Chronic I₁-Imidazoline Agonism
Sympathetic Mechanisms in Hypertension

John P. Greenwood, Eleanor M. Scott, John B. Stoker, David A. Mary

Abstract—Evidence exists for a state of sympathetic hyperactivity in essential hypertension, and moxonidine, a new central sympathetic inhibitor, has been introduced for its treatment. Acute administration of moxonidine lowers peripheral sympathetic neural output. This study examined the effect of chronic moxonidine therapy, at increasing therapeutic doses, on resting peripheral sympathetic activity and vascular resistance and their responses to physiological reflex maneuvers. Twelve newly diagnosed patients with essential hypertension were studied sequentially at least 1 month apart, initially on no therapy, then on 200 μg, and finally on 400 μg of oral moxonidine daily. Changes in heart rate, arterial blood pressure, calf vascular resistance, and peripheral sympathetic drive were assessed at rest and during reflex maneuvers. Peroneal microneurography was used to quantify peripheral sympathetic vasoconstrictor activity by single-unit and multitunit techniques. Moxonidine therapy progressively reduced resting mean arterial pressure (P<0.0001) without affecting heart rate. At 200 μg daily, there was a significant reduction in sympathetic nerve activity (P<0.01) and calf vascular resistance (P<0.01). At 400 μg daily, further reductions were smaller and insignificant. Responses to cold stimulus and isometric handgrip exercise showed a similar pattern, with the greatest magnitude of change at 200 μg daily. In patients with essential hypertension, chronic moxonidine therapy inhibited resting sympathetic vasoconstrictor drive and also its reflex responses. The magnitude of inhibition became less as the therapeutic dose was increased, suggesting that moxonidine may be more effective under conditions of high sympathetic activity. (Hypertension. 2000;35:1264-1269.)

Key Words: sympathetic nervous system ■ hypertension, essential ■ blood pressure ■ antihypertensive agents ■ moxonidine

Hyperactivity of the sympathetic nervous system has long been implicated in the pathogenesis of essential hypertension.¹⁻³ Evidence for this has been derived from pharmacological studies, from the assay of plasma catecholamines, and also from direct recordings from peripheral nerves.⁴⁻⁶ This latter technique, termed microneurography, is the only direct method for assessing the sympathetic nervous system in humans and allows assessment to be made under both resting and dynamic conditions. As a result, it is ideally suited to investigate the control of central sympathetic outflow and, hence, the neural control of vascular resistance.

Centrally acting antihypertensive agents affecting the sympathetic system have been used extensively in the past. However, their use was often limited by their adverse side-effect profile, which resulted from stimulation of central α₂-receptors. Recently, moxonidine, an I₁-imidazoline receptor agonist with much less α₂ activity, has been introduced for the treatment of hypertension.⁷⁸ Research in experimental animals has shown that moxonidine lowers blood pressure by its action in the rostral ventrolateral medulla, inhibiting central sympathetic output to the peripheral vasculature, heart, and kidney.⁹⁻¹¹ In humans, this sympatholytic effect is suggested by the findings that moxonidine reduces peripheral vascular resistance and also the level of plasma catecholamines and renin activity.¹²¹³ By use of microneurography, data have shown that acute administration of a single oral dose of moxonidine reduced sympathetic activity in normotensive individuals compared with their baseline values. Although it also decreased sympathetic activity in hypertensive patients, the effect seemed to be more pronounced in the healthy volunteers.¹⁴ The reasons for this remain unclear but have been related to the variable firing frequency of units within a sympathetic burst.¹⁴ More recently, assessment from single vasoconstrictor units has been shown to give further insight into central sympathetic control.¹⁵⁻¹⁶ As of yet, no evidence exists as to the long-term effect of moxonidine therapy on peripheral sympathetic activity and vascular resistance.

The present study was designed to determine the effect of chronic moxonidine therapy (at increasing therapeutic doses)
on peripheral sympathetic vasoconstrictor activity in patients with essential hypertension. Sympathetic activity was assessed by single-unit and multiunit microneurographic techniques, both at rest and during physiological reflex responses.

