The Hemodynamic Effects of Hypotensive Drugs in Man

IV. 1-Hydrizinophthalazine

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Further data are presented concerning the unusual hemodynamic effects of 1-hydrizinophthalazine. Previous observations demonstrating a marked increase in cardiac output in normotensive subjects are confirmed in hypertensive patients. The splanchnic vascular bed is one of the sites of increased blood flow. The similarity between the hemodynamic effects of 1-hydrizinophthalazine and pyrogens is pointed out and the pharmacologic basis for the clinically observed additive effects of 1-hydrizinophthalazine and hexamethonium is discussed.

G. Ross and his co-workers, in animals, and Reubi, in man, were the first to demonstrate that 1-hydrizinophthalazine (Apresoline) produces a reduction of arterial pressure and simultaneously an increase in renal blood flow. Since then considerable attention has been directed toward the further elucidation of the hemodynamic effects of this agent. Moyer and his associates, working with dogs, noted a marked increase in cardiac output and decrease in total peripheral resistance following administration of 1-hydrizinophthalazine. This observation was confirmed in normal and hypertensive pregnant women by Assali and his co-workers using the ballistocardiographic method and in normal subjects by Wilkinson and his associates using the intravenous catheterization technic (Fick). Several of these investigators postulated that the total splanchnic vascular bed probably shares in the vasodilatation.

In respect to blood flow through vascular areas other than the kidney, coronary blood flow was found to be increased in rabbits and in the dog heart-lung preparation, but has not been studied in man. Hafkenschiel and his associates in a preliminary report observed that blood flow through the cerebral vessels was essentially unchanged in man, while skin blood flow as measured in the toes did not increase significantly. In view of the apparently greater elevation of cardiac output than could be explained on the basis of the increases observed in renal and coronary flow, it seemed pertinent to determine the effects of 1-hydrizinophthalazine on blood flow through two other large areas, namely, the hepatic-portal (splanchnic minus renal and adrenal) vascular bed and the muscles, and to assess cardiac output changes in hypertensive patients.

Materials and Methods

The experimental procedures were carried out in hypertensive patients and normotensive subjects at Georgetown University Hospital and the Veterans Administration Hospital in Washington, D. C. Cardiac output, using the intravenous catheterization technic, and muscle blood flow in the calf, using a limb segment plethysmograph, were determined by methods described elsewhere. The method of Bradley and his associates was used to estimate hepatic-portal blood flow. All determinations were carried...
out in the postabsorptive state. The peripheral blood samples were taken from the femoral artery. 1-Hydrizinophthalazine was rapidly administered, usually intravenously, in a dose of approximately 0.25 mg per kilogram of body weight. During the 0.25 mg per kilogram of body weight. During the 6 cm. above the level of the skin of the patient's back. The zero point used for pressures in the right auricle, ventricle and pulmonary artery was 5 cm. below the angle of the sternum. During the determinations of muscle blood flow the arterial pressure was recorded in the brachial artery by the standard auscultatory method.

**RESULTS**

1. Cardiac Function and Total Peripheral Resistance

The cardiac output increased markedly in all of the six hypertensive patients studied (table 1, fig. 1), the average maximum increase over the control values being 128.2 per cent, S.D. 77.4. The average decrease in mean arterial pressure at this time was 28.4 per cent, S.D. 10.7. There was no correlation between the degree of increase in cardiac output and the extent of the blood pressure reduction. The mean decrease in total peripheral resistance was 62.1 per cent, S.D. 8.3. The heart rate increased in all cases, the mean increase being 32.1 per cent, S.D. 16.6. The average increase in stroke volume was 45 per cent.

The right auricular pressure was determined in two instances and increased from 1 to 2 mm. Hg in one instance and from 1.5 to 2 mm. Hg in the other. The mean pulmonary arterial pres-
sure also increased in two patients studied. In one it rose from a control value of 13 to 17 mm. Hg and in the other from 11 to 18 mm. Hg.

