentrations between 0.05 and 1.0 ng/ml. Determination of catecholamine concentrations was obtained by using an external standard series injected before and after a series of samples. A portion (40 µl) of each of the extracted samples was injected into the HPLC-EC system composed of the High Precision Pump (Gynotek) and electrochemical detector (The decade; ANTEC Leyden), with a Luna C18(2) separation column (Phenomenex). The mobile phase was 0.015 mol/l K$_2$HPO$_4$, 0.035 mol/l citric acid in MilliQ water (pH 2.7–2.9), 15 % (ν/ν) methanol, 0.26 mmol/l sodium octyl sulphate and 0.054 mmol/l sodium EDTA. The flow rate was 1.0 ml/min. The current signal was monitored using a Chromel version 4.32 software (Dionex-softron). Lactate and glucose concentrations in plasma were analysed enzymatically on a YSI 2300 glucose and lactose analyser. Insulin was analysed using an RIA (Insulin RIA 102; Pharmacia), and the concentration of NEFAs was determined with a colorimetric enzymatic method (Wako Chemicals).

**Measurement of NA spillover**

The following formulae were used for calculating NA kinetics [13]:

\[
\text{Systemic NA spillover (ng/min)} = \frac{3\text{H-labelled NA infusion rate}}{\text{plasma NA specific activity}}
\]

\[
\text{Total NA clearance (l/min)} = \frac{3\text{H-labelled NA infusion rate}}{\text{plasma 3H-labelled NA concentration}}
\]

**Cardiac net NA spillover (ng/min)**

\[
= [(\text{NAV} - \text{NAA}) + (\text{NAA} \times \text{NAEX})] \times \text{CSF}
\]

\[
= (\text{NAV} - \text{NAA}) + (\text{NAA} \times \text{NAEX})
\]

where NAV is the plasma NA concentration in the coronary sinus, NAA is the arterial plasma NA concentration, NAEX is the fractional extraction of titrated NA in single passage through the heart, and CSF is coronary sinus flow.

**Derived haemodynamic and metabolic variables**

The following variables were derived:

\[
\text{Cardiac index (litres \cdot min^{-1} \cdot m^{-2})} = \frac{\text{cardiac output}}{\text{body surface area}}
\]

\[
\text{Stroke volume index (ml/m²)} = \frac{\text{stroke volume}}{\text{body surface area}}
\]

\[
\text{LV stroke work index (g \cdot m \cdot m^{-2})} = \left(\frac{\text{mean arterial pressure} - \text{pulmonary capillary wedge pressure}}{\text{stroke volume index}}\right) \times \text{stroke volume index} \times 0.0136
\]

\[
\text{Systemic vascular resistance (dyn \cdot s \cdot cm^{-5})} = \left(\frac{\text{mean arterial pressure} - \text{mean right atrial pressure}}{\text{cardiac output}}\right)
\]

\[
\text{MVO}_2 \text{(myocardial oxygen consumption; ml)} = \text{CSF} \times (\text{arterial oxygen content} - \text{coronary sinus oxygen content})
\]

\[
\text{Myocardial extraction of lactate, glucose, insulin, NEFA and catecholamines respectively}
\]

\[
= \text{CSF} \times (\text{arterial concentration} - \text{coronary sinus concentration})
\]

**Statistical analysis**

Friedman’s repeated measures ANOVA on ranks was used for analysis of changes between baseline and consecutive measurements within each group, followed by Dunnett’s test for pairwise comparison as appropriate. Consumption of myocardial substrates was calculated for the incremental AUC (area under the curve) adjusted to baseline (0)

\[
\text{Area} = \frac{(y_1 + y_0) \times (x_1 - x_0)}{2}
\]

where $y$ denotes substrate concentrations and $x$ denotes time (h). The Mann–Whitney rank sum test was used to compare differences between groups. A SigmaStat for Windows statistical software (SPSS) was used. A $P < 0.05$
Table 2 Haemodynamic variables during catheterization before drug administration

