Orthostatic Hypertension
Pathogenetic Studies

DAVID H. P. STREETEN, J. HOWLAND AUCHINCLOSS, JR., GUNNAR H. ANDERSON, JR., ROBERT L. RICHARDSON, F. DEAVER THOMAS AND JEFFREY W. MILLER

SUMMARY Among 1800 referred hypertensive patients, 181 had recumbent diastolic blood pressures (DBP) below 90 mm Hg and standing DBP above 90 mm Hg. Orthostatic increments in DBP were greater in these orthostatic hypertensive patients than in 181 persistently hypertensive patients and 134 normotensive subjects. In 12 patients with orthostatic hypertension, the orthostatic fall in cardiac output (27.3 ± 2.9%, measured by a respiratory method) was double that in 8 normotensive subjects (13.3 ± 3.7%, p < 0.01). An inflated pressure suit over the pelvis and lower limbs prevented the excessive fall in cardiac output and significantly reduced (p < 0.02) the excessive rise in standing DBP in orthostatic hypertensive patients. Gravitational pooling of blood in the legs and reduction of blood in the head was measured by external gamma counting of autologous erythrocytes labeled with sodium pertechnetate Tc 99m through ports in fixed positions over the leg and the temple. Orthostatic intravascular pooling was significantly greater (p < 0.01) in orthostatic hypertensive subjects than in normotensive subjects, and the magnitudes of orthostatic pooling and orthostatic increases in DBP were closely correlated (r = +0.85). Plasma norepinephrine concentrations were similar in recumbency and after sustained handgrip exercise, but significantly greater (p < 0.01) after 5 to 60 mins of standing in orthostatic hypertensive subjects than in normotensive subjects. Our results indicate that orthostatic hypertension is common and that its mechanism in representative patients involves excessive orthostatic blood pooling, which results in decreased venous return, decreased cardiac output, increased sympathetic stimulation (presumably through low-pressure cardiopulmonary receptors), and excessive arteriolar, but not venular, constriction. (Hypertension 7: 196–203, 1985)

KEY WORDS • orthostatic hypertension • gravitational pooling • labile hypertension • norepinephrine changes • cardiac output reduction • antigravity suit • cardiac volume • borderline hypertension • subnormal preload • pooling measurement

In the course of analyzing data derived from studies of the mechanisms of hypertension in 1800 referred, untreated patients, we were surprised to find that 181 patients were normotensive (diastolic blood pressure [DBP] ≤ 90 mm Hg) in the supine posture but hypertensive (DBP > 90 mm Hg) when standing. They usually had been referred because their DBP remained above the recommended level of 90 mm Hg¹ (measured while the patient is seated) despite conventional stepped-care therapy. An orthostatic increase in DBP from below 90 to above 90 mm Hg — orthostatic hypertension — was reported in 1922, in 4.2% of 2000 apparently healthy airmen examined after World War I.² Hull et al.³ found that orthostatic hypertension was present in 71% (15) of 21 patients with borderline hypertension, which suggests that the incidence of this abnormality in the population might be considerably higher than it was in our group of patients. Frohlich et al.⁴ studied a group of persistently hypertensive (i.e., hypertensive in recumbent and standing postures) patients and found that those whose orthostatic rise in DBP was greater than normal showed excessive increases in peripheral resistance during tilting and excessive increases in DBP after the Valsalva maneuver. In a single patient with orthostatic hypertension, Sapru et al.⁵ found excessive responsiveness to other known stimuli of the sympathetic nervous system (i.e., cold pressor test, mental arithmetic, and isometric exercise). Apart from these observations, little is known of the pathogenesis of orthostatic hypertension.
In our initial studies of these patients we were struck by three clinical findings. In comparison with normotensive subjects these patients had (1) excessive orthostatic tachycardia, (2) intolerance of diuretic therapy, and (3) bluish discoloration of the legs when they were standing. As these findings suggested, among other possibilities, that excessive orthostatic pooling might be occurring in these patients, we investigated the role of pooling and the mechanisms whereby it might influence orthostatic changes in blood pressure.

