Treatment of Chronic Orthostatic Hypotension with Ergotamine

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SUMMARY  The acute and chronic effects of ergotamine were examined in four patients with chronic orthostatic hypotension. Chronic oral administration of ergotamine tartrate produced significant increases in standing blood pressure and marked clinical improvement, without appreciable recumbent hypertension. The blood pressure increases were not associated with significant changes in plasma norepinephrine or plasma renin activity. No major toxicity was observed at doses of 2-6 mg/day over treatment periods of 3-18 months.

Hemodynamic studies on the effects of i.v. ergotamine tartrate (0.25-0.50 mg) revealed that the ergotamine-induced increase in blood pressure in the supine position was associated with an increase in total peripheral resistance (from 161 ± 165 to 2574 ± 583 U) without a change in cardiac output. During 45-60° upright tilt, ergotamine increased both total peripheral resistance (1801 ± 296 to 3262 ± 1107 U) and cardiac output (2.42 ± 0.46 to 3.34 ± 0.54 l/min). Forearm plethysmographic studies revealed decreased forearm blood flow and venous volume and increased vascular resistance with ergotamine. The orthostatic hypotensives had more platelet α-receptors (390 ± 31 receptors/cell) than the control subjects (234 ± 17 receptors/cell). The increased receptor level was associated with abnormally low circulating levels of norepinephrine and increased pressor responsiveness to infused norepinephrine in three of the four patients. Chronic ergotamine therapy appeared to reduce platelet α-receptor number to normal.

The results indicate that ergotamine is of value in certain patients with chronic orthostatic hypotension and that the blood pressure effects are related to vasoconstriction in both arterial and venous beds.

THE MANAGEMENT of chronic orthostatic hypotension is a difficult clinical problem. Many approaches have been advocated, including mechanical supports to minimize peripheral pooling of blood, mineralocorticoid drugs, sympathimetic agents either alone or in combination with a monoamine oxidase inhibitor, β blockers, indomethacin, vasopressin, metoclopramide or atrial pacing.1-7 These treatments generally have been only partially effective, and at times, they have induced significant side effects.

Recent reports indicate that parenteral administra-

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Materials and Methods

Four patients with chronic orthostatic hypotension were studied. All had very low blood pressures in the upright position and had experienced several presyncopal or syncopal attacks despite trials with other therapies, including fludrocortisone, ephedrine, indomethacin and atrial pacing. Diagnostic evaluation to exclude secondary forms of orthostatic hypotension and to assess sympathetic function were performed as previously described. The blood pressure responses to graded doses of norepinephrine, ranging from 5 to 160 ng/min/kg, were examined. The study was terminated when an increase in mean arterial pressure of 30-40 mm Hg was achieved. The results were compared with the range of responses we have observed in normal subjects.

Two of the patients had idiopathic orthostatic hypotension with probable peripheral sympathetic nerve degeneration, suggested by severe postural hypotension without postural tachycardia, abnormally low plasma norepinephrine levels in both recumbent and upright positions, and pressor hyperresponsiveness to infused norepinephrine. In one patient, the autonomic dysfunction appeared after an accident that had damaged the spinal cord at the level of the fourth and fifth cervical vertebrae. The fourth patient was on chronic hemodialysis for end-stage renal disease and previously had developed orthostatic hypotension after bilateral nephrectomy to control hypertension. The etiology of the orthostatic hypotension was uncertain but was not related to volume contraction. It was associated with normal levels of plasma norepinephrine and normal pressor sensitivity to infused norepinephrine.

Control measurements of blood pressure and heart rate were made serially in the recumbent position and after 1 minute of standing (if tolerated) for at least 4 days before institution of ergotamine therapy. All hypertensive medications were discontinued for at least 2 weeks before ergotamine administration except for fludrocortisone, which in two of the patients was maintained at doses of 0.3-0.4 mg/day. All studies were performed in the metabolic unit of University Hospital. Dietary intake of sodium ranged between 120 to 180 mmol/day. Plasma norepinephrine was measured according to the technique of Henry et al.

