Effects of midodrine on exercise-induced hypotension and blood pressure recovery in autonomic failure

William G. Schrage, John H. Eisenach, Frank A. Dinenco, Shelly K. Roberts, Christopher P. Johnson, Paola Sandroni, Philip A. Low, and Michael J. Joyner

Departments of 1Anesthesiology and 2Neurology, Mayo Clinic and Foundation, Rochester, Minnesota 55905

Submitted 26 May 2004; accepted in final form 19 July 2004

Schrage, William G., John H. Eisenach, Frank A. Dinenco, Shelly K. Roberts, Christopher P. Johnson, Paola Sandroni, Philip A. Low, and Michael J. Joyner. Effects of midodrine on exercise-induced hypotension and blood pressure recovery in autonomic failure. J Appl Physiol 97: 1978–1984, 2004. First published July 23, 2004; doi:10.1152/japplphysiol.00547.2004.—We tested the hypothesis that the oral α1-adrenergic agonist, midodrine, would limit the fall in arterial pressure observed during exercise in patients with pure autonomic failure (PAF). Fourteen subjects with PAF underwent a stand test, incremental supine cycling exercise (25, 50, and 75 W), and ischemic calf exercise, before (control) and 1 h after ingesting 10 mg midodrine. Heart rate (ECG), beat-to-beat blood pressure (MAP, arterial catheter), cardiac output (Q, open-circuit acetylene breathing), forearm blood flow (FBF, Doppler ultrasound), and calf blood flow (CBF, venous occlusion plethysmography) were measured. The fall in MAP after standing for 2 min was similar (~60 mmHg; P = 0.62). Supine MAP immediately before cycling was greater after midodrine (124 ± 6 vs 117 ± 6 mmHg; P < 0.03), but cycling caused a workload-dependent hypotension (P < 0.001), whereas increases in Q were modest but similar. Midodrine increased MAP and total peripheral resistance (TPR) during exercise (P < 0.04), but the exercise-induced fall in MAP and TPR were similar during control and midodrine (P = 0.27 and 0.14). FBF during cycling was not significantly reduced by midodrine (P > 0.2). By contrast, recovery of MAP after cycling was faster (P < 0.04) after midodrine (~25 mmHg higher after 5 min). Ischemic calf exercise evoked similar peak CBF in both trials, but midodrine reduced the hyperemic response over 5 min of recovery (P < 0.02). We conclude midodrine improves blood pressure and TPR during exercise and dramatically improves the recovery of MAP after exercise.

During exercise in healthy humans, activation of the sympathetic nervous system is critical to maintain arterial blood pressure. Blood pressure increases because of increased cardiac output and vasoconstriction of inactive muscle and other tissues (11, 12). Additionally, the sympathetic nerves appear to restrain metabolic vasodilatation in the active muscles; however, the efficacy of the adrenergic vasoconstriction is reduced as part of the phenomenon termed “functional sympatholysis” (1, 9). Together, these adjustments maintain or increase blood pressure despite marked vasodilatation in the active muscles.

Patients suffering from pure autonomic failure (PAF) exhibit 80% loss of sympathetic postganglionic neurons in the intermedialateral cell columns of the spinal cord (5, 7), abolishing their ability to constrict peripheral blood vessels. Without vasoconstrictor activity, autonomic failure patients are exposed to three potentially serious medical problems: 1) severe reduction in blood pressure during standing, 2) a severe fall in blood pressure during exercise, and 3) a delayed recovery of blood pressure after exercise. Although there is amelioration of the orthostatic fall in blood pressure with regular use of midodrine (6, 21), its effect on exercise-induced fall in blood pressure, and especially the prolonged postexercise hypotension (8, 17, 19), is unknown.