Materials and Methods

Patient Selection

All the patients were originally referred for an 8-hour evaluation of their hypertensive mechanisms, which included blood pressure (BP) measurements lying and standing, serum electrolyte and creatinine measurements, determinations of plasma renin activity (after furosemide, 40 mg i.v., followed by recumbency for 1 hour and standing for 2 hours), a saralasin test, and measurement of plasma aldosterone and cortisol concentrations after an intravenous infusion of 2 liters of 0.9% NaCl solution. The physiological studies reported here were performed on 12 patients with orthostatic hypertension (DBP < 90 mm Hg in recumbency, > 90 mm Hg while standing), 3 patients with persistent hypertension (DBP > 90 mm Hg in both the recumbent and the standing posture), and 8 healthy volunteers, normotensive in both postures. All subjects were white, with similar sex distributions and healthy volunteers, normotensive in both postures. The patient's arm was supported at the approximate level of the heart and heart rate in the 12 patients with orthostatic hypertension are shown in Table 1. None of the individuals whose data were reported had visible varicose veins, evidence of venous insufficiency, or a body weight more than 15% above the normal range.

Pressure Suit Studies

Blood pressure was measured with an automatic device (Arteriosonde, Hoffmann La Roche, Cranbury, NJ, or Dinamap, Critikon, Inc., Tampa, FL), and many of the readings were verified by auscultation while the subjects lay flat in bed, with one pillow, in a deflated pressure suit (MAST garment, David Clark Company, Inc., Worcester, MA) for 10 minutes. The subjects then stood for 5 to 10 minutes, after which the suit was inflated and measurements continued for 10 minutes in the standing posture. The suit was deflated while BP and pulse rate measurements continued, and was frequently reinflated for further BP determinations after another 10 minutes.

Cardiac Output Measurements

Cardiac output measurements were made by the CO₂ rebreathing method of Farhi et al. The subject rebreathed from a bag of known volume (1.0-1.5 liters) at a frequency of 60 breaths per minute, or as close to this as possible, for 15 seconds. The composition of the gas initially present in the bag was FiO₂ (fractional concentration of O₂ in inspired gas) = 0.6, remainder N₂. The CO₂ concentration was monitored constantly at the mouthpiece with an infrared CO₂ meter (Statham, Godart Co., Bithoven, Holland) and recorded oscillographically. As recommended by Farhi et al., the fourth breath of the rebreathing period was used for beginning the calculation of mixed venous CO₂ tension (PSCO₂), and the calculation included all breaths during the 15-second rebreathing period. After several (usually 5 or 6) measurements with the subjects in the supine posture, the determinations were repeated until satisfactory tracings were obtained with the subject standing. Results were not known by the technician at the time of study because the tracings were always analyzed later. Standing determinations were also performed with the subjects in the inflated Mast pressure suit.

Measurements of Plasma Norepinephrine Concentrations

Blood obtained for plasma catecholamine measurements was heparinized and kept in an ice bucket until it was centrifuged at 4°C. The plasma was pipetted off and frozen at −70°C until assayed. High-performance liquid chromatography and electrochemical detection were used after alumina adsorption and separation by ion exchange. The catecholamines were quantitated by the current produced when the norepinephrine and epinephrine, after separation, were oxidized during exposure to an electrical field. Plasma samples handled in this way showed no significant reduction in plasma norepinephrine or epinephrine concentrations after having been stored for up to 8 months. The coefficients of variation of replicate plasma norepinephrine determinations were 7.7% (interassay) and 3% (intraassay).