Platelet α-adrenergic number and affinity were assayed according to our slight modification of the method of Newman and associates. Approximately 30 ml of blood were obtained and the platelets were isolated. In the standard incubation mixtures, duplicate aliquots of the platelet membrane fraction (0.2-0.4 mg protein) were incubated for 18 minutes at 25°C with [3H] dihydroergocryptine (New England Nuclear Corp., specific activity 20-50 Ci/mmol) in concentrations of 1, 2, 5, 10, 20, 30 and 40 nM. After incubation, the material was rapidly filtered through Whatman GB/F filters, washed, dried and counted in a liquid scintillation spectrometer. Nonspecific binding was determined by performing incubations in the presence or absence of 10-5 M phenolamine. The binding levels in the duplicate aliquots differed by an average of 10% with concentrations of [3H] dihydroergocryptine of less than 10 nM and by 6% at concentrations of 10-40 nM. Receptor number was obtained from the Scatchard plots of the binding data. The receptor measurements were made at least twice during the pretreatment period, after 1 week of therapy, and on at least two other occasions after 1 month or more of chronic administration. In separate experiments, the effect of the addition of unlabeled dihydroergotamine (10-9 to 10-6 M) to blood samples from control subjects before the receptor assays was also examined to exclude the possibility that any apparent effect of administered ergotamine on platelet α-receptor number could be secondary to retention of the ergotamine on the platelet membranes.

Blood pressure, heart rate and plasma norepinephrine levels were measured in both recumbent and upright positions before and at varying intervals after 0.5 mg of i.v. ergotamine tartrate. Hemodynamic studies were also carried out several days after efficacy of the drug had been demonstrated. Right-heart catheterization was performed through an antecubital vein using a #7 thermocouple Swan-Ganz catheter. A radial artery cannula was also placed in each patient. Pressures were measured using a Bentley model 508 strain-gauge transducer and recorded on a direct-writing Hewlett Packard multigraph. Mean pressures were obtained by electrical integration with a zero reference to the midaxillary line. Cardiac output measurements were made by thermodilution using an Edwards cardiac output computer and averaging at least three replicate determinations varying less than 10%. The measurements were made both during recumbency and 3-5 minutes after 45-60° upright tilt. The studies were repeated 30 minutes after 0.5 mg of i.v. ergotamine tartrate.

Venous occlusion strain-gauge plethysmography was performed on a separate day in a 25°C temperature-controlled room to study the influence of ergotamine on forearm blood flow and forearm venous volume. The arm was positioned above heart level and hand blood flow was excluded by use of a sphygmomanometric cuff placed around the wrist and inflated to at least 50 mm Hg above systolic pressure during the measurements. Venous occlusion was produced by sudden inflation of a sphygmomanometric cuff on the upper arm. The lowest venous occlusion pressure required to obtain the maximum rate of increase in forearm circumference was determined at the beginning of each study. Forearm blood flow was derived from the change in forearm circumference during venous occlusion, which was measured with a calibrated strain gauge. The forearm blood flow data were expressed as ml/100 ml of tissue/min. Forearm vascular resistance was calculated as the ratio of mean arterial pressure to forearm blood flow. Venous volume was measured by inflation of the venous occlusion cuff to 30 mm Hg above effective venous filling pressure, and the volume was calculated from the change in forearm circumference expressed as ml/100 ml of tissue. Each series of measurements included at least five determi-
nations of forearm blood flow and one of forearm venous volume. They were made every 10 minutes before treatment to assure stability before intervention. Ergotamine tartrate, 0.25 mg, was then given intravenously to each patient and forearm blood flow, forearm venous volume and blood pressure were measured 15 and 30 minutes after the infusion. In two of the patients, the studies were also performed after 3 minutes of 60° upright tilt both before and after drug administration. Separate experiments were also performed before and up to 2 hours after a single 2.0-mg oral dose of ergotamine tartrate.