Values are means ± S.D. No significant differences were observed between the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Moxonidine</th>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>74 ± 12</td>
<td>93 ± 19</td>
</tr>
<tr>
<td>Mean right atrial pressure (mmHg)</td>
<td>6 ± 6</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>Systolic pulmonary artery pressure (mmHg)</td>
<td>45 ± 21</td>
<td>45 ± 24</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>29 ± 15</td>
<td>30 ± 16</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>17 ± 9</td>
<td>14 ± 8</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>151 ± 25</td>
<td>147 ± 16</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>98 ± 14</td>
<td>104 ± 14</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn · s · cm⁻¹)</td>
<td>1461 ± 493</td>
<td>1403 ± 394</td>
</tr>
<tr>
<td>Cardiac index (litres · min⁻¹ · m⁻２)</td>
<td>2.7 ± 0.6</td>
<td>2.8 ± 0.6</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>38 ± 13</td>
<td>32 ± 7</td>
</tr>
<tr>
<td>Coronary sinus flow (ml/min)</td>
<td>185 ± 65</td>
<td>175 ± 91</td>
</tr>
<tr>
<td>Stroke work index (g · m · m⁻²)</td>
<td>27 ± 9</td>
<td>28 ± 12</td>
</tr>
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</table>

was considered statistically significant. Data are expressed as means ± S.D.

RESULTS

Haemodynamic evaluation
During the catheterization procedure, HR tended to be higher at baseline in the moxonidine-treated group com-
pared with the placebo group, but there were no sign-
ificant differences between the two groups (Table 2). Moxonidine decreased mean right atrial pressure as well as systemic and pulmonary artery pressures in parallel with a decrease in cardiac index (Table 3). Although HR was not significantly reduced in the moxonidine group as determined by ANOVA, the decrease in HR was significantly greater (P = 0.03) than in the placebo group 2 h after drug administration. Pulmonary capillary wedge pressure was reduced in both groups. CSF and systemic vascular resistance displayed large variations and without statistically significant alterations during the study.

NA and myocardial metabolic data
There were no significant differences in NA levels between the placebo and moxonidine groups at baseline (Table 4). During treatment with moxonidine, there was a significant reduction in arterial NA concentration as well as in cardiac and systemic NA spillover (Figure 1). Cardiac NA arterio–venous difference increased significantly in the moxonidine group (Table 5). Also, net cardiac NA spillover decreased in the moxonidine group, although the large variations in CSF were probably responsible for the smaller differences observed between the groups. There were no statistically significant alterations in systemic and cardiac release of NA in the placebo group. AUC of NA spillover during the entire

Table 3 Changes in haemodynamic data compared with baseline measurements after administration of moxonidine or placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Moxonidine</th>
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<tbody>
<tr>
<td></td>
<td>1.5 h</td>
<td>2.0 h</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>−1.0 ± 5.3</td>
<td>2.2 ± 6.7</td>
</tr>
<tr>
<td>Mean right atrial pressure (mmHg)</td>
<td>−0.9 ± 1.5</td>
<td>−0.8 ± 1.6</td>
</tr>
<tr>
<td>Systolic pulmonary artery pressure (mmHg)</td>
<td>−5.5 ± 8.7</td>
<td>−4.8 ± 12</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>−4.6 ± 6.9</td>
<td>−3.1 ± 9.0</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>−4.2 ± 4.0</td>
<td>−4.0 ± 5.3</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>3.8 ± 8.6</td>
<td>7.1 ± 12</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>2.0 ± 6.6</td>
<td>4.9 ± 10</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn · s · cm⁻¹)</td>
<td>−77 ± 237</td>
<td>118 ± 153</td>
</tr>
<tr>
<td>Cardiac index (litres · min⁻¹ · m⁻２)</td>
<td>−0.1 ± 0.34</td>
<td>−0.1 ± 0.18</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>20 ± 8.8</td>
<td>0.7 ± 7.1</td>
</tr>
<tr>
<td>Coronary sinus flow (ml/min)</td>
<td>−68 ± 65</td>
<td>−51 ± 80</td>
</tr>
<tr>
<td>Stroke work index (g · m · m⁻²)</td>
<td>2.1 ± 6.3</td>
<td>5.1 ± 7.1</td>
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</table>
Cardiac and systemic NA data before drug administration in the two groups