Table 1. Blood Pressures and Heart Rates in Patients with Orthostatic Hypertension

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Recumbent</th>
<th>Standing</th>
<th>Recumbent</th>
<th>Standing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>37</td>
<td>106/80</td>
<td>108/92</td>
<td>84</td>
<td>102</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>70</td>
<td>134/72</td>
<td>164/106</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>53</td>
<td>128/74</td>
<td>130/102</td>
<td>76</td>
<td>144</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>36</td>
<td>118/80</td>
<td>122/108</td>
<td>68</td>
<td>112</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>46</td>
<td>144/76</td>
<td>132/102</td>
<td>56</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>27</td>
<td>132/88</td>
<td>142/100</td>
<td>66</td>
<td>124</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>56</td>
<td>162/88</td>
<td>158/104</td>
<td>104</td>
<td>120</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>18</td>
<td>134/78</td>
<td>130/106</td>
<td>92</td>
<td>124</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>48</td>
<td>148/86</td>
<td>160/118</td>
<td>52</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>33</td>
<td>124/80</td>
<td>122/118</td>
<td>88</td>
<td>116</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>36</td>
<td>134/90</td>
<td>128/104</td>
<td>64</td>
<td>104</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>34</td>
<td>128/82</td>
<td>142/102</td>
<td>64</td>
<td>88</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>133/81</td>
<td>137/105</td>
<td>68</td>
<td>105</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td></td>
<td>4.0/1.6</td>
<td>4.7/2.0</td>
<td>7.1</td>
<td>6.4</td>
</tr>
</tbody>
</table>
Measurement of Orthostatic, Intravascular Blood Pooling

Subjects were studied between 0800 and 1300 hours. A heparinized blood sample (6 ml) was removed and labeled with 2 to 4 mCi of sodium pertechnetate Tc 99m, under aseptic conditions, with the Brookhaven National Laboratory (Upton, NY) red cell labeling kit. The blood was reinjected intravenously, and 20 minutes later, emitted gamma rays were counted over the calf and (usually) over the right temple. The counting equipment comprised a Nuclear-Chicago scintillation detecting probe (Searle Co., Chicago, IL), pulse height analyzer, and scaler/timer. The probe had a 1-inch (2.5 cm) NaI crystal and a straight collimator with an internal diameter of 1¼ inches. It was mounted on a portable x-ray machine chassis and could be moved rapidly, easily, and precisely in three planes. To ensure that the counts were made over identical sites on each occasion, the collimator engaged an aluminum "port" with a thin aluminum flange at its base, which was secured to the lateral aspect of the right midcalf by Velcro bands that enveloped the calf (Figure 1). Radiation emanating from the opposite calf was shielded from the detector by a thin sheet of lead strapped to the left leg. For measurements over the right temporal area the probe engaged a polyethylene port that had been glued into a hole in the side of a football helmet worn by the subjects. Replicate counts after repeated reengagements of the probe with the ports showed coefficients of variation of 0.5 to 3.8% (mean, 1.6%) in repeated counts over the calves of six subjects and 0.8 to 3.4% (mean, 1.5%) in repeated counts over the right temporal area of the same six subjects.

In individual studies, three to five counts (each for 0.5 minute) were made after each of two to six repositionings of the leg port in the probe and a similar number of counts were recorded over the temporal area during 20 to 30 minutes of recumbency. The subject was then asked to stand and, starting 3 to 4 minutes later, a similar number of counts were made over the leg and the temporal area during a period of 20 minutes in the standing posture. The mean of all counts made between 3 and 20 minutes in each posture and corrected for decay was used to calculate the percentage change in blood content resulting from orthostasis over the parts of the calf and temple counted. In 15 subjects duplicate determinations of orthostatic changes in blood content of the leg, made within 1 hour of one another, showed a mean difference of 3.7 ± 1.0 (SEM)%.

While the isotopic measurements of blood pooling in the recumbent and the upright postures were in progress, blood pressure and pulse rate were recorded every 2 minutes with a Dinamap.

Cardiac Volume Studies
Radionuclide ventriculography was performed in the customary manner after labeling autologous blood cells with 99mTc-pertechnetate, 20 mCi, and counting over the heart with a scintillation camera, while the patient was first recumbent for 10 minutes and then standing for 10 minutes. The data from the scintillation camera were transferred to a dedicated minicomputer system (Gamma 11 system, Digital Equipment Corporation, Maynard, MA). Electrocardiographic signals from the patient were obtained simultaneously, and the R wave was used as a gate signal to allow framing of 16 frames equally spanning the cardiac cycle. Each of these individual studies was analyzed by the placement of a searching region of interest around the left ventricle from which a computer program selected an edge threshold that traced the left ventricular margin throughout the cardiac cycle. Each frame was individually corrected for background, and a new volume curve was calculated from which end-diastolic and end-systolic counts and stroke counts were obtained.