All patients also were treated chronically with orally administered ergotamine tartrate in doses of 2–6 mg/day. They were followed initially for at least 10 days as inpatients and later as outpatients for 3–18 months. Serial electrocardiographic tracings and measurements of serum creatine kinase and lactic dehydrogenase were performed during the period of therapy. In addition, complete blood counts, studies of hepatic and renal function, serum electrolytes, thyroxine, calcium, uric acid and lipids were monitored to exclude possible untoward toxicity of therapy. The patients were readmitted to the hospital at least once during treatment to reevaluate the clinical benefits of therapy.

**Results**

The clinical characteristics of the patients are shown in Table 1. They were 32–74 years old. One patient had severe chronic obstructive pulmonary disease and episodes of supraventricular tachycardia and was maintained on other chronic therapy including digoxin, quinidine and theophylline.

The acute hemodynamic effects of i.v. ergotamine tartrate are summarized in Table 2. All patients had marked increases in blood pressure during upright tilt after administration of the drug, and the differences between supine and upright pressures were virtually eliminated. In two patients, transient hypertension was induced in both supine and upright positions with levels of blood pressure as high as 220/100 mm Hg. Stroke volume and cardiac output during tilt were higher in all subjects after ergotamine than before, but no consistent pattern of results was present during re-

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**Table 1. Clinical Characteristics of Patients with Chronic Orthostatic Hypotension**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Etiology of hypertension</th>
<th>Prior therapeutic trials</th>
<th>Concurrent therapy</th>
<th>Other clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>F</td>
<td>Idiopathic</td>
<td>Ephedrine, indomethacin, propranolol, atrial pacing</td>
<td>Fludrocortisone</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>M</td>
<td>Idiopathic</td>
<td>Ephedrine, indomethacin</td>
<td>Fludrocortisone, digoxin, theophylline, quinidine</td>
<td>Chronic obstructive pulmonary disease, atrial arrhythmias, peripheral neuropathy</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>M</td>
<td>Cervical cord injury</td>
<td>Fludrocortisone, indomethacin, ephedrine</td>
<td>None</td>
<td>Migraine headaches</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>F</td>
<td>Anephric state</td>
<td>Ephedrine, propranolol, indomethacin, lysine vasopressin</td>
<td>None</td>
<td>Chronic hemodialysis, anephric, anemia</td>
</tr>
</tbody>
</table>