## Methods

### Subjects

Fourteen patients (9 males and 5 females) with newly diagnosed untreated essential hypertension were examined between February 1998 and April 1999. All were screened by history and physical and laboratory examinations; subjects were excluded if there was evidence of secondary hypertension, arrhythmia, or chronic disease that may influence the autonomic nervous system. At least 3 blood pressure readings were taken on separate occasions and averaged, and hypertension was defined as systolic blood pressure $\geq 140$ mm Hg or diastolic blood pressure $\geq 90$ mm Hg. Of the 14 patients, 4 had stage-2 disease, 9 had stage-3 disease, and 6 had left ventricular hypertrophy confirmed echocardiographically. Their demographic details are shown in Table 1.

### Study Design

The study group was examined on 3 occasions: first, in the absence of therapy; second, after 4 weeks of treatment with moxonidine at a dose of 200 $\mu$g daily; and third, after a further 4 weeks of moxonidine at 400 $\mu$g daily. All patients were recruited after an independent decision to start oral antihypertensive therapy. Because of the severity of disease and the presence of end-organ damage, it was felt inappropriate to delay treatment by administering a placebo. In addition, the longitudinal study design meant that individuals acted as their own controls. Comparable longitudinal studies in this laboratory have shown that sympathetic activity does not change significantly or systematically over a similar time period (95% CIs of differences, 7%; authors’ unpublished data, 1999).

### Protocol

Under the approval of St James’s University Hospital Ethics Committee, each subject provided informed written consent for the investigation. All subjects were studied between the hours of 9:00 AM and 12:00 noon and were asked to avoid nicotine and caffeine products for 12 hours and alcohol and strenuous exercise for 24 hours before the investigation. Subjects maintained a normal dietary intake of sodium, and they were requested to have had a light breakfast and to empty their bladders before beginning the study. During each session, all subjects were in the semisupine position for study. Measurements were made in a darkened laboratory in which the temperature was constant at 22°C to 24°C. Subjects were requested to relax and remain silent for 10 minutes, so as to reach a steady state. All subjects then had continuous monitoring of heart rate, blood pressure, sympathetic neural activity, respiration, and calf vascular resistance (CVR) during the resting steady state for at least

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**TABLE 1. Demographic Data for All 14 Patients and Characteristics of the 12 Patients Studied at Each Level of Moxonidine Therapy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Therapy</th>
<th>200 $\mu$g</th>
<th>400 $\mu$g</th>
<th>$P$ (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±2.4 (46–74)</td>
<td>...</td>
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</tr>
<tr>
<td>Follow-up patients</td>
<td>58±2.1 (46–74)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Weight, kg</td>
<td>81±3.8 (55–106)</td>
<td>81±3.9 (55–107)</td>
<td>80±3.7 (55–107)</td>
<td>0.587</td>
</tr>
<tr>
<td>Follow-up patients</td>
<td>81±3.5 (55–106)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All patients</td>
<td></td>
<td></td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>28±0.9 (23–34)</td>
<td>28±0.9 (23–34)</td>
<td>28±0.8 (23–32)</td>
<td>0.552</td>
</tr>
<tr>
<td>Follow-up patients</td>
<td>28±0.9 (23–34)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All patients</td>
<td></td>
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<tr>
<td>Heart rate, bpm</td>
<td>69±3.9 (54–104)</td>
<td>69±3.6 (56–94)</td>
<td>67±2.7 (55–85)</td>
<td>0.590</td>
</tr>
<tr>
<td>Follow-up patients</td>
<td>70±3.6 (54–104)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All patients</td>
<td></td>
<td></td>
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<tr>
<td>BRS, ms/mm Hg</td>
<td>2.7±0.5 (0.9–4.7)</td>
<td>3.3±0.7 (0.7–10.1)</td>
<td>2.3±0.4 (0.6–4.6)</td>
<td>0.413</td>
</tr>
<tr>
<td>Follow-up patients</td>
<td>3.0±0.4 (0.9–4.7)</td>
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<td></td>
<td></td>
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<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial pressure, mm Hg</td>
<td>Mean</td>
<td>136±2.5 (123–150)</td>
<td>126±2.2 (115–143)*</td>
<td>118±2.1 (110–133)*‡</td>
</tr>
<tr>
<td>Follow-up patients</td>
<td>136±2.2 (123–150)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>192±7.3 (160–240)</td>
<td>174±5.3 (145–200)*</td>
<td>164±4.6 (148–200)*§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Follow-up patients</td>
<td>192±6.3 (160–240)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diastolic</td>
<td>108±2.2 (90–120)</td>
<td>101±1.9 (90–114)†</td>
<td>96±2.0 (86–110)*§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Follow-up patients</td>
<td>108±2.0 (90–120)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
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</tr>
</tbody>
</table>