Table 2.—Effects of 1-Hydrazinophthalazine on Arterial Pressure and Estimated Hepatic-Portal Blood Flow

<table>
<thead>
<tr>
<th>Patient and Diagnosis</th>
<th>Sex</th>
<th>Age</th>
<th>Surface Area</th>
<th>Control</th>
<th>After 1-Hydrazinophthalazine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>sq. M.</td>
<td>Mean Arterial Pressure</td>
<td>EHBF</td>
</tr>
<tr>
<td>W. W. Ess. Hyper.</td>
<td>M</td>
<td>54</td>
<td>1.80</td>
<td>160 mm. Hg</td>
<td>960 ml. per min.</td>
</tr>
<tr>
<td>E. G. Ess. Hyper.</td>
<td>M</td>
<td>53</td>
<td>1.75</td>
<td>140 mm. Hg</td>
<td>690 ml. per min.</td>
</tr>
<tr>
<td>A. P. Ess. hyper.</td>
<td>M</td>
<td>45</td>
<td>1.58</td>
<td>160 mm. Hg</td>
<td>845 ml. per min.</td>
</tr>
<tr>
<td>M. H. Ess. hyper.</td>
<td>M</td>
<td>50</td>
<td>1.64</td>
<td>170 mm. Hg</td>
<td>1292 ml. per min.</td>
</tr>
<tr>
<td>L. J. Malig. hyper.</td>
<td>M</td>
<td>33</td>
<td>1.73</td>
<td>195 mm. Hg</td>
<td>1555 ml. per min.</td>
</tr>
<tr>
<td>J. Me. Malig. hyper.</td>
<td>M</td>
<td>38</td>
<td>1.82</td>
<td>160 mm. Hg</td>
<td>1126 ml. per min.</td>
</tr>
<tr>
<td>L. F. Normal</td>
<td>M</td>
<td>30</td>
<td>1.75</td>
<td>107 mm. Hg</td>
<td>873 ml. per min.</td>
</tr>
</tbody>
</table>

Fig. 2. Chart showing elevation of estimated hepatic-portal blood flow and reduction of mean arterial pressure and estimated hepatic-portal vascular resistance in W. W., a white male, age 54, with essential hypertension.

II. Estimated Hepatic-Portal Blood Flow

One patient with essential hypertension exhibited no significant change in estimated hepatic blood flow. In the remaining six cases which included three patients with essential hypertension, two patients with malignant hypertension and one normal subject, there was considerable increase in hepatic-portal blood flow (table 2, fig. 2). The maximum increase over control values ranged between 31 and 110 per cent (mean 75 per cent, S.D. 32). During the period of maximum change in estimated hepatic-portal flow the mean arterial pressure decreased between 9 and 47 per cent (mean 23 per cent, S.D. 13). It was apparent, therefore, that a marked decrease in hepatic-portal vascular resistance had occurred.

The hepatic venous pressure was measured in three patients. In two cases the pressure in the hepatic vein rose from 8 mm. Hg before 1-hydrazinophthalazine to 11 mm. Hg after, and in the remaining case it rose from 10 to 11 mm. Hg.

III. Blood Flow in the Calf (Muscle Blood Flow)

Calf blood flow was determined in seven subjects three of whom were hypertensive and four normotensive. In six of these cases which included all of the hypertensive patients there was a moderate decrease in blood flow ranging
under the fluoroscope or by observing the apex impulse. The increased circulatory rate is not shared by the entire body since the muscles, brain\(^7\) and skin\(^8\) show no appreciable change in blood flow, but is directed primarily through the total splanchnic vascular tree including the

Table 3.—The Effect of 1-Hydrazinophthalazine on Arterial Pressure and Blood Flow in the Calf

