Comparison of Visceral and Peripheral Vascular Beds in Hypertensive Patients

Their Responses to Various “Hypotensive” Drugs

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The responses of the kidney and the lower extremities to single intravenous doses of six “hypotensive” drugs were measured in eight patients diagnosed as having essential hypertension. Use of Hexamethonium, Ildar and Hydrgine was followed by increase in the flow to the extremity and simultaneous decrease in renal blood flow. In contrast, the administration of Apresoline was followed by decrease in flow to the extremity and an increase in renal blood flow. Regitine produced no significant change in either. After the administration of protoveratrine, renal blood flow decreased but a significant change in blood flow to the extremity was not observed. Changes in arterial pressure which occurred with some of the drugs were not correlated with the changes in blood flow to the extremities or to the kidney.

When studying the effect of reflex heating (Gibbon-Landis procedure) by simultaneously measuring the rate of blood flow in different vascular beds in normal subjects and arteriosclerotic and hypertensive patients, it was found that the procedure affected inversely the blood flow to the kidneys (a decrease) and to the lower extremity (an increase) in all three groups. These observations suggested that the regional effects on the vascular tree of hypotensive and vasodilator drugs studied with the same technics might be of interest. This paper deals with the responses of the vascular beds of the kidney and the lower extremity to single intravenous doses of hypotensive drugs in patients with essential hypertension.

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Methods

Direct plethysmography with an air transmission apparatus which has previously been described in detail was used for measuring blood flow in the extremities.

Changes in renal plasma flow were measured by the technic of maintaining a constant infusion of sodium para-aminohippurate. The assumption was made that the rate of infusion of the substance was the same as the rate of excretion in the urine. Plasma flow was calculated by dividing the rate of infusion by the plasma level. Blood flow was then calculated on the basis of the hematocrit and renal plasma flow.

The base lines for testing responses have all been obtained in an environment of 20 C. and 50 to 55 per cent humidity. These conditions afford a mild vasoconstrictor stimulus.

Eight patients classified as having “essential hypertension” have been studied. The clinical findings are summarized in table 1. The effects of Apresoline upon the vascular beds of the extremities and the kidneys were also studied in a preliminary way in a patient in whom unilateral subtotal sympathectomy had been performed and in two nonhypertensive paraplegic subjects with traumatic transection of the cord, one at T-4 and one at a somewhat lower level.

The following six drugs have been used:

1. Hexamethonium was given intravenously in dosages of 5 and 10 mg. This drug is capable of blocking both sympathetic and parasympathetic ganglia. The sympathetic blockade is manifested by hypotension, particularly of the postural variety,
increase in skin temperature and diminished sweating. Parasympathetic blockade is manifested by a decrease in salivation and gastric secretion, constipation and impaired visual accommodation. Cardiac output is supposed to be either unchanged or slightly decreased.\textsuperscript{4,11}

2. \textit{Apresoline} (1-hydrazinophthalazine) was given intravenously in a dosage of 15 mg. This hypotensive agent has been shown to increase renal blood flow, heart rate and cardiac output without increasing cerebral blood flow, and to lower arterial pressure. It has been found to antagonize certain humoral pressor substances and is supposed to block vasopressor reflexes from breathholding and immersion of the hand in ice water.\textsuperscript{6,15}

3. \textit{Ilidar} (6-allyl-6,7-dehydro-5 H-dibenzazepinephosphate) was given intravenously in dosages of 5 and 10 mg. This new drug has been described as a "vasodilator compound with adrenergic blocking action." Green and co-workers have shown that in dogs 1 mg. of Ilidar per kilogram prevented a rise in arterial pressure in response to a subsequent injection of epinephrine.\textsuperscript{4} It appeared, therefore, that this compound is capable of completely blocking the usual vasoconstrictor response to epinephrine.

4. \textit{Hydergine}, an equal mixture of three hydrogenated ergot alkaloids, namely, dihydroergocornine, dihydroergocystine and dihydroergokryptine, was given intravenously in dosages of 0.6 mg. It is supposed to act centrally on the vasomotor center and peripherally to a small extent by blocking sympathetic vasoconstrictor impulses in the