Values are mean±SEM (range) for follow-up patients (n=12) and all patients (n=14).

*P<0.001 and †P<0.01 vs no therapy (repeated measures ANOVA); ‡P<0.01 and §P<0.05 vs 200-$\mu$g values (repeated-measures ANOVA).
5 minutes. After this, reflex response data were obtained during the Valsalva maneuver, isometric handgrip exercise (IHG), and a cold pressor test (CPT).

**Measurements**
Heart rate and arterial blood pressure were monitored and recorded with use of a standard ECG and a Finapres device (model 2300, Ohmeda). A pneumograph consisting of a corrugated rubber tube placed round the chest and connected to a pressure transducer was used to monitor and record respiration. Calf blood flow was recorded by using the standard technique of venous occlusion plethysmography (D.E. Hokansen Inc), and simultaneously, peripheral sympathetic nerve activity was recorded by the technique of microneurography.

**Microneurography**
Postganglionic muscle sympathetic nerve activity (MSNA) was recorded from the right peroneal nerve and was differentiated from skin sympathetic activity and afferent activity as previously described. Briefly, single units were sought by making repeated tiny adjustments to the exploring electrode position. These were defined on the basis of a consistent action potential morphology and an amplitude greater than the rest of the discharge. When a unit was identified, confirmation as to its vasoconstrictive nature came from observing its appropriate response to the spontaneous changes in arterial blood pressure, the Valsalva maneuver, IHG, and CPT. Further confirmation was made by obtaining a direct relationship between the frequency of sympathetic discharge and CVR.

Multunit bursts of MSNA and action potentials from single vasocostrictor units (s-MSNA) were recorded. The neural signal was amplified (×50 000), and for the purpose of generating MSNA bursts, this was filtered (bandwidth of 700 to 2000 Hz) and integrated (time constant 0.1 seconds). The output from this assembly was passed to a data-acquisition system (FASTDAQ, Lectromed UK Ltd) for online monitoring and computer storage (Elonex UK Ltd). The FASTDAQ system digitized the action potentials at 12 000 samples per second and all other data channels (MSNA bursts, ECG, respiration, and Finapres blood pressure) at 2000 samples per second (8 bits).

**Other Procedures**
The Valsalva maneuver was performed at a pressure of 40 mm Hg for 15 seconds after a number of practice attempts. IHG was performed by use of a dynamometer (MIE Medical Research Ltd) at 30% of maximal voluntary contraction for 2 minutes. CPT was performed by dipping the right hand into iced water (<4°C for a minimum of 1 minute until discomfort was felt. Between each of these maneuvers, subjects relaxed until a resting steady state was reestablished.