**Table 2. Effects of Intravenous Ergotamine Tartrate on Cardiovascular Hemodynamics in Patients with Idiopathic Orthostatic Hypotension**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Procedure</th>
<th>HR (beats/min)</th>
<th>BP (mm Hg)</th>
<th>RAP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>SV (ml/beats)</th>
<th>CO (l/min/m²)</th>
<th>SVR (dyn-sec-cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control, supine</td>
<td>55</td>
<td>130/60</td>
<td>6</td>
<td>38/12</td>
<td>10</td>
<td>56</td>
<td>3.09</td>
<td>1942</td>
</tr>
<tr>
<td></td>
<td>ERG, supine</td>
<td>52</td>
<td>225/95</td>
<td>0</td>
<td>60/20</td>
<td>23</td>
<td>58</td>
<td>3.00</td>
<td>3733</td>
</tr>
<tr>
<td></td>
<td>Control, 45° tilt</td>
<td>60</td>
<td>65/45</td>
<td>0</td>
<td>35/18</td>
<td>14</td>
<td>31</td>
<td>1.88</td>
<td>2340</td>
</tr>
<tr>
<td></td>
<td>DHE, 45° tilt</td>
<td>50</td>
<td>220/100</td>
<td>0</td>
<td>36/17</td>
<td>15</td>
<td>45</td>
<td>2.27</td>
<td>5462</td>
</tr>
<tr>
<td>2</td>
<td>Control, supine</td>
<td>72</td>
<td>130/60</td>
<td>1</td>
<td>28/18</td>
<td>6</td>
<td>59</td>
<td>4.28</td>
<td>1495</td>
</tr>
<tr>
<td></td>
<td>ERG, supine</td>
<td>65</td>
<td>200/90</td>
<td>1</td>
<td>37/15</td>
<td>13</td>
<td>73</td>
<td>4.76</td>
<td>2101</td>
</tr>
<tr>
<td></td>
<td>Control, 45° tilt</td>
<td>74</td>
<td>67/45</td>
<td>2</td>
<td>23/16</td>
<td>8</td>
<td>45</td>
<td>3.33</td>
<td>1321</td>
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<tr>
<td></td>
<td>ERG, 45° tilt</td>
<td>65</td>
<td>180/85</td>
<td>2</td>
<td>22/10</td>
<td>5</td>
<td>72</td>
<td>4.03</td>
<td>2382</td>
</tr>
<tr>
<td>3</td>
<td>Control, supine</td>
<td>50</td>
<td>115/60</td>
<td>2</td>
<td>15/4</td>
<td>4</td>
<td>85</td>
<td>4.25</td>
<td>1412</td>
</tr>
<tr>
<td></td>
<td>ERG, supine</td>
<td>45</td>
<td>120/65</td>
<td>9</td>
<td>26/12</td>
<td>9</td>
<td>80</td>
<td>3.60</td>
<td>1889</td>
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<td></td>
<td>Control, 60° tilt</td>
<td>50</td>
<td>65/35</td>
<td>3</td>
<td>15/6</td>
<td>5</td>
<td>41</td>
<td>2.06</td>
<td>1743</td>
</tr>
<tr>
<td></td>
<td>ERG, 60° tilt</td>
<td>52</td>
<td>125/70</td>
<td>1</td>
<td>15/5</td>
<td>4</td>
<td>71</td>
<td>3.71</td>
<td>1941</td>
</tr>
</tbody>
</table>

Abbreviations: HR = heart rate; BP = blood pressure; RAP = right atrial pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; SV = stroke volume; SVR = systemic vascular resistance; ERG = ergotamine; DHE = [³H]dihydroergocryptine.
TABLE 3. Effects of Intravenous Ergotamine Tartrate on Forearm Hemodynamics in Patients with Chronic Orthostatic Hypotension

<table>
<thead>
<tr>
<th>Pt</th>
<th>Position</th>
<th>BP (mm Hg)</th>
<th>Mean BP (mm Hg)</th>
<th>FBF (ml/100 g/min)</th>
<th>FVR (U)</th>
<th>FVV (ml/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Ergot</td>
<td>Control</td>
<td>Ergot</td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>Supine</td>
<td>151</td>
<td>223</td>
<td>106</td>
<td>150</td>
<td>1.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85</td>
<td>114</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tilt</td>
<td>70</td>
<td>200</td>
<td>56</td>
<td>133</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Supine</td>
<td>109</td>
<td>179</td>
<td>76</td>
<td>124</td>
<td>1.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tilt</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Supine</td>
<td>95</td>
<td>127</td>
<td>83</td>
<td>100</td>
<td>2.65</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>Tilt</td>
<td>81</td>
<td>110</td>
<td>67</td>
<td>91</td>
<td>2.17</td>
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<td></td>
<td></td>
<td>70</td>
<td>82</td>
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</tbody>
</table>

Abbreviations: BP = blood pressure; FBF = forearm blood flow; FVR = forearm vascular resistance; FVV = forearm venous volume.

cumbency. Systemic vascular resistance was increased by the drug in all subjects during both recumbency and tilting. Pulmonary artery and pulmonary capillary wedge pressures were increased by ergotamine during recumbency but were unaffected with upright tilt.

The effects of i.v. ergotamine tartrate on forearm hemodynamics are summarized in table 3. Forearm blood flow decreased and forearm vascular resistance increased in all subjects during both recumbency and after 60° upright tilt. Forearm venous volume was reduced by ergotamine in both supine and 60° tilt positions. A similar action could not be elicited with administration of a single oral dose of ergotamine tartrate, but the lack of consistent effect on the peripheral vascular system was not surprising, since the effects on blood pressure with a single oral dose were delayed and at times were variable. The measurements, therefore, had to be made over long periods and the patients often could not comply adequately to permit stable plethysmographic recordings.