<table>
<thead>
<tr>
<th>Patient and Diagnosis</th>
<th>Sex</th>
<th>Age</th>
<th>Control Arterial Pressure mm. Hg</th>
<th>Blood Flow per 100 ml. Limb Volume ml. per min.</th>
<th>Dose I.V. mg.</th>
<th>Time after Drug min.</th>
<th>Arterial Pressure mm. Hg</th>
<th>Blood Flow per 100 ml. Limb Volume ml. per min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. G.</td>
<td>M</td>
<td>53</td>
<td>235/115</td>
<td>6.26</td>
<td>24</td>
<td>15</td>
<td>180/90</td>
<td>5.40</td>
</tr>
<tr>
<td>Ess. hyper.</td>
<td></td>
<td></td>
<td>235/115</td>
<td>6.41</td>
<td>28</td>
<td>190/95</td>
<td>5.77</td>
<td></td>
</tr>
<tr>
<td>L. C.</td>
<td>M</td>
<td>57</td>
<td>190/125</td>
<td>5.99</td>
<td>25</td>
<td>7</td>
<td>160/115</td>
<td>4.41</td>
</tr>
<tr>
<td>Ess. hyper.</td>
<td></td>
<td></td>
<td>195/125</td>
<td>5.13</td>
<td>10</td>
<td>170/110</td>
<td>4.37</td>
<td></td>
</tr>
<tr>
<td>R. Me.</td>
<td>M</td>
<td>50</td>
<td>230/140</td>
<td>3.71</td>
<td>20</td>
<td>7</td>
<td>190/110</td>
<td>3.14</td>
</tr>
<tr>
<td>Ess. Hyper.</td>
<td></td>
<td></td>
<td>230/142</td>
<td>4.40</td>
<td>10</td>
<td>190/104</td>
<td>2.80</td>
<td></td>
</tr>
<tr>
<td>J. F.</td>
<td>M</td>
<td>29</td>
<td>120/78</td>
<td>2.65</td>
<td>24</td>
<td>13</td>
<td>115/55</td>
<td>2.74</td>
</tr>
<tr>
<td>Pneumonia (convalescent)</td>
<td></td>
<td></td>
<td>120/78</td>
<td>2.76</td>
<td>20</td>
<td>120/55</td>
<td>2.49</td>
<td></td>
</tr>
<tr>
<td>J. B.</td>
<td>M</td>
<td>29</td>
<td>120/60</td>
<td>2.82</td>
<td>22</td>
<td>11</td>
<td>115/45</td>
<td>2.56</td>
</tr>
<tr>
<td>Hodgkin's Disease</td>
<td></td>
<td></td>
<td>120/55</td>
<td>3.37</td>
<td>26</td>
<td>110/45</td>
<td>2.43</td>
<td></td>
</tr>
<tr>
<td>J. H.</td>
<td>M</td>
<td>27</td>
<td>120/75</td>
<td>9.14</td>
<td>14</td>
<td>2</td>
<td>120/60</td>
<td>7.67</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td></td>
<td></td>
<td>120/65</td>
<td>8.50</td>
<td>13</td>
<td>120/55</td>
<td>7.99</td>
<td></td>
</tr>
<tr>
<td>T. B.</td>
<td>M</td>
<td>30</td>
<td>120/80</td>
<td>2.96</td>
<td>30</td>
<td>125/55</td>
<td>7.88</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td>120/80</td>
<td>3.65</td>
<td>30</td>
<td>130/60</td>
<td>7.83</td>
<td></td>
</tr>
</tbody>
</table>

HYPOTENSIVE DRUGS IN MAN

between 3 and 24 per cent (mean 15 per cent). In the remaining normotensive subject there was an increase in muscle blood flow of 14 per cent. Since, in most instances, both arterial pressure and blood flow decreased there probably was little or no change in vascular resist-

ance in the calf segment following 1-hydrazinophthalazine.