**Analysis**
Data analysis was performed offline by a single experienced operator with no knowledge of patient details who used signal processing software (FASTDAQ, Lectromed UK Ltd). An electronic discriminator was used objectively to count the impulses of s-MSNA and the R wave of the ECG. The former was quantified as mean frequency of impulses per minute and impulses per 100 cardiac beats; this avoided any interference by the length of the cardiac cycle. The MSNA bursts were identified by inspection and similarly quantified. The variability of such measurements from this laboratory is <10%. The slope of the linear relationship between the heart period and systolic blood pressure from stage IV of the Valsalva maneuver was used to represent cardiac baroreceptor reflex sensitivity (BRS). This was taken as the best linear fit with use of phase 0 and phase 1 of the heart period and was expressed in ms/mm Hg. CVR, expressed in arbitrary units, was derived from the quotient of mean arterial pressure and calf blood flow. The latter was obtained in terms of mL/100 mL tissue per minute. Responses to IHG and the CPT were taken as the difference between either the first half (response 1) or the last half (response 2) of the test and the baseline period.

**Statistics**
Repeated measures 1-way ANOVA was used to examine the changes in data from 12 patients. Posttest analysis by Newman-Keuls multiple comparison tests was used to examine individual group pairs. The least squares technique was used to assess the linear relationship between variables. Values of P<0.05 were considered statistically significant. All data are presented as mean±SEM.

**Results**
Twelve of the 14 patients completed all 3 stages of the study. The other 2 patients were only able to be examined while initially taking no therapy and then on 400 μg of moxonidine daily. Moxonidine significantly reduced all indices of arterial pressure progressively with increasing levels of therapy (Table 1). Moxonidine at 200 μg daily reduced the average systolic blood pressure by 9%, diastolic blood pressure by 7%, and mean blood pressure by 7%. With 400 μg of moxonidine, the further respective reductions were 6%, 5%, and 6%. There was no statistically significant change in heart rate, although there was a trend toward a reduction at 400 μg of therapy (≈3%). Furthermore, moxonidine did not significantly affect the subject’s body weight or cardiac BRS.

Moxonidine reduced peripheral sympathetic output, but this reduction was not progressive with increasing therapeutic doses (Figure 1). Moxonidine at 200 μg daily significantly reduced the mean frequency of MSNA bursts and s-MSNA, whether expressed as activity per minute or per 100 cardiac beats. These reductions amounted to an average of 19% for MSNA bursts per minute, 18% for MSNA bursts per 100 cardiac beats, and 21% for s-MSNA regarding both measurement expressions. With a dose of 400 μg daily, any further decreases in MSNA per minute or per 100 cardiac beats (7% and 6%, respectively) and those of s-MSNA (8% and 7%, respectively) were relatively small and insignificant. There was a significant correlation (r=0.37, P=0.04) between the initial frequency of s-MSNA (obtained over 100 cardiac beats) and the magnitude of its reduction by moxonidine.
The changes in CVR (Figure 2) were similar to those in peripheral sympathetic output, in that the largest decrease (21%) occurred at a dose of 200 mg daily. Increasing the dose of moxonidine to 400 mg daily was not associated with any further changes in CVR. As in the case of s-MSNA, there was a significant correlation ($r = 0.64, P = 0.0004$) between the initial values of CVR and the magnitude of its reduction by moxonidine.

The responses of sympathetic activity (MSNA and s-MSNA) and CVR to CPT were obtained at all 3 stages of the protocol in 8 of the 12 patients (Figure 3 and Table 2). Moxonidine had no significant effect on the responses of heart rate and mean arterial pressure, although it reduced the peak levels obtained during the test. At 200 µg daily, moxonidine significantly attenuated the peak increases in mean frequency of MSNA (by 75%) and s-MSNA (by 83%), expressed as activity per 100 cardiac beats. This was associated with a 42% attenuation in the peak CVR response to the CPT. As in the resting state, increasing the dose to 400 µg daily was not associated with any further decrease in the responses of sympathetic activity, or CVR, to CPT. There was a significant correlation between the magnitude of the initial responses and the degree of attenuation produced by moxonidine for s-MSNA per 100 cardiac beats ($r = 0.99, P = 0.0001$) and for CVR ($r = 0.51, P = 0.01$).