In this context, improving the blood pressure responses during exercise is desirable in patients with PAF for the following reasons. First, it is likely to improve the ability to sustain submaximal exercise (exercise tolerance) by providing a greater “cushion” of blood pressure to avoid syncope. Second, regular exercise increases plasma volume, muscle mass and muscle tone, which will all enhance orthostatic tolerance. Finally, regular aerobic exercise reduces overall cardiovascular risks (lower body fat, lower cholesterol, and lower risks of stroke, heart attack, and Type 2 diabetes). Together, these three adaptations may improve overall quality of life. Although midodrine is a common treatment for orthostatic hypotension in PAF patients, the systemic and regional effects of midodrine on exercise-induced hypotension remain unknown. The purpose of this study was to test the hypothesis that midodrine would limit the exercise-induced fall in blood pressure in PAF patients and would improve postexercise blood pressure recovery. To address possible mechanisms for blood pressure changes, we measured forearm blood flow (FBF) and calf blood flow (CBF) to determine whether midodrine would evoke greater vasoconstriction in the forearm (nonexercising) or calf (exercising) muscles.

MATERIALS AND METHODS

Patients

Fourteen patients (9 men, 5 women, ages 49–76 yr) with PAF or autonomic neuropathy with orthostatic hypotension were studied from June through September of 2003. The protocols were approved by the Mayo Clinic Institutional Review Board, and each patient gave written, informed consent. PAF was defined as orthostatic hypotension without central nervous or somatic peripheral nerve involvement. Orthostatic hypoten-
sion was defined as a systolic blood pressure (SBP) reduction \( \geq 20 \) mmHg or mean blood pressure reduction of \( \geq 20 \) mmHg on standing (2). The patients were nonobese (body mass index \( \leq 30 \)) and free of organ system dysfunction or systemic illness that could affect the study results. All subjects were taking some form of medication to control their clinical symptoms (midodrine, fluodrocortisone, or pyridostigmine). These agents were discontinued for at least five half-lives before the study, and salt tablets were discontinued 5 days before the study. No medications were allowed on the day before the study; therefore, all patients were admitted to the Mayo General Clinical Research Center (GCRC) 24–48 h before the study for safety and monitoring purposes. A forearm intravenous line was placed on GCRC admission. After ingesting nothing by mouth except water after midnight, patients were awakened at 6:30 AM and transported to the GCRC exercise laboratory.

**Patient Instrumentation and Hemodynamic and Catecholamine Measures**

Heart rate (HR) was obtained by a three-lead electrocardiogram. To monitor arterial blood pressure throughout the study, a 20-gauge, 5-cm catheter was placed in the radial or brachial artery of the nontandom arm under aseptic conditions after local anesthesia (1% lidocaine). Arterial pressure was calibrated from 0 to 300 mmHg from a Cardiopac/5 monitor (Datex-Ohmeda) and digitally recorded on a laptop computer. A three-way connector was placed in series with a catheter-transducer system so that blood samples could be drawn to assay catecholamines. To ensure patient hydration, an infusion of normal saline at 100–120 mL/h was administered intravenously until completion of the study.

**Cardiac output.** Cardiac output (Q; l/min) was estimated by using an open-circuit acetylene washin method validated in humans vs. the direct Fick approach (4). This method allows the noninvasive determination of Q that can be repeated every 4–6 min.

**Measurement of FBF or CBF.** During supine bike exercise, continuous FBF was measured as described previously (1, 10, 13). Briefly, a 4-MHz pulsed Doppler probe (model 500V, Multigon Industries, Mt. Vernon, NY) measured brachial arterial mean blood velocity (MBV) proximal to the elbow. The probe insonation angle was 60°. A linear 7.0-MHz echo Doppler ultrasound probe (model 128XP, Acuson, Mountain View, CA) was placed immediately proximal to the velocity probe to measure brachial artery diameter. FBF was calculated as FBF = MBV/II/radial arterial diameter/2 - 60, where FBF is in milliliters per minute, the MBV is in centimeters per second, the brachial diameter is in centimeters, and 60 is used to convert from milliliters per second to milliliters per minute. Forearm vascular resistance (FVR) was calculated as mean arterial pressure (MAP)/FBF and expressed as millimeters of Hg per minute per milliliter per deciliter.