Table 4  Cardiac and systemic NA data before drug administration in the two groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Moxonidine</th>
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<tbody>
<tr>
<td>Arterial NA concentration (pg/ml)</td>
<td>434 ± 191</td>
<td>317 ± 129</td>
</tr>
<tr>
<td>Coronary sinus NA concentration (pg/ml)</td>
<td>714 ± 315</td>
<td>568 ± 278</td>
</tr>
<tr>
<td>Cardiac a–v difference (pg/ml)</td>
<td>−279 ± 875</td>
<td>−251 ± 211</td>
</tr>
<tr>
<td>Cardiac NA spillover (ng/min)</td>
<td>94 ± 49</td>
<td>74 ± 53</td>
</tr>
<tr>
<td>Cardiac NA spillover (pg/ml)</td>
<td>507 ± 0.225</td>
<td>411 ± 197</td>
</tr>
<tr>
<td>Systemic NA spillover (ng/min)</td>
<td>1446 ± 616</td>
<td>1320 ± 906</td>
</tr>
<tr>
<td>Total NA clearance (litres/min)</td>
<td>3.41 ± 0.48</td>
<td>3.93 ± 1.1</td>
</tr>
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</table>

Study was not statistically different between the groups (96 ± 56 ng·2.5 h−1·l−1 in the moxonidine group and 142 ± 123 ng·2.5 h−1·l−1 in the placebo group; P = 0.40).

No change in total NA clearance was observed in either group.

Changes in the radial artery concentrations of the metabolic substrates are shown in Table 6. Arterial insulin levels decreased in both groups compared with baseline, whereas lactate tended to decrease in the placebo group. Point estimations of lactate, glucose, MVO2 and NEFAs were not altered significantly. Metabolism during the entire study period was estimated by computing the AUC (Figure 2). During the study, there was a significant increase in NEFA uptake in the moxonidine group compared with the placebo group, which was accompanied by a trend towards an increase in MVO2. There were no differences in uptake of lactate or glucose between the two groups.

**DISCUSSION**

In the present study, oral administration of sustained-release moxonidine in patients who were predominantly on β-blockers caused a significant decrease in total body NA spillover and a parallel reduction in cardiac NA spillover. These potentially beneficial effects were, however, not accompanied by improvements in cardiac metabolism. On the contrary, there were signs of increased...
metabolism of NEFAs and M\(\dot{V}O_2\). It is plausible that such effects on myocardial metabolism might be a reason for the lack of survival benefits in the previous long-term studies with moxonidine in CHF.

**Effects on NA kinetics**

In the present study, we have shown for the first time that administration of moxonidine induced a rapid and sustained reduction in peripheral NA concentration and in systemic NA spillover, without any change in clearance rates. These findings are in agreement with previous experiences with this drug and are congruent with the proposed mechanism of a centrally mediated reduction in sympathetic outflow [8]. A decrease in peripheral levels of NA has also been demonstrated in a long-term study with moxonidine [9]. The evaluation of cardiac NA kinetics was in parallel with these findings. There was a significant increase in the arterio–venous myocardial concentration gradient of \(^3\)H-labelled NA (less production). The spillover estimation included CSF measurements that showed variation over time which did not reach statistical significance. These variations in CSF explain the great variation in net cardiac NA spillover; however, despite this variability in CSF, the present results clearly show that acute administration of moxonidine causes a reduction in cardiac spillover of NA, concurrent with moxonidine causing a centrally mediated decrease in sympathetic activity to the heart.

**Effects on haemodynamics**

The acute haemodynamic effects of moxonidine were well tolerated. The reduction in systemic and cardiac NA spillover in the moxonidine group induced a number of expected haemodynamic changes, such as a reduction in right atrial pressure, pulmonary artery pressure, systemic artery pressure and cardiac index. Although the reduction in HR and stroke volume was not statistically significant, the significant decrease in cardiac index was attributable to a decrease in both of these components. The lack of effect on HR may be explained by the fact that the majority of the patients were on \(\beta\)-blockers. There was also a reduction in pulmonary capillary wedge pressure in the placebo group. The reason for this change may be the prolonged catheterization period including a fasting state. Fluids were equally administered to both study groups via injection of saline during estimation of cardiac output and CSF.