The effective oral dose of the drug was 1–4 mg administered once or twice daily. All subjects had significant increases in standing blood pressure that persisted for the 2-minute standing period while the measurements were being made (table 4). The duration of effect was generally 4–8 hours. The anephric patient, however, appeared to have a more prolonged response, which usually persisted longer than 24 hours. Three of the four subjects had substantial long-term benefit from treatment and were generally free of presyncopal or syncopal episodes despite a substantial increase in physical activity. The fourth patient also had some improvement in postural hypotension but because of chronic anorexia, which was unrelated to the ergot therapy, he occasionally became dehydrated and at such times responded poorly to ergotamine. The maximum dose used on a chronic basis has been restricted to 6 mg/day or less, and no medication has been given after 6 p.m. to minimize supine hypertension. No symptoms suggestive of ergotism have been observed, and no angina pectoris or electrocardiographic changes have developed as a result of treatment. No evidence of other toxicity to ergots has been observed over treatment periods of 3–18 months. A

TABLE 4. Clinical Effects of Ergotamine Bitartrate in Patients with Chronic Orthostatic Hypotension

<table>
<thead>
<tr>
<th>Pt</th>
<th>Dose (mg/day)</th>
<th>BP (mm Hg) treatment period</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
<th>Syncope/ presyncope</th>
<th>Control</th>
<th>Ergot (# per week)</th>
<th>Other</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rec</td>
<td>Up</td>
<td>Rec</td>
<td>Up</td>
<td>Rec</td>
<td>Up</td>
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</tr>
<tr>
<td>1</td>
<td>2</td>
<td>148 ± 3</td>
<td>52 ± 4</td>
<td>164</td>
<td>104</td>
<td>146</td>
<td>96</td>
<td>166</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84 ± 2</td>
<td>32 ± 4</td>
<td>90</td>
<td>60</td>
<td>82</td>
<td>62</td>
<td>88</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>128 ± 5</td>
<td>48 ± 6</td>
<td>148</td>
<td>76</td>
<td></td>
<td></td>
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<td></td>
</tr>
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<td></td>
<td></td>
<td>64 ± 4</td>
<td>28 ± 5</td>
<td>82</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>116 ± 4</td>
<td>66 ± 7</td>
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<td>110</td>
<td>90</td>
<td>110</td>
<td>90</td>
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<td>60 ± 3</td>
<td>36 ± 6</td>
<td>60</td>
<td>50</td>
<td>70</td>
<td>60</td>
<td>80</td>
<td>62</td>
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<tr>
<td>4</td>
<td>2</td>
<td>72 ± 4</td>
<td>42 ± 2</td>
<td>104</td>
<td>92</td>
<td>94</td>
<td>90</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 ± 2</td>
<td>24 ± 3</td>
<td>68</td>
<td>70</td>
<td>72</td>
<td>66</td>
<td>62</td>
<td>64</td>
</tr>
</tbody>
</table>

Blood pressure values represent the mean ± SEM.

Blood pressure was measured 1–3 hours after administration of ergotamine.

Abbreviations: BP = blood pressure; Rec = recumbent; Up = upright.
representative blood pressure response to the drug is shown in Figure 1.

The results of the measurement of platelet α receptors are summarized in Table 5. Detailed binding data in one of the patients before and during ergotamine therapy are illustrated in Figure 2. All patients except the anephric patient had levels of platelet α receptors greater than those in the control population. Ergotamine therapy reduced the apparent number of platelet α receptors in all subjects to or below the normal range. The decreases occurred during the first week of therapy and persisted throughout treatment. No significant change in affinity of platelet membranes for \([3H]\) dihydroergocryptine was apparent (Table 5).