Calf vascular resistance (CVR) was calculated as (MAP/CBF), and expressed as millimeters of Hg per minute per milliliter per deciliter. Catecholamine assays. Catecholamines in plasma were measured by reverse-phase HPLC with electrochemical detection after extraction with activated alumina. Three milliliters of arterial blood were collected before exercise and at peak exercise in control and midodrine conditions. Samples were placed on ice immediately, and 1 ml of plasma was absorbed onto activated alumina at pH 8.6, washed, and eluted with dilute acid. Eluates were injected onto a reverse-phase (C18) column, which separates the individual catecholamines (norepinephrine, epinephrine, and dopamine), and were detected coulometrically and quantified with the aid of an internal standard (3,4-dihydroxybenzylamine).

**Experimental Protocol**

After instrumentation and 20 min of supine rest, a stand test was performed to assess orthostatic hypotension (see protocol, Fig. 1). After hemodynamic measurements were recorded for 2 min, subjects stood for 2 min or until they became symptomatic (dizziness, light-headedness, etc.) and could no longer stand. After resumption of the supine position and stabilization of vital signs, baseline cardiovascular variables (HR, MAP, and Q), and FBF were recorded at 5-min intervals over the subsequent 15 min. Continuous, incremental supine cycling exercise was then performed at 25, 50, and 75 W (55–70 rpm) for 7–10 min at each workload, with cardiovascular and FBF measures repeated at 3 min (steady state) and at the end of each workload. Exercise was terminated by the inability to maintain at least 50 rpm or by the desire to discontinue because of fatigue. Arterial blood samples were collected at rest and during peak cycling exercise for measurement of catecholamines. On completion of cycling exercise, recovery measures were repeated at 5, 10, and 20 min postexercise.

After 10 more min of rest, ischemic calf exercise was performed to evoke maximum metabolic vasodilation (20) of the calf muscle to determine whether midodrine restrains blood flow to maximally dilated muscles. CBF, HR, and arterial pressure were recorded during a 2-min baseline period, and then a cuff around the midthigh was inflated to 50 mmHg above SBP. Subjects began rhythmic calf exercise at a rate of 0.5–1 contraction/s until volitional fatigue. Immediately on fatigue, the thigh cuff was deflated, and CBF, MAP, and HR were measured for 5 min of postexercise hyperemia. After these control trials, each patient then orally ingested a midodrine tablet (10 mg) and rested for 1 h. The level of the active form of midodrine (desglymidodrine) reaches peak blood concentrations \( \sim 1 \) h after a 10-mg dose of midodrine and has a half-life of 3–4 h (21). This dose of midodrine raised supine blood pressure \( \sim 35 \) mmHg for 2–3 h (21). The entire protocol (stand test, supine cycling, ischemic calf exercise) was then repeated.

**Data Acquisition and Calculations**

Arterial pressure was measured directly from the radial artery. Physiological signals (HR, arterial pressure, MBV) were digitized (200 Hz) and analyzed offline by using a Windaq-based acquisition system.
system. SBP, diastolic blood pressure (DBP), and mean blood pressures were calculated from the arterial pressure tracing. HR, MAP, MBV, and CBF data were taken as 30- to 60-s averages at rest and 30 s during exercise. Because some patients were unable to finish the entire cycling protocol, the last observation carried forward, or the MAP at the end of each patient’s cycling bout, was used to analyze the blood pressure recovery postexercise. Total peripheral resistance (TPR) was calculated as TPR = MAP/Q.