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Type and Duration of Hypertension</th>
<th>Blood Pressure (Base Line)</th>
<th>Hist. of Cerebrovascular Accident</th>
<th>Hist. of Congest. Fail.</th>
<th>Cardiac Size (X-ray)</th>
<th>Electrocardiogram</th>
<th>Blood Urea Nitrogen (mg. %)</th>
<th>Urinary Examination</th>
<th>Other Studies or Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. J.</td>
<td>60</td>
<td>M.</td>
<td>Essential 25 yrs.</td>
<td>210/135</td>
<td>None</td>
<td>None</td>
<td>Left vent. enlarg.</td>
<td>Left axis deviation</td>
<td>18.8</td>
<td>Negative</td>
<td>Regitine test negative</td>
</tr>
<tr>
<td>M. H.</td>
<td>60</td>
<td>F.</td>
<td>Essential 15 yrs.</td>
<td>220/130</td>
<td>5 yrs. before complete recovery</td>
<td>None</td>
<td>No enlarg.</td>
<td>Left axis deviation</td>
<td>18.3</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>S. S.</td>
<td>37</td>
<td>M.</td>
<td>Essential 10 yrs.</td>
<td>210/140</td>
<td>None</td>
<td>None</td>
<td>No enlarg.</td>
<td>Left axis deviation</td>
<td>19.2</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>P. W.</td>
<td>64</td>
<td>F.</td>
<td>Essential 10 yrs.</td>
<td>280/140</td>
<td>None</td>
<td>None</td>
<td>Left vent. enlarg., slight</td>
<td>Left axis deviation</td>
<td>13.5</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>C. S.</td>
<td>46</td>
<td>F.</td>
<td>Essential 20 yrs.</td>
<td>210/140</td>
<td>None</td>
<td>None</td>
<td>Left vent. enlarg., mod.</td>
<td>Left axis deviation</td>
<td>14.2</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>R. J.</td>
<td>48</td>
<td>M.</td>
<td>Essential 7 yrs.</td>
<td>220/120</td>
<td>Several with complete recovery</td>
<td>None; anginal syndrome present 6 yrs.</td>
<td>Cardiac enlarg., slight</td>
<td>Left axis deviation</td>
<td>14.2</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>O. R.</td>
<td>54</td>
<td>M.</td>
<td>Essential 2 yrs.</td>
<td>200/100</td>
<td>None</td>
<td>None</td>
<td>No enlarg.</td>
<td>No axis deviation</td>
<td>26</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>S. H.</td>
<td>50</td>
<td>F.</td>
<td>Essential 3 yrs.</td>
<td>190/100</td>
<td>None</td>
<td>None</td>
<td>Left vent. enlarg.</td>
<td>Left axis deviation</td>
<td>15.4</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2.—Average Changes Observed in Response to
Reflex Heating and to Six “Hypotensive” Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Skin Temp. Toes Max. Change</th>
<th>Basal Flow</th>
<th>Maximal Response</th>
<th>Renal Blood Flow</th>
<th>Change in Arterial Pressure</th>
<th>Pulse Rate Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat</td>
<td>+5.8</td>
<td>1.3</td>
<td>4.3</td>
<td>-12%</td>
<td>0</td>
<td>0 +22</td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>+5.6</td>
<td>0.9</td>
<td>2.4</td>
<td>-12%</td>
<td>-57 -21 +13</td>
<td></td>
</tr>
<tr>
<td>Protoveratrine</td>
<td>+1.7</td>
<td>0.8</td>
<td>0.8</td>
<td>-7%</td>
<td>-16 -10 -4</td>
<td></td>
</tr>
<tr>
<td>Ilidar</td>
<td>+4.1</td>
<td>0.8</td>
<td>2.7</td>
<td>-7%</td>
<td>-21 -5 +3</td>
<td></td>
</tr>
<tr>
<td>Hydergine</td>
<td>+3.3</td>
<td>1.2</td>
<td>1.6</td>
<td>-11%</td>
<td>-24 -15 -5</td>
<td></td>
</tr>
<tr>
<td>Apresoline</td>
<td>-0.5</td>
<td>0.7</td>
<td>0.4</td>
<td>+37%</td>
<td>-5 -5 +18</td>
<td></td>
</tr>
<tr>
<td>Regitine</td>
<td>0</td>
<td>0.9</td>
<td>0.9</td>
<td>0</td>
<td>+4 +5 0</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. The graph shows the peripheral (leg) and visceral (kidney) response to Apresoline.

Fig. 1. The graph shows the peripheral (leg) and visceral (kidney) response to hexamethonium.

nerve endings. It produces mild hypotension and bradycardia not abolished by atropine.17, 18, 19

5. Prototveratrine, the first pure alkaloid from veratrum album shown to have hypotensive properties in man without significant side effects,20 was given in amounts of 100 to 170 micrograms intravenously. Its depressor effect has been ascribed to the inhibition of pressoreceptors of the carotid sinus in the aortic arch and of a similar vasodepressor reflex pathway arising in the heart itself. Prototveratrine produces marked vagal slowing of the heart which can be effectively blocked by atropine without affecting the depressor effect. Hoobler and co-workers found vasodilatation of the extremities and a slight increase in renal blood flow after administration of prototveratrine. Meil-

man, however, could not observe any increase in renal blood flow; he did not measure peripheral flow.20, 21, 22