**Discussion**

1-Hydrazinophthalazine is the only hypotensive agent studied thus far in which the reduction of blood pressure is associated with a significant increase in cardiac output. The increase is accompanied by a tachycardia and a more forceful action of the heart clearly visible...
because of the marked decrease in total peripheral resistance, the diastolic pressure falls considerably more than the systolic.

This pattern of hemodynamic response is similar to that observed during the pyrogenic reaction. Here also, as demonstrated by Bradley, there is a reduction of arterial pressure in hypertensive patients accompanied by marked increases in cardiac output and hepatic-portal and renal blood flows. Bradley has shown in addition that these hemodynamic responses are not dependent on activation of the temperature center, per se, since they occur when the febrile response is blocked by administering aminopyrine. The site of action of pyrogen in producing these hemodynamic responses is unknown, but it seems possible that it may be similar to the site of action of 1-hydrazinophthalazine. In this connection Gross and his co-workers believe that the drug acts centrally. It has been reported from this laboratory as well as by Schroeder that 1-hydrazinophthalazine and hexamethonium have an additive hypotensive effect. The hemodynamic responses to these agents lend support to this clinical impression. Hexamethonium usually decreases cardiac output as well as right auricular and pulmonary arterial pressures. Thus, the combination of markedly decreased peripheral resistance following 1-hydrazinophthalazine and decreased right heart pressures and cardiac output after hexamethonium may have a powerful additive effect in reducing systemic arterial pressure. Moyer has shown in dogs that the increase in cardiac output following 1-hydrazinophthalazine is prevented if hexamethonium is given concurrently.

The hemodynamic effects of 1-hydrazinophthalazine differ radically from those produced by other hypotensive agents thus far studied. For example, in patients with compensated hearts the cardiac output remains unchanged after veratrum viride or dihydroergocornine and usually decreases slightly after hexamethonium. Following veratrum there is a generalized rather than regional decrease in peripheral resistance, while after hexamethonium marked vasodilation occurs only in the distal extremities. Following dihydroergocornine there is an increased resistance in the hepatic-portal area. After all of these agents (except 1-hydrazinophthalazine) renal blood flow and glomerular filtration rate decrease at least transiently. Thus, it seems evident that each of these hypotensive drugs differs somewhat from the others in its effects on blood flow through various areas.

The ideal agent for the treatment of essential hypertension would be one which restores blood flow to normal in those areas in which it has been reduced and which does not disturb otherwise the normal distribution of blood flows or cardiac output. In respect to its ability to increase renal blood flow 1-hydrazinophthalazine would appear to be ideal, but the drug also markedly increases cardiac output to levels which often are above the physiologic range for resting subjects.

**SUMMARY AND CONCLUSIONS**

1-Hydrazinophthalazine administered to hypertensive and normotensive subjects produced the following hemodynamic effects:

1. The cardiac output increased markedly in hypertensive patients despite a definite reduction in mean arterial pressure. The calculated total peripheral resistance fell sharply.

2. Estimated hepatic-portal blood flow also increased significantly.

3. Blood flow through the muscles (calf segment) usually decreased slightly.

4. The similar hemodynamic patterns produced by 1-hydrazinophthalazine and pyrogen are noted and the pharmacologic basis for the clinically observed additive effects of 1-hydrazinophthalazine and hexamethonium is discussed.

**ACKNOWLEDGMENTS**

The authors wish to thank Miss Jean Pietras, Miss Barbara Allison, Mr. Victor Landi and Mr. Larry C. Gaskins for valuable technical assistance.

**SUMARIO Español**

La observación de que el 1-hydrazinophthalazine aumenta marcadamente la producción total cardíaca se comprueba y además se demuestra que la circulación calculada hepático portal aumenta con la droga. La circulación de la pantorrilla generalmente disminuye...
ligeramente. La similaridad entre las respuestas hemodinámicas al 1-hidrazinophthalazine y pirógenos se indica.

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Circulation. 1953;8:199-204
doi: 10.1161/01.CIR.8.2.199
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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