Results
Orthostatic Blood Pressure Changes
The phenomenon of orthostatic hypertension in 1 of the 181 patients in whom this was found is depicted in Figure 2. Measurements of BP made every 2 minutes
with an Arteriosonde averaged 122/83 mm Hg when the patient was supine for 30 minutes and immediately rose to 130/96 mm Hg (mean) when she sat up, increasing gradually over the next 2 hours to 135/100 mm Hg and falling promptly when she lay down again to a mean value of 122/79 mm Hg. The mean orthostatic BP changes in the 181 patients with orthostatic hypertension were compared with the corresponding postural changes in 181 patients with persistent hypertension and 134 normotensive subjects of similar mean age and of the same racial background, including 67 normal volunteers and 67 normotensive patients with corrected or unrelated disorders (e.g., thyrotoxic and hypothyroid patients who were euthyroid on treatment, obese individuals, patients with menstrual irregularities). In all subjects of all three groups, DBP rose by 2 mm Hg or more when the subjects were upright. The results (Table 2) showed a far greater orthostatic rise in DBP (+16.3 ± 0.9 mm Hg) in the orthostatic hypertensive patients than in the normotensive subjects (+8.9 ± 0.8 mm Hg, p < 0.001) or in the persistently hypertensive subjects (+9.5 ± 0.5 mm Hg, p < 0.001). Plasma renin activity was slightly higher in the orthostatic hypertensive subjects (mean, 4.73 ± 0.38 ng/ml/hr) than in the persistently hypertensive subjects (3.68 ± 0.37 ng/ml/hr, p < 0.05).

Table 2. Recumbent and Standing Blood Pressure Measurements in Three Groups of Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>Recumbent blood pressure</th>
<th>Standing blood pressure</th>
<th>Orthostatic change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
</tr>
<tr>
<td>Normotensives</td>
<td>134</td>
<td>125.5±2.3</td>
<td>73.5±1.4</td>
<td>117.6±3.1</td>
</tr>
<tr>
<td>Persistently hypertensive</td>
<td>181</td>
<td>166.5±2.0</td>
<td>108.4±0.9</td>
<td>160.8±2.2</td>
</tr>
<tr>
<td>Orthostatic hypertensive</td>
<td>181</td>
<td>141.2±1.1</td>
<td>86.7±0.4</td>
<td>141.8±1.2</td>
</tr>
</tbody>
</table>

Values are means ± SEM in mm Hg.

The orthostatic rise in diastolic blood pressure was significantly greater in the subjects with orthostatic hypertension than in the normotensive subjects (p < 0.001) and the persistently hypertensive subjects (p < 0.001).
FIGURE 4. Effects of inflated pressure suit on orthostatic BP changes in 7 patients with orthostatic hypertension. The mean orthostatic rise in DBP was reduced by the pressure suit from 29.5 ± 3.5 mm Hg to 18.5 ± 1.9 mm Hg (p < 0.02).

The 12 patients with orthostatic hypertension had a more striking orthostatic reduction in cardiac output from a very similar recumbent mean, 6.88 ± 0.58 to 4.77 ± 0.31 L/minute; the mean change, −27.3 ± 2.9%, was highly significant (p < 0.001) and significantly greater than the change in the normotensive subjects (p < 0.01). When tested in the inflated pressure suit, these patients were found to have an orthostatic fall in cardiac output (10.7 ± 4.3%) that was significantly less than the fall observed in the uninflated suit (p < 0.001) and very similar to that observed in the untreated normotensive subjects.