Statistical Analysis

Data are expressed as means ± SE. Hemodynamic variables were analyzed by two-way repeated measures analysis of variance (control vs. midodrine). The repeated-measures analysis corrects for dropout and accounts for the fact that measurements taken on the same subject over time tend to be correlated. Under this approach, dropout is assumed to be missing at random, which allows the probability of a subject dropping out to depend on their observed response measurement history. Information from the observed data is used to provide information about the missing data, but the missing data are not explicitly imputed. Paired t-tests or Tukey post hoc comparisons were also performed where appropriate. The level of significance was P < 0.05. On the basis of differences seen in previous studies for measurements of Q, we anticipated that 10 subjects were needed in each experiment for this level of statistical significance to be reached with a power of 0.8.

RESULTS

Patients, Stand Test, and Exercise Tolerance

The subjects’ mean age (± SE) was 64 ± 3 yr, and the mean length of diagnosis was 10 ± 2 yr. Their mean height was 173 ± 3 cm, weight was 76 ± 3 kg, and body mass index was 25 ± 1 kg/m². The medication regimens (discontinued before the study) included midodrine in 12 patients, fludrocortisone in 9 patients, and pyridostigmine in 8 patients.

The effect of midodrine on postural hypotension was modest. As shown in Table 1, all patients displayed severe orthostatic hypotension. Comparison of the change in SBP, DBP, MAP, and HR indicated the response from supine to standing was similar before and after midodrine (P > 0.4, midodrine × time interaction for all variables).

Not all patients were able to complete the incremental supine cycling trial due to leg fatigue, and there was no evidence to suggest midodrine affected exercise duration. Total cycling times in control and midodrine trials were 21.1 ± 1 and 21.7 ± 2 min, respectively (P = 0.48 by t-test).

Table 1. Hemodynamic response to standing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trial</th>
<th>Supine (2-min Average)</th>
<th>Standing Steady State</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>Control</td>
<td>68 ± 3</td>
<td>82 ± 4</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>65 ± 3</td>
<td>82 ± 4</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>Control</td>
<td>161 ± 10</td>
<td>77 ± 6</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>175 ± 10*</td>
<td>85 ± 6</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>Control</td>
<td>107 ± 6*</td>
<td>49 ± 4</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>114 ± 6*</td>
<td>54 ± 4</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>Control</td>
<td>76 ± 4</td>
<td>35 ± 3</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>83 ± 5</td>
<td>40 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. Changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were similar in control and midodrine trials (all P > 0.4). *Significantly different from control, P < 0.05.

Blood Pressure During and After Supine Cycling

As shown in Fig. 2A, midodrine increased the preexercise resting MAP from 117 ± 6 to 124 ± 6 mmHg (P = 0.03 by t-test). Next, cycling induced a workload-dependent drop in MAP (summarized in Table 2). This higher MAP represents a significant effect of midodrine on blood pressure during exercise (P < 0.02). However, the decrease in MAP during exercise was similar between conditions (P = 0.14, midodrine × time interaction).

As shown in Fig. 2B, before midodrine, MAP fell in the first minute of postexercise recovery, and remained low for 5 min. In contrast, midodrine significantly increased MAP during recovery (Fig. 2B). For example, after 5 min of recovery, the change in MAP was −1 ± 5 in control vs. 17 ± 7 mmHg higher after midodrine (P < 0.01, main effect of midodrine; P < 0.04, midodrine × time interaction). In the subsequent 5–20 min of the recovery period, the MAP continued to be
higher overall after midodrine trial ($P < 0.008$, main effect of midodrine), but the increase became similar between midodrine and control ($P = 0.27$, midodrine $\times$ time interaction).

**Other Cardiovascular Variables During and After Supine Cycling**

Supine cycling to fatigue evoked a subnormal but significant increase in HR in both trials ($P < 0.001$, main effect of exercise). Midodrine did not affect HR at rest or during exercise. Heart rate, SBP, MAP, and DBP responses to cycling are summarized in Table 2.

As shown in Fig. 3A, $Q$ increased during exercise in both trials ($P < 0.0001$, main effect of exercise). Midodrine did not affect $Q$ at rest, during exercise, or during recovery ($P = 0.4$, main effect of midodrine; $P = 0.74$, midodrine $\times$ time interaction).