Even though arterial pressure was reduced in the moxonidine group, any changes in systemic vascular resistance were very variable and there was no obvious vasodilator effect of moxonidine. In an acute study in patients without \(\beta\)-blockers, a vasodilatory effect of moxonidine has been shown [6]. Thus it might be argued that sympathetic blockade was already present as most patients were on \(\beta\)-blocker treatment. However, this is an unlikely explanation, as the \(\beta\)-blocker used was a compound with minor peripheral effects and all patients were taking \(\beta_1\)-selective metoprolol. Alternatively, it may be that the centrally mediated reduction in sympathetic activity caused by moxonidine was counteracted to variable extents in different subjects by the influence of vasoconstrictor hormones such as angiotensin and vasopressin.

**Effects on myocardial metabolism**

In the present study, myocardial consumption of substrates, including the carbohydrates glucose and lactate and the lipid substrate NEFAs, were analysed. Calculations of the AUC provided descriptions of metabolism over the total study period. We and others [14–17] have demonstrated that sympathetic blockade with adrenergic \(\beta\)-blockers causes both acute and long-term alterations in myocardial metabolism, implying that \(\beta\)-blockers promote carbohydrate metabolism and limit lipid consumption. These positive metabolic effects are found both after acute and long-term administration. It is thought that these effects are perhaps the most important reasons for the beneficial effects of long-term \(\beta\)-blocker treatment in patients with CHF and coronary heart disease. Indeed, it has been shown that estimation of glucose metabolism may select good responders to \(\beta\)-blocker treatment [18]. The aim of the present study was to establish whether central inhibition of sympathetic

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**Table 6 Changes in concentration of arterial metabolic substrates compared with baseline measurement after administration of moxonidine or placebo**

<table>
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<th>Placebo</th>
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<th>Moxonidine</th>
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<tr>
<td></td>
<td>1.5 h</td>
<td>2.0 h</td>
<td>2.5 h</td>
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<td>1.5 h</td>
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<td>2.5 h</td>
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<tr>
<td>Insulin (m-units/l)</td>
<td>−4.6 ± 5.2∗</td>
<td>−5.9 ± 6.2</td>
<td>−7.9 ± 9.6∗</td>
<td>0.026</td>
<td>−6.2 ± 5.4∗</td>
<td>−4.4 ± 5.9∗</td>
<td>−4.5 ± 7.2∗</td>
<td>0.047</td>
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<tr>
<td>Glucose (mmol/l)</td>
<td>0.017 ± 0.77</td>
<td>−0.52 ± 1.3</td>
<td>−0.13 ± 0.69</td>
<td>0.35</td>
<td>0.60 ± 1.3</td>
<td>0.18 ± 1.4</td>
<td>0.10 ± 1.6</td>
<td>0.51</td>
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<tr>
<td>Lactate (mmol/l)</td>
<td>−0.021 ± 0.14</td>
<td>−0.11 ± 0.17</td>
<td>0.018 ± 0.25</td>
<td>0.09</td>
<td>−0.013 ± 0.14</td>
<td>−0.082 ± 0.20</td>
<td>−0.055 ± 0.16</td>
<td>0.76</td>
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<tr>
<td>NEFAs (mmol/l)</td>
<td>0.14 ± 0.50</td>
<td>0.10 ± 0.55</td>
<td>0.023 ± 0.44</td>
<td>0.72</td>
<td>−0.029 ± 0.35</td>
<td>−0.050 ± 0.46</td>
<td>0.041 ± 0.47</td>
<td>0.98</td>
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Values are means ± S.D. ∗\(P < 0.05\) and ∗∗\(P < 0.01\) compared with baseline measurement (0 h), as determined by ANOVA.
activity can produce additional similar changes in myocardial metabolism. In patients with a compromised metabolic state of the myocardium, such as in ischaemic heart disease or CHF, it is considered beneficial for the myocardial tissue to prefer carbohydrate as substrate. Therefore the finding that moxonidine did not decrease M\(\dot{V}_{\text{o}_2}\) but tended to increase M\(\dot{V}_{\text{o}_2}\) was unexpected. In fact, NEFA consumption was significantly increased by moxonidine, which would explain the lack of decrease in M\(\dot{V}_{\text{o}_2}\). A beneficial effect on carbohydrate metabolism was not observed, at least under the condition of existing β-receptor blockade in the majority of patients.