Orthostatic Changes in Intravascular Pooling

When five normotensive subjects changed from recumbency to quiet standing, the amount of labeled blood in the part of the leg counted showed a rise to 227.4 ± 8.2% of the amount present in recumbency (p < 0.001; Figure 6). A similar orthostatic increase in blood content of the leg was found in three patients with persistent hypertension (mean, 220.7%). In contrast, five patients with orthostatic hypertension were found to show an orthostatic increase in the amount of blood in the leg to 282.8 ± 14.2% (p < 0.001) of the amount present in recumbency, a significantly greater orthostatic increase in intravascular pooling than in the normal subjects (p < 0.01). Although the counts over the head were too few to allow statistical comparisons, it is evident from Figure 6 that there was a tendency to greater orthostatic reduction in the labeled blood content of the part of the head that was monitored in the orthostatic hypertensive subjects than in the normotensive and persistently hypertensive subjects.

When the orthostatic change in pooling in the legs was plotted against the concomitant orthostatic rise in DBP in the 13 subjects studied in this way (5 orthostatic hypertensive, 3 persistently hypertensive, and 5 normotensive subjects), a close correlation between these variables was found (r = +0.85, p < 0.001; Figure 7). The relationship was expressed by the equation: A DBP = 0.2 (standing counts/recumbent counts) − 39.

Orthostatic Changes in End-Diastolic Cardiac Volume

The effects of orthostasis on the volume of blood in the heart at end diastole, measured by the total number of counts recorded over the left ventricle during 10-minute periods in recumbency and while standing, are shown in Table 3. It is evident that end-diastolic volume of the left ventricle was only slightly reduced by standing in the control subjects but was more severely reduced (to 65% of recumbent volume) in the patients with orthostatic hypertension.
Plasma Norepinephrine Concentrations

Plasma norepinephrine concentrations were similar in 12 normotensive (232 ± 21 pg/ml) and 4 orthostatic hypertensive subjects (198 ± 50 pg/ml; Figure 8) after recumbency for 1 hour. After the subjects had been standing 5 minutes, however, plasma norepinephrine concentrations were significantly higher in the orthostatic hypertensive subjects (441 ± 10 pg/ml) than in the normotensive subjects (353 ± 34 pg/ml, p < 0.01), and they continued to be higher as the subjects remained standing for an hour.

In contrast with these differences, there was no significant difference between five patients with orthostatic hypertension and five normotensive controls in their plasma norepinephrine concentrations after one-third maximum handgrip on a dynamometer for 2 minutes. Mean (± SEM) norepinephrine concentrations changed in the orthostatic hypertensive patients from preexercise values of 160 ± 29 pg/ml (versus 203 ± 34 pg/ml in the controls) to 219 ± 37 pg/ml at 1 minute (controls, 201 ± 44) and 252 pg/ml (controls, 300 ± 86) at the end of the handgrip exercise. Blood pressure increases in response to handgrip exercise were similar in the orthostatic hypertensive subjects (+ 24.8 ± 2.1/ + 6.6 ± 3.5 mm Hg) and the normal subjects (+ 26.0 ± 5.1/ + 25.3 ± 6.4 mm Hg), while heart rate changes were also not significantly different, being +11.0 ± 2.4 beats/minute in the orthostatic hypertensive subjects and +20.8 ± 3.8 beats/minute in the normotensive subjects.

Discussion

In normal human subjects orthostasis results in translocation of blood from the intrathoracic vascular compartment into the legs.9-10 This gravitational pooling has been shown to result normally in reduction of end-diastolic ventricular volume, which leads to a fall in stroke volume and, despite the concurrent tachycar-