As shown in Fig. 3B, midodrine increased TPR at rest, although this did not reach statistical significance ($P = 0.10$ by $t$-test). TPR decreased during exercise in both trials ($P < 0.0001$, main effect of exercise). TPR during exercise was significantly greater in the midodrine trial ($P < 0.04$), but the decrease in TPR was similar between cycling trials ($P = 0.93$, midodrine $\times$ time interaction). Similar to the effect of midodrine on MAP during postexercise recovery, midodrine significantly increased TPR during recovery ($P < 0.04$, main effect of midodrine), but the increase was similar between conditions ($P = 0.15$, midodrine $\times$ time interaction).

**FBF During Cycling**

As shown in Fig. 4A, midodrine did not alter FBF at rest ($P = 0.95$ by $t$-test) or during exercise ($P = 0.66$, main effect of midodrine; $P = 0.28$, midodrine $\times$ time interaction). Furthermore, during postexercise recovery, midodrine did not affect FBF ($P = 0.43$, main effect of midodrine; $P = 0.44$, midodrine $\times$ time interaction). As shown in Fig. 4B, midodrine did not alter FVR at rest ($P = 0.12$ by $t$-test). FVR decreased significantly during exercise ($P = 0.0001$, main effect of exercise), but the fall in FVR was similar between exercise trials ($P = 0.26$, main effect of midodrine; $P = 0.87$, midodrine $\times$ time interaction). Furthermore, during postexercise recovery, midodrine did not affect FVR ($P = 0.13$, main effect of midodrine; $P = 0.33$, midodrine $\times$ time interaction).

---

**Table 2. Hemodynamic response to cycling**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trial</th>
<th>Rest</th>
<th>25 W</th>
<th>50 W</th>
<th>75 W</th>
<th>Postexercise, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2 (13/13)</td>
<td>1 (11/12)</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>Control</td>
<td>67 ± 4</td>
<td>85 ± 5</td>
<td>85 ± 5</td>
<td>90 ± 6</td>
<td>88 ± 4</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>68 ± 3</td>
<td>82 ± 3</td>
<td>84 ± 3</td>
<td>87 ± 5</td>
<td>87 ± 4</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>Control</td>
<td>175 ± 10</td>
<td>150 ± 11</td>
<td>149 ± 11</td>
<td>139 ± 10</td>
<td>137 ± 11</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>187 ± 9*</td>
<td>160 ± 10</td>
<td>158 ± 9</td>
<td>147 ± 9</td>
<td>153 ± 11</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>Control</td>
<td>117 ± 6</td>
<td>90 ± 6</td>
<td>88 ± 5</td>
<td>80 ± 5</td>
<td>78 ± 5</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>124 ± 6*</td>
<td>100 ± 6</td>
<td>97 ± 5</td>
<td>87 ± 4</td>
<td>90 ± 6</td>
</tr>
<tr>
<td>DBP mmHg</td>
<td>Control</td>
<td>83 ± 4</td>
<td>62 ± 4</td>
<td>61 ± 4</td>
<td>55 ± 3</td>
<td>54 ± 3</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>88 ± 4</td>
<td>68 ± 4</td>
<td>66 ± 4</td>
<td>58 ± 3</td>
<td>61 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE for 14 for all time points except where nos. in parentheses denote the no. of subjects completing a given workload in control/midodrine trials. 1 and 2, 1st and 2nd Q measured during cycling at each workload (25, 50, and 75 W). Although midodrine increased blood pressure ($P < 0.04$, main effect of midodrine), the changes were similar between trials. *Significantly different from control, $P < 0.05$.