6. Regitine (2-(m-hydroxy-N-p-tolylanilino)-methyl]-2-imidazoline methanesulfonate) was given intravenously in a dosage of 5 mg. It is described as a potent sympatholytic drug. Some degree of transient hypotension was seen in a small number of subjects. Regitine at present is used chiefly in the detection of epinephrine-producing tumors.23, 24

RESULTS

Hexamethonium produced a marked increase in skin temperature and extremity flow, a decrease in renal blood flow and a well-marked fall in arterial pressure (table 2, fig. 1). Apresoline caused a decrease in skin temperature and extremity flow, marked increase in renal blood flow and no significant change in arterial pressure (table 2, fig. 2). It emerged that the interruption of certain nervous pathways alters the response of vascular beds to Apresoline: the two paralgesics showed increase in extremity flow and no change in renal flow; so did the hypertensive on the sympathectomized side, while her normal side reacted as seen in the eight hypertensive subjects who comprise the main body of this study.

Ilidar and Hydergine produced marked increase in skin temperature and extremity flow, moderate decrease in renal flow and a moderate fall in arterial pressure.

Prototveratrine caused no significant change
in skin temperature or extremity flow, moderate decrease in renal flow and a marked fall in arterial pressure.

Regitine produced no significant change in any of the measurements with the dosage used.

**DISCUSSION**

The inverse effect observed with a simple vasodilator procedure (Gibbon-Landis test) upon different vascular beds has been evident also in the majority of experiments testing the response to hypotensive agents. Increase in blood flow to the periphery was regularly accompanied by decrease in renal blood flow, and increase in renal blood flow was usually accompanied by decrease in extremity flow. Changes in blood flow, both peripheral and visceral, could not be correlated with changes in arterial pressure in these experiments. Bull has just recently stressed that blood pressure changes do not always accompany "circulatory adjustments." In perfusion experiments, changes in pressure between 100 and 170 mm. Hg did not influence renal blood flow. Decrease in renal blood flow has been observed to occur in the absence of any change in blood pressure.

The question as to what mechanisms are responsible for these "circulatory adjustments" remains largely unanswered. Of considerable interest in this connection are certain observations made with Apresoline. It was known that this drug caused marked increase in cardiac output along with a proportionately smaller increase in renal blood flow and also an increase in hepatic blood flow. The fact that in our experiments blood flow to the extremities never participated in this increase and usually even decreased after Apresoline suggests that the vasodilatory effect of this drug (when given intravenously) is chiefly in the visceral regions when the nerve supply is intact.

It is hoped that continuation and extension of the studies on paraplegic, hemiplegic and partially sympathectomized patients may shed some light at least on the neural factors involved in circulatory adjustments between various vascular beds.

**SUMARIO ESPAÑOL**

Las respuestas del riñón y las extremidades inferiores a una dosis sencilla intravenosa de seis drogas hipotensivas fueron medidas en ocho pacientes diagnosticados como hipertensos. El uso de Hexamethonium, Ilidar y Hydergine fue seguido por un incremento de circulación en la extremidad y un decremento en la circulación renal. En contraste la administración de apresolina fue seguida por un decremento en circulación de la extremidad y un incremento en circulación renal. Regitine no produjo cambio significativo alguno ni en uno o el otro. Luego de la administración de protoveratrine, la circulación renal disminuyó pero un cambio significativo en circulación de la extremidad no se observó. Cambios en presión arterial que ocurrieron con algunas de las drogas no coincidieron con los cambios en circulación de la extremidad o el riñón.

**Summary**

1. Blood flow to the lower extremities and renal blood flow were measured simultaneously in eight patients suffering from essential hypertension, and the responses to single intravenous injections of Hexamethonium, Apresoline, Ilidar, Hydergine, Protoveratrine and Regitine were recorded.

2. Hexamethonium, Ilidar and Hydergine produced increase in extremity flow and decrease in renal blood flow. In contrast, Apresoline caused decrease in extremity flow and increase in renal blood flow. Protoveratrine did not change significantly the blood flow to the extremity, but did lower the renal blood flow. Regitine produced no significant changes in either.

3. There seemed to be no correlation between changes in arterial pressure and changes in blood flow to the regions measured.

4. In the vascular beds measured, the response to Apresoline was markedly altered in two cases of transection of the cord (increase in extremity flow, no change in renal blood flow); the same modification in response was observed on the sympathectomized side of a hypertensive patient who had been subjected to unilateral subtotal sympathectomy.
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