<table>
<thead>
<tr>
<th>TABLE 3.</th>
<th>99mTc-Counts over Left Ventricle in End Diastole: Ratio of Orthostatic/Recumbent Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive subjects (%)</td>
</tr>
<tr>
<td>97</td>
<td>39</td>
</tr>
<tr>
<td>80</td>
<td>56</td>
</tr>
<tr>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>81</td>
<td>73</td>
</tr>
<tr>
<td>123</td>
<td>61</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>95.0 ± 7.0</td>
</tr>
<tr>
<td>p &lt; 0.05.</td>
<td></td>
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</tbody>
</table>
Orthostatic hypertension have shown qualitatively the same responses to orthostasis as have been reported previously in normotensive subjects. Quantitatively, all of the measured orthostatic changes were excessive in the patients with orthostatic hypertension. Gravitational pooling, measured directly in these studies, was found to be significantly (p < 0.01) more severe than in the control groups and to be positively correlated with the orthostatic rise in DBP. The implied causal relationship between these changes is supported by the finding that reduction of excessive pooling with a pressure suit significantly diminished the orthostatic hypertension, though it did not completely prevent the orthostatic rise in DBP. In our studies, the orthostatic pooling could be measured only as a percentage change from recumbent observations. As some mild hypertensive subjects are reported to have reduced venous distensibility, it is conceivable that there might be a greater percentage change but not a greater absolute increase in orthostatic pooling in patients with orthostatic hypertension. If this were true, however, it is unlikely that the pressure suit would have reduced the orthostatic rise in DBP so much more effectively in these patients than in the normal subjects. The orthostatic fall in cardiac output probably resulted mainly, if not entirely, from the orthostatic decrease in venous return caused by pooling. It is possible, however, that the excessive orthostatic reduction in cardiac output in the patients with orthostatic hypertension might have resulted, in part, from the orthostatic rise in afterload. This could certainly not have been the entire cause of the excessive fall in cardiac output, as (1) an increase rather than an excessive decrease in left ventricular end-diastolic volume would have been found and (2) the observed amelioration of the excessive fall in cardiac output would not have been expected during use of the inflated pressure suit.

The patients with orthostatic hypertension showed excessive increases in plasma norepinephrine concentrations in response to standing but not in response to handgrip exercise. It is reasonable to conclude, therefore, that the excessive sympathetic response to standing resulted not from an inherent hyperexcitability of the autonomic nervous system but from an appropriate response to an abnormally strong stimulus. The pathogenetic sequence leading to orthostatic hypertension in the patients studied, seems, therefore, to be as follows: orthostasis → excessive gravitational pooling of blood in dependent veins → reduced venous return → decreased cardiac volume. These changes are presumed to trigger the observed sympathetic hyperactivity, arterial constriction, and rise in DBP largely by low-pressure, cardiopulmonary receptors, as systolic and mean BP did not fall. The observed reduction in cardiac output might well have contributed to a fall in blood flow to the head and the periphery but is unlikely to have been the proximate stimulus to sympathetic hyperactivity. Our data have not excluded the possibility that the observed postural changes in blood pressure might have been the result of an abnormality in baroreceptor afferent mechanisms or in the central integra-

dia, a decrease in cardiac output during standing.11,12 A slight reduction in pulse pressure is the normal consequence of these changes, all of which can be prevented by the use of an antigravity suit.9,10,12 Peripheral resistance rises in the upright posture because of venoconstriction,12 which is probably mediated, at least in part, by sympathetic stimulation, as urinary excretion of norepinephrine is stimulated by orthostasis.13 Zoller et al.14 showed that when orthostasis was simulated by the application of negative pressure to the lower body, forearm vasoconstriction occurred before any change in blood pressure took place. These results have been confirmed and extended by others.15,16 More recently, Abboud et al.17 have shown that lower body negative pressure stimulates splanchnic vasoconstriction through the carotid baroreceptors and stimulates forearm vasoconstriction through low-pressure, cardiopulmonary baroreceptors. It appears likely, therefore, that while the vasoconstriction stimulated by orthostasis in normal subjects may be mediated by "the drive from all baroreceptor regions in the high — as well as the low — pressure system,"1112 the low-pressure receptors are the initial mediators of peripheral vasoconstriction in the upright posture.