The responses of sympathetic activity (MSNA and s-MSNA) and CVR to IHG were obtained at all 3 stages of the protocol in only 6 of the 12 patients. Although increasing the dose of moxonidine did not produce statistically significant differences regarding the responses of heart rate, blood pressure, sympathetic activity, and CVR, there were trends that were similar to those observed during CPT (Figure 3 and Table 2). Moxonidine at 200 µg daily attenuated the peak increases in the mean frequency of MSNA and s-MSNA (59% and 71%, respectively; expressed as activity per 100 cardiac beats) and that of the peak CVR response by 61%, in response to IHG. Increasing the dose of moxonidine to 400 µg daily was not associated with further large-scale reductions in the responses to IHG. However, there was a significant correlation between the magnitude of initial responses and the degree of attenuation produced by moxonidine for s-MSNA per 100 cardiac beats ($r = 0.96, P = 0.0001$) and for CVR ($r = 0.78, P = 0.0001$).

**Discussion**

The present study has shown for the first time that chronic moxonidine administration to patients with untreated essential hypertension reduced resting peripheral sympathetic vasocostrictor activity and its responses to physiological reflex maneuvers. These findings were greatest after initiating therapy at 200 µg daily, with proportionally less effect as the dose was increased to 400 µg daily. The findings indicate that moxonidine inhibited the central sympathetic discharge frequency to levels that curtailed any further inhibition produced by increasing the dose.

Given that hypertension has been associated with sympathetic hyperactivity in cardiac, renal, and skeletal muscle regions and that moxonidine is likely to exert a sympatholytic effect, it was timely that a recent report investigated the acute effects of moxonidine on peripheral sympathetic activity. The authors found that a single oral dose of moxonidine (0.4 mg) reduced the mean frequency of multi-unit bursts and the burst amplitude in both hypertensive and normotensive subjects. However, the mean discharge fre-
frequency was decreased to a greater extent in the normotensive than in the hypertensive subjects, which was attributed to the fact that bursts can contain a variable number of firing units. Thus, an important question was raised regarding whether bursts can contain a variable number of firing units. 

In the present study, mean arterial pressure was reduced by ≈13%, which is in keeping with previous hypertension trials with moxonidine, and is also comparable to that produced by most other classes of antihypertensive agents.7,13,23–27 The fall in resting arterial pressure was progressive and significant at each therapeutic dose. In addition, moxonidine was also shown to reduce the peak levels of blood pressure attained during IHG and CPT. These findings are consistent with those previously reported, which have shown that moxonidine reduced the maximum blood pressure attained during a mental stress test.28 Finally, moxonidine produced no significant effect on heart rate, which is also consistent with the results of earlier trials.27,29,30 This may be related to a lack of effect on the vagal control of heart rate, which is greater than the sympathetic control at rest, as confirmed by an absence of change in cardiac BRS. Also, any moxonidine-mediated decrease in heart rate due to its sympatholytic effect may be opposed by a reflex increase in heart rate through vagal inhibition resulting from the decrease in arterial pressure. These factors could also explain the absence of a significant effect of moxonidine on the heart rate response to IHG and CPT.

Chronic low-dose moxonidine therapy produced a significant reduction in resting sympathetic discharge and vascular resistance, but increasing the therapeutic dose resulted in proportionally smaller effects. The finding of a smaller effect of the higher dose of moxonidine suggests that the attenuation occurred to a greater extent in cases of high rather than low sympathetic activity. Indeed, there was a relationship between the magnitude of baseline activity and the decrease effected by the 2 doses of moxonidine. The initial dose of moxonidine reduced the sympathetic activity to values much

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**TABLE 2. Increases in Measured Data Relative to Control Values During First (Response 1) and Second (Response 2) Periods of CPT in 8 Subjects or IHG in 6 Subjects**