Addition of unlabeled dihydroergotamine to the blood before the assay at concentrations of \(10^{-9} \text{M}\), \(10^{-8} \text{M}\), and \(10^{-7} \text{M}\) did not affect either the dissociation constant or the apparent number of platelet alpha receptors. Not until a concentration of \(10^{-6} \text{M}\) was tested was there a reduction of binding of \([3H]\) dihydroergocryptine to the platelet membranes with a decrease in the apparent number of platelet receptors and in the dissociation constant.

### Figure 1
Blood pressure response to a single oral dose of ergotamine tartrate in a patient with idiopathic orthostatic hypotension.

### Figure 2
Specific binding of \([3H]\) dihydroergocryptine to platelet membranes in a patient with orthostatic hypotension before and after ergotamine. The data points represent the means of duplicates. Scatchard plots of the specific binding are shown in the inset.

### Discussion
All patients included in this study had severe postural hypotension that markedly restricted activity. They had been treated with several other medications with only minimal or variable improvement in symptoms or in blood pressure. Ergotamine therapy, either oral or parenteral, produced impressive increases in supine and upright blood pressure, along with substantial symptomatic improvement. The number of syncopal and presyncopal episodes decreased markedly, and the patients ambulated for much longer periods before developing hypotension. The relative rise in upright blood pressure was always appreciably greater than that occurring while supine. Supine hypertension was not a major problem with chronic therapy, although during the acute studies with i.v. administration of the drug, moderate-to-severe hypertension was at times induced. However, with most forms of therapy of this condition, hypertension may frequently be observed.

### Table 5
Effects of Ergotamine Therapy on Platelet Alpha-receptor Affinity and Number in Patients with Orthostatic Hypotension

<table>
<thead>
<tr>
<th>Pt</th>
<th>Plasma norepinephrine (ng/ml)</th>
<th>Pressor responsiveness to infused norepinephrine</th>
<th>Platelet α receptor</th>
<th>Number</th>
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<tbody>
<tr>
<td></td>
<td>Recumbent</td>
<td>Upright</td>
<td>Increased</td>
<td>(K_D) Control</td>
</tr>
<tr>
<td>1</td>
<td>0.098</td>
<td>0.125</td>
<td>Increased</td>
<td>11.7</td>
</tr>
<tr>
<td>2</td>
<td>0.140</td>
<td>0.184</td>
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<td>10.0</td>
</tr>
<tr>
<td>3</td>
<td>0.175</td>
<td>0.160</td>
<td>Increased</td>
<td>11.1</td>
</tr>
<tr>
<td>4</td>
<td>0.285</td>
<td>0.320</td>
<td>Normal</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Control subjects \((n = 20)\)
Plasma norepinephrine (recumbent) \(0.284 \pm 0.020 \text{ ng/ml}\)
Plasma norepinephrine (upright) \(0.464 \pm 0.038 \text{ ng/ml}\)
Platelet \(K_D\) for \([3H]\) dihydroergocryptine \(12.4 \pm 1.3 \times 10^n \text{ nM}\)
Platelet α-receptor number \(234 \pm 17 \text{ platelet}\)

*Values represent the average of two separate assays performed between 2 and 6 weeks of ergotamine therapy.

Abbreviation: \(K_D\) = disappearance rate.
during recumbency, and patients should be monitored closely for this potential complication.

The duration of blood pressure effect of chronically administered ergotamine tartrate was generally 4–8 hours except in the anephric patient, who often experienced benefit for 24 or more hours. This patient’s blood pressure in the supine position had been as low as 60/30 mm Hg, and was even lower on standing or after hemodialysis. Dialysis had often been difficult because of the low blood pressures. However, with ergotamine, blood pressure levels of 90/50 mm Hg or greater were achieved consistently during both recumbency and standing, and the difficulties with hemodialysis resulting from inadequate perfusion pressure were prevented.