---

Fig. 3. $Q$ (A) and total peripheral resistance (TPR; B) response to supine cycling. $Q$ was measured 3 times at rest (15 min), twice during each cycling workload, and 3 times during recovery (20 min). Values are means ± SE. $Q$ increased during exercise ($P < 0.0001$), but Q values during baseline, exercise, and recovery were similar between trials ($P = 0.74$). Because of higher MAP, TPR tended to be higher at baseline ($P = 0.10$). TPR was higher during cycling and recovery in the midodrine trial ($P = 0.04$). Midodrine did not alter the decrease in TPR during cycling or the recovery of TPR after cycling ($P = 0.93$ and 0.15, respectively).
Capuchin monkeys were used for this study. Baseline CBF was unaffected by midodrine (Fig. 5A). CBF increased ∼15-fold after ischemic exercise and decreased slowly over 5 min (P < 0.0001, main effect of exercise in both trials). The peak CBF was similar between conditions (P = 0.44). However, in contrast to the nonexercising forearm, after ischemic calf exercise the CBF returned toward baseline faster after midodrine (P < 0.02, action). Baseline CVR was unaffected by midodrine (Fig. 5B). CVR was sharply reduced after ischemic calf exercise (P < 0.0001), and CVR returned toward baseline faster after midodrine (P < 0.02). The hemodynamic responses to ischemic calf exercise are summarized in Table 4.

**Discussion**

The purpose of this study was to test the hypothesis that midodrine would limit the exercise-induced fall in blood pressure and improve postexercise blood pressure recovery, thereby partially mimicking the actions of the sympathetic nervous system in PAF patients. The new findings of this study are that midodrine increases exercise blood pressure and TPR overall. However, the exercise-induced decrease in blood pressure and TPR is unaffected by midodrine. Importantly, midodrine improves blood pressure from recovery postexercise. Midodrine also improves the recovery leg blood flow after local ischemic exercise. Taken together, acute treatment with a single dose of midodrine is effective at increasing blood pressure in PAF subjects, and it appears to act as a surrogate for sympathetic nerve activity during and after exercise. Higher exercise blood pressures and faster recovery of blood pressure after exercise may improve submaximal exercise tolerance and safety, and ultimately improve quality of life in humans suffering from autonomic failure.

This is the first study designed to examine the acute effects of midodrine on exercise hemodynamics in autonomic failure. Our results confirm previous reports of severe hypotension during exercise in autonomic failure (8, 17, 19), and tested possible mechanisms that contribute to the hypotension. Midodrine improved resting supine blood pressure, as expected (6, 21). In the midodrine trial, subjects exhibited higher blood pressure that was maintained throughout exercise, although the decrease in blood pressure was similar. This main effect of midodrine is probably due to generalized vasoconstriction or better distribution of Q to exercising and nonexercising muscles (12).

Despite higher blood pressure during exercise in the midodrine trial, the Q response to cycling was similar. The increase in Q confirms similar findings in cardiac index measured previously (8, 16–18). Because TPR was higher during exercise after midodrine (Fig. 3B), we sought to determine whether this vasoconstriction was generalized or whether it was directed to more or less metabolically active tissues.

First, we measured blood flow in the nonexercising forearm during cycling. In both conditions, FBF was similar at rest and}

**Catecholamine Levels During Cycling**

The catecholamine responses to cycling exercise are summarized in Table 3. Cycling produced a subnormal but significant increase in norepinephrine in both trials (P = 0.02). Midodrine decreased the norepinephrine response during exercise (P = 0.04). Epinephrine levels did not significantly increase with cycling in either trial (P = 0.16). Cycling increased dopamine in both trials (P = 0.02), but the increase was similar between trials (P = 0.46).