<table>
<thead>
<tr>
<th>Data</th>
<th>No Therapy</th>
<th>Moxonidine Therapy</th>
<th>No Therapy</th>
<th>Moxonidine Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 µg</td>
<td>400 µg</td>
<td>200 µg</td>
<td>400 µg</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response 1</td>
<td>5 ± 2.3</td>
<td>2 ± 1.4</td>
<td>4 ± 1.4</td>
<td>5 ± 1.0</td>
</tr>
<tr>
<td>Response 2</td>
<td>7 ± 1.5</td>
<td>5 ± 1.5</td>
<td>5 ± 1.5</td>
<td>9 ± 2.6</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response 1</td>
<td>6 ± 3.8</td>
<td>4 ± 2.6</td>
<td>8 ± 3.5</td>
<td>9 ± 1.0</td>
</tr>
<tr>
<td>Response 2</td>
<td>19 ± 3.5*</td>
<td>20 ± 5.5*</td>
<td>22 ± 5.8*</td>
<td>23 ± 5.0*</td>
</tr>
<tr>
<td>MSNA frequency, bursts/100b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response 1</td>
<td>53 ± 29.7</td>
<td>5 ± 7.1</td>
<td>4 ± 2.8</td>
<td>12 ± 10.3</td>
</tr>
<tr>
<td>Response 2</td>
<td>121 ± 33.9*</td>
<td>30 ± 10.0†</td>
<td>42 ± 10.9†</td>
<td>75 ± 40.4</td>
</tr>
<tr>
<td>s-MSNA frequency, impulses/100b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response 1</td>
<td>79 ± 38.2</td>
<td>6 ± 8.7</td>
<td>5 ± 4.5</td>
<td>18 ± 8.0</td>
</tr>
<tr>
<td>Response 2</td>
<td>226 ± 84.9*</td>
<td>38 ± 11.9†</td>
<td>38 ± 11.4†</td>
<td>149 ± 58.8*</td>
</tr>
<tr>
<td>CVR, units</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response 1</td>
<td>8 ± 6.1</td>
<td>0.3 ± 2.3</td>
<td>1.2 ± 1.8</td>
<td>13 ± 4.1</td>
</tr>
<tr>
<td>Response 2</td>
<td>26 ± 8.2</td>
<td>15 ± 4.9</td>
<td>27 ± 8.6</td>
<td>28 ± 6.8*†</td>
</tr>
</tbody>
</table>

Values are mean ± SEM and relate to studies before and after each level of moxonidine therapy. *P<0.05 vs response 1 (repeated-measures ANOVA); †P<0.05 vs no therapy (repeated-measures ANOVA).
closer to normal resting activity,14,15 which may have curtailed any further decreases during higher dose therapy.

Chronic moxonidine therapy markedly attenuated the response of an increase in sympathetic activity and CVR to CPT. However, increasing the dose was not associated with any further attenuation. A similar effect of moxonidine on these responses to IHG was also observed, although this effect did not attain statistical significance. As in the case of resting sympathetic activity, the effect of moxonidine in attenuating the response of an increase in s-MSNA and CVR showed a direct correlation with the magnitude of their initial response. Thus, the results indicate that moxonidine also inhibits the reflex increase in central sympathetic vasoconstrictor output in a manner dependent on the level of sympathetic hyperreactivity.

The results from the present investigation are consistent with animal studies showing that moxonidine and I1-imidazoline agonism reduce central sympathetic output to the viscera and periphery.9–11 The different effects of moxonidine on sympathetic activity and arterial pressure suggest that the initial large sympatholytic effect of moxonidine imposed a limitation on any further decrease of sympathetic activity that could occur by increasing its dose. Also, mechanisms in addition to the withdrawal of peripheral sympathetic vasoconstrictor discharge could have affected arterial pressure. For instance, a reduction of sympathetic discharge to other major viscera may change urinary sodium excretion and the activity of the renin-angiotensin system,13 leading to a reduction in blood pressure.

In conclusion, this is the first study to show that chronic moxonidine therapy inhibits resting sympathetic vasoconstrictor drive and sympathetic reflex responses. However, as the inhibition became less with increasing levels of therapy, there are indications that moxonidine may be more effective under conditions of high sympathetic drive.

Acknowledgments

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References

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