Although ergotamine therapy has been well-tolerated in these patients, our study group is small and the longest duration of follow-up has been 18 months. Ergotamine is a potent peripheral vasoconstrictor that can adversely affect both the coronary circulation and the peripheral vasculature. The diagnostic use of ergonovine in patients with angina pectoris takes advantage of this effect of the drug to identify patients with coronary vasospastic disease. Long-term use of large doses of ergotamine can induce marked peripheral vasoconstriction and resultant pain, numbness and ischemia of the hands or feet. To minimize the risk for ergot toxicity, we have maintained the dose of the drug at low levels and have administered it no more than twice daily, using schedules that would maximize its effects during the daytime hours, when the patient generally has the greatest need to be functional. Evening doses should be kept low or not used to avoid excessive increases in blood pressure during recumbency.

Nordenfeldt and Mellander observed only minimal increase in standing blood pressure after i.v. dihydroergotamine. Their subjects differed from the present group in that they were young patients who had orthostatic tachycardia and decreases in systolic pressure but no significant reduction in diastolic or mean blood pressure on standing. None had clear-cut evidence of autonomic insufficiency. More recently, Jennings et al. administered dihydroergotamine both intravenously and orally to patients with autonomic insufficiency and observed clinical improvement in orthostatic hypotension, which was maintained over a 4-week treatment period. The acute blood pressure effects were associated with a slight increase in peripheral vascular resistance. The central blood volume and cardiac output were higher upon upright tilting after dihydroergotamine administration than during the pre-treatment period. On the other hand, Fouad and associates found varying patterns of hemodynamic response to the drug with tilting. In some patients, a less severe reduction in cardiac output with upright tilt was apparent with or without increases in peripheral resistance, while others showed only an increase in total peripheral resistance.

Our own hemodynamic studies demonstrated that the increases in supine blood pressure with ergotamine tartrate were associated with marked increase in systemic vascular resistance but without change in cardiac output. With 45–60° upright tilt, the blood pressure after ergotamine increased dramatically and much of the differential between supine and upright pressures was obliterated. The degree of reduction in cardiac output with tilting also was much less after ergotamine than in the untreated state. The increase in systemic vascular resistance and resultant increase in left ventricular afterload produced by the drug could be a problem, particularly because many patients with orthostatic hypotension have compromised cardiac function.

However, the increase in preload would have the opposite effect and may have prevented major changes in cardiac output despite the dramatic increase in systemic resistance.

The blood pressure effects of ergotamine appear related primarily to its action on capacitance and resistance vessels. Supine and upright forearm blood flow decreased and forearm vascular resistance increased after i.v. ergotamine. The increase in forearm vascular resistance is consistent with the observed increase in systemic resistance. Our results differ from those of Mellander and Nordenfelt, who observed an increase in hand, but not in calf or forearm, vascular resistance in orthostatic hypotensives treated with dihydroergotamine. The conflicting findings may reflect the different ergotamine preparations used, but their patients also only had a modest blood pressure response.

Our forearm studies demonstrated evidence of venoconstriction after ergotamine administration in both recumbent and upright positions. The effect on cardiac output during tilting presumably was related to this action, with decrease in venous capacitance, less peripheral pooling of blood, and an increase in venous return to the heart. Impaired ability to venoconstrict because of sympathetic denervation with abnormal venous pooling of blood has long been recognized in patients with autonomic insufficiency and has been thought to be a key factor in orthostatic hypotension.

The venous action of ergots has also been suggested. In the autoperfused hind leg preparation of cats, dihydroergotamine caused constriction of venous capacitance vessels. In normal man, a venoconstrictive effect of dihydroergotamine during upright tilt was suggested initially by the work of Rieckert and Pauschinger. A decrease in hand vein diameter was observed after local infusion of either dihydroergotamine, dihydroergostine, dihydroergovaline, and ergotamine, the latter being the most active compound.

Also, a reduction in forearm venous compliance has been observed in normal subjects after administration of ergotamine or ergometrine.

In all three patients studied during 45° tilt, pulmonary capillary wedge pressure did not change after ergotamine administration, while cardiac output increased. Although we have assumed that the increase in cardiac output is related to an increase in preload, the pulmonary capillary wedge pressure would be expected to increase as well unless a change in ventricular compliance also occurred. The improved cardiac output may have resulted from an increase in myocardial...
dial contractility but further study is required to determine the mechanism of the hemodynamic response.