**Ischemic Calf Exercise**

Twelve patients completed this protocol. Baseline CBF was unaffected by midodrine (Fig. 5A). CBF increased ∼15-fold after ischemic exercise and decreased slowly over 5 min (P < 0.0001, main effect of exercise in both trials). The peak CBF was similar between conditions (P = 0.44). However, in contrast to the nonexercising forearm, after ischemic calf
Table 4. Hemodynamic response to ischemic calf exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trial</th>
<th>Rest (2 min Average)</th>
<th>Last 30 s of Calf Exercise</th>
<th>Postexercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>+1</td>
<td>+2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>Control</td>
<td>73 ± 3</td>
<td>80 ± 4</td>
<td>77 ± 3</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>71 ± 3</td>
<td>79 ± 3</td>
<td>75 ± 3</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>Control</td>
<td>145 ± 9</td>
<td>135 ± 10</td>
<td>123 ± 8</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>174 ± 10*</td>
<td>158 ± 8*</td>
<td>141 ± 8</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>Control</td>
<td>96 ± 6</td>
<td>89 ± 6</td>
<td>78 ± 4</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>115 ± 6*</td>
<td>107 ± 5*</td>
<td>93 ± 6</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>Control</td>
<td>71 ± 4</td>
<td>66 ± 4</td>
<td>58 ± 3</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>85 ± 4*</td>
<td>78 ± 4*</td>
<td>68 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE; 12 of the 14 subjects completed both calf exercise trials. Blood pressure decreased after ischemic calf exercise in both trials, and midodrine caused an increase in pressure (P < 0.05, main effect of midodrine) but a similar rate of recovery (5 min) after ischemic exercise. * Significantly different from control, P < 0.05.
we did not measure splanchnic blood flow, we cannot state whether or not midodrine augments vasoconstriction in this vascular bed during exercise. Second, we were unable to randomize the drug treatment due to the long half-life of midodrine. However, because PAF patients exhibit prolonged vasodilatation after a single bout of exercise, we may have underestimated the effects of midodrine on MAP, because the first bout would have potentially worsened the hypotension during the second exercise bout (15). Another consideration is the single acute dose used in this study may give different results than chronic daily treatment with midodrine. Finally, we wonder whether combined treatment with pyridostygmine and/or fludrocortisone would alter the present results. Recent work on the acute effects of acetylcholinesterase inhibition with pyridostygmine suggests it improves orthostatic tolerance in relation to the severity of hypotension (14). It remains to be tested whether midodrine plus pyridostygmine may act synergistically to improve blood pressure during exercise.

What are the implications of the present findings for daily living in patients with autonomic failure? It is known that midodrine improves symptoms of orthostatic hypotension (21), and we present important insight into how midodrine can improve the blood pressure response to exercise. Importantly, midodrine appears to generally improve the hemodynamic response to exercise by increasing baseline blood pressure, which might lessen the chances of critical hypotensive events during daily physical activity. Additionally, faster recovery of blood pressure after midodrine may also make exercise (and activities of daily living) more tolerable and safe. Because many daily activities require short bursts of “exercise,” this faster recovery suggests that midodrine treatment in autonomic failure patients would lessen the potential for profound hypotensive events after short bursts of activity during daily living.

In summary, we tested the hypothesis that the oral α1-adrenergic agonist, midodrine, would limit the fall in arterial pressure observed during and after exercise in patients suffering from autonomic failure. Despite an overall increase in arterial pressure and TPR, the exercise-induced decrease in MAP was unaltered by midodrine. However, midodrine dramatically improved postexercise blood pressure recovery. This improved recovery of blood pressure after exercise may improve the overall stability of blood pressure during daily life.

ACKNOWLEDGMENTS

The authors thank Pamela Engrav, Karen P. Krucker, Diane E. Wick, Branton Walker, and Amanda Palm for technical assistance, and Dr. Sunni Barnes for expert statistical analysis. We also thank the enthusiastic patients for participating.

GRANTS

This study was supported by grants from the National Institutes of Health (W. G. Schräge, HL-69692; J. H. Eisenach, RR-017520; F. A. Dinenno, AG-05912; P. Sandroni, RR-15537; P. A. Low, NS-32352, M. J. Joyner, NS-32352; and General Clinical Research Center, RR-00585)

REFERENCES