Our present study does not provide an explanation for the cellular mechanisms of moxonidine on myocardial metabolism. It would be expected that inhibition of sympathetically induced release of NA would decrease the release of NEFAs from peripheral tissues, and thus favour myocardial uptake of carbohydrates. Therefore a possible explanation for the present findings is that acute administration of moxonidine resulted in an increase in the release of adrenaline or other neurohormonal substances that increase myocardial NEFA uptake [19]. This suggestion must remain speculation as the effect of acute moxonidine on plasma levels of neurohormones has not been monitored. It is not known whether acute administration of moxonidine is accompanied by an increase in the release of adrenaline or other neurohormonal substances that affect cardiac metabolism.

The present study was planned and performed before the MOXCON study had been terminated due to an increased mortality rate in the moxonidine group [10]. There are numerous examples of contradictory results regarding short- and long-term effects of drugs for CHF treatment [20–24]. Nevertheless, it was difficult to understand why moxonidine was not beneficial in CHF patients, given the good indications gained from studies involving acute administration [8,9]. The MOXCON study investigators suggested that too high a dose or too rapid a dose up-titration might have caused a too extensive blockade of the sympathetic nervous system [10], as patients in that study were also taking β-blockers. The results of the present study now allow the possibility that the effects of moxonidine we have shown on myocardial NEFA uptake and M\(\dot{V}_{\text{o}_2}\) may also have occurred during long-term moxonidine. Unfortunately, because a direct comparison between the effects of acute and chronic administration of moxonidine alone on myocardial metabolism has not been made and because moxonidine was given on top of β-blockers in the present study, it is impossible to deduce whether the effects of moxonidine described are due to the actions of moxonidine itself or to the effect of moxonidine given in the presence of β-blockers. Whichever is the case, it should be noted that during initiation of β-blocker treatment the negative inotropic effect of the drug is counterbalanced by the beneficial effects on myocardial metabolism [14]. If moxonidine lacks these positive effects, it would not be surprising if the drug was less effective for treatment of CHF, regardless of doses or titration schedules. Indeed, an increase in NEFA uptake and M\(\dot{V}_{\text{o}_2}\) would lead to increased energy expenditure and increased pump failure over time.

Our findings also raise the intriguing question of whether there is a difference between the effects of β-receptor blockade and of a reduction in sympathetic activity on myocardial metabolism. It has been suggested that β-receptor blockade achieves intracellular effects not only by blocking β-receptors, but by modulating other receptor pathways [25]. Moreover, β-blockers also have the capacity to act as inverse agonists, a concept which is of high scientific interest in the search for new pharmaceuticals [26]. It is plausible that receptor blockers with inverse agonism reduce the basal state and metabolism of myocytes and that this is more efficient than a mere reduction in agonist concentration. Furthermore, we have found previously [27] that a naturally occurring gene polymorphism of the β1-adrenergic receptor was associated with different responses to inverse agonism, pointing to the possibility of differences between subjects. None of these effects would be expected to follow moxonidine administration.

**Study limitations**

The study included only a small number of patients, which hampers a more general conclusion of drug effects. Furthermore, only one dose of moxonidine was tested (0.6 mg) and, of course, different doses might have produced different effects. Thus, in the study performed by Dickstein et al. [6], in which 0.4 and 0.6 mg of moxonidine were compared, only 0.6 mg produced significant haemodynamic effects. In that study, patients had somewhat higher baseline concentrations of NA and had also a more pronounced reduction in arterial levels after 0.6 mg of moxonidine compared with our present study. However, their patients had less efficient background therapy, as they were not treated with β-blockers. Therefore it may be that, in the present study, the effects of 0.6 mg of moxonidine on plasma NA were limited by the presence of β-receptor blockade. In addition, as noted above, we studied the acute effects of moxonidine on myocardial metabolism; the effects of chronic treatment remain unknown. Finally, for fear of causing adverse vasodilation and hypotension, we chose to withdraw the morning dose of ACEIs. It cannot be excluded that unopposed effects of angiotensin II influenced myocardial metabolism, although major effects are unlikely as only a single dose was withheld.

**Conclusions**

The present results indicate that a single oral dose of sustained-release moxonidine (0.6 mg) administered to
patients with moderate CHF and already on treatment with a β-blocker reduced cardiac as well as systemic sympathetic nerve activity. We propose that the lack of beneficial effects on myocardial metabolism might be a reason for the failure of moxonidine to prevent deaths in long-term survival studies in CHF.

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