Ergotamines are thought to act primarily by stimulation of $\alpha$ adrenoreceptors, but their action may differ from that of norepinephrine. Recent studies by Henry and Yokoyama in isolated rabbit aortas have suggested that ergotamines may act through a serotonin-mediated mechanism that is not blocked by phentolamine. In isolated spiral strips of saphenous vein, indomethacin inhibits some of the ergotamine effect, suggesting that the action of ergots may, in part, be mediated through the prostaglandin system.

Studies with tissue membrane fractions have indicated that ergotalkoids bind to both $\alpha_1$- and $\alpha_2$-adrenergic receptors. With washed platelet membrane preparations in the absence of added guanine nucleotides, $\alpha_2$ receptors appear to exist in two conformational states: one with high affinity for binding agonists and the other with greater affinity for antagonists than agonists. Ergots that have agonist activity bind to both types of $\alpha_2$ receptors. Blood platelets have been shown to contain only $\alpha_2$ receptors. The predominant postjunctional $\alpha$-receptor subtype in arterial smooth muscle that mediates vasoconstriction appears to be $\alpha_1$, although postsynaptic $\alpha$ receptors in venous smooth muscle also have been demonstrated recently. We cannot conclude from our findings that similar changes occur in vascular receptors as in the platelets.

We recently observed an increase in both $\alpha$- and $\beta$-receptor number in platelets and polymorphonuclear leukocytes in patients who have idiopathic orthostatic hypotension. Increased $\beta$-receptor number also has been reported by Hui and Conolly in patients with orthostatic hypotension and autonomic dysfunction, and of both $\alpha$- and $\beta$-receptor number in patients with the Shy-Drager syndrome in a very recent study by Davies et al. The patients in our current study all had elevated platelet $\alpha$-receptor number above the control range and, with one exception, had markedly reduced circulating levels of norepinephrine. Experimental studies in animals demonstrate that adrenergic membrane receptors of nonvascular tissue are in a dynamic state and that their level can be regulated by exposure to adrenergic agonists or by chemical sympathectomy.

A recent study involving binding of the selective $\alpha$, ligand [H] WB-4101 to membrane fractions of rat mesenteric artery indicates that chemically induced sympathectomy and exogenous administration of epinephrine can regulate arterial $\alpha$-receptor levels. The elevated levels of platelet $\alpha$ receptors in our patients also may have been secondary to the reduced plasma catecholamine concentrations. The functional importance of such changes is uncertain, and it is unclear whether the alteration in platelet receptors would reflect parallel changes in arterial tissue. However, the pressor hypersensitivity to infused norepinephrine could, in part, result from a similar regulation of adrenergic vascular receptors.

In studies using rat uterine membranes, ergotamine has been shown to compete with [H] dihydriergocryptine. It is intriguing to speculate that the observed reduction in [H] dihydriergocryptine binding to platelets after ergotamine therapy could have been due to down-regulation of platelet $\alpha$ receptors because of the chronic presence of ergotamine. However, another possibility is that the previously administered ergotamine was retained in the platelet membrane fraction during the assay procedure. The likelihood of this occurring is relatively small in view of our findings that the addition in vitro of ergotamine to control blood samples before assay of $\alpha$ receptors did not influence significantly the receptor number unless exceedingly high concentrations of 10$^5$ M ergotamine, which presumably would be greater than those achieved in the blood.

The differences in long-term results with orally administered ergots between our present studies and those reported by Fouad et al. could have been related to differences in bioavailability between oral dihydroergotamine and ergotamine tartrate used in the two studies. No comparison of the pharmakokinetics of the two drugs has been made in these patients to confirm this possibility. However, our study indicates that ergotamine tartrate can produce important long-term benefits in patients with severe orthostatic hypotension and should be considered as part of the therapeutic regimen for this condition.

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