The observations on our patients with orthostatic hypertension have shown qualitatively the same responses to orthostasis as have been reported previously in normotensive subjects. Quantitatively, all of the measured orthostatic changes were excessive in the patients with orthostatic hypertension. Gravitational pooling, measured directly in these studies, was found to be significantly (p < 0.01) more severe than in the control groups and to be positively correlated with the orthostatic rise in DBP. The implied causal relationship between these changes is supported by the finding that reduction of excessive pooling with a pressure suit significantly diminished the orthostatic hypertension, though it did not completely prevent the orthostatic rise in DBP. In our studies, the orthostatic pooling could be measured only as a percentage change from recumbent observations. As some mild hypertensive subjects are reported to have reduced venous distensibility, it is conceivable that there might be a greater percentage change but not a greater absolute increase in orthostatic pooling in patients with orthostatic hypertension. If this were true, however, it is unlikely that the pressure suit would have reduced the orthostatic rise in DBP so much more effectively in these patients than in the normal subjects. The orthostatic fall in cardiac output probably resulted mainly, if not entirely, from the orthostatic decrease in venous return caused by pooling. It is possible, however, that the excessive orthostatic reduction in cardiac output in the patients with orthostatic hypertension might have resulted, in part, from the orthostatic rise in afterload. This could certainly not have been the entire cause of the excessive fall in cardiac output, as (1) an increase rather than an excessive decrease in left ventricular end-diastolic volume would have been found and (2) the observed amelioration of the excessive fall in cardiac output would not have been expected during use of the inflated pressure suit.

The patients with orthostatic hypertension showed excessive increases in plasma norepinephrine concentrations in response to standing but not in response to handgrip exercise. It is reasonable to conclude, therefore, that the excessive sympathetic response to standing resulted not from an inherent hyperexcitability of the autonomic nervous system but from an appropriate response to an abnormally strong stimulus. The pathogenetic sequence leading to orthostatic hypertension in the patients studied, seems, therefore, to be as follows: orthostasis → excessive gravitational pooling of blood in dependent veins → reduced venous return → decreased cardiac volume. These changes are presumed to trigger the observed sympathetic hyperactivity, arterial constriction, and rise in DBP largely by low-pressure, cardiopulmonary receptors, as systolic and mean BP did not fall. The observed reduction in cardiac output might well have contributed to a fall in blood flow to the head and the periphery but is unlikely to have been the proximate stimulus to sympathetic hyperactivity. Our data have not excluded the possibility that the observed postural changes in blood pressure might have been the result of an abnormality in baroreceptor afferent mechanisms or in the central integra-
tion of cardiopulmonary baroreflexes. This possibility seems unlikely, however, because the evidence for an excessive magnitude of afferent stimulation is convincing in the patients with orthostatic hypertension, unlike the findings in patients with borderline hypertension studied by Mark and Kerber.

In patients whose DBP is below 90 mm Hg in recumbency and above this level in the upright posture (orthostatic hypertensive subjects), one might wonder whether the prognosis would be less serious than in persistently hypertensive patients whose standing pressures are similar but whose recumbent pressures are also above 90 mm Hg. In fact, they might resemble or might even have been classified as having mild or borderline hypertension by other authors in the past. At present, there is really no evidence to show whether patients with orthostatic hypertension have any adverse long-term consequences of their exclusively orthostatic elevation of blood pressure. Moreover, as our anecdotal evidence indicates that these patients are usually worsened, symptomatically as well as in their orthostatic rise in BP, by diuretic therapy, it would seem reasonable to employ a therapeutic approach other than the currently fashionable stepped care in these patients. Further evidence is needed on how best to treat these individuals, and studies of their therapy are in progress. As our data suggest that patients with orthostatic hypertension may constitute as much as 10% of some hypertensive populations, it is clearly important to accumulate more data on the pathogenesis and optimal therapy of their disorder as soon as possible.

Conclusion
The pathogenesis of the abnormally high orthostatic rise in diastolic blood pressure that patients with orthostatic hypertension manifest involves excessive pooling of blood in the veins, the correction of which (with an antigavity suit) largely overcomes the disorder. Excessive pooling of blood in the capacitance vessels reduces venous return and cardiac filling, thus stimulating, by means of the low-pressure cardiopulmonary receptors, an abnormally vigorous sympathetic discharge. Abnormally intense arteriolar constriction occurs and raises the diastolic blood pressure above 90 mm Hg in the upright posture. Inadequate orthostatic constriction of the dependent veins despite excessive sympathetic stimulation seems to be the initiating defect that leads to orthostatic diastolic hypertension in these patients.

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