Acute and Chronic Cardiovascular Effects of Pentolinium in Hypertensive Patients

By Josef R. Smith, M.D., and S. W. Hoobler, M.D.

Using a tracer injection technic, modified to provide accurate and repeated determinations of cardiac output in the ambulatory patient, the authors have shown that chronic pentolinium therapy for hypertension lowers blood pressure by reducing cardiac output in the seated position. From these observations and the work of others, they believe that the effect of ganglionic blockade on venoconstrictor tone deserves greater emphasis.

Despite the widely accepted use of ganglionic-blocking agents in the treatment of severe hypertension, surprisingly little is known of the mechanism whereby the blood pressure is reduced in the ambulatory patient. In particular, it has not been possible heretofore to make repeated observations of the effect of these agents on the cardiac output in the orthostatic hypertensive patient before and at various time intervals following initiation of treatment. This report deals with certain modifications of the dye injection method for cardiac output, which permits such repeated examinations, and is, to our knowledge, the first study of the effect of chronic pentolinium treatment on the cardiac output and peripheral resistance in hypertensive patients.

Methods

Patients studied were those with severe essential hypertension (blood pressures of 180–225/117–129). The cardiac output was performed in the seated position. The dye-dilution method of Stewart and Hamilton as modified by Pritchard and his group for the use of iodinated serum albumin (RISA) was the basic principle used in measuring cardiac output, except that arterial samples were collected in tubes rather than passed through the counting device they describe. Pritchard’s method was further modified as follows: 1. The RISA-containing syringe was weighed before and after injection to determine accurately the quantity of isotope injected. 2. A flushing syringe containing 10 ml of normal saline was attached by a T connection and a 1-way valve to propel more rapidly the bolus of injected substance. 3. Individual brachial artery samples were collected every 2 sec. by means of a circular test tube rack placed on a simple rotating stool and moved by hand, in time with the clicks of a metronome set at 60 beats/min. 4. Representative samples were pipetted into radioactively clean test tubes and counted individually in an iodine crystal-type well scintillation counter.* The measured samples were compared to known dilutions of the stock RISA solution injected. Each sample and standard was counted for 6400 or more counts, which gives a theoretical counting error of 1.25 per cent or less in each sample. The cardiac output was calculated from Hamilton’s formula, the curves being plotted on semilogarithmic paper extrapolated to 0 to exclude recirculated test substance. The formula used was

\[
\text{Cardiac output (L/min.)} = \frac{\text{Total counts injected} \times 60 \times 1}{\text{Sum of counts/sec./ml. at each } 1 \text{ sec. interval as determined under the extrapolated curve}}.
\]

Mean circulation time was calculated from the formula,

\[
\text{MCT} = \sum \frac{C \cdot t}{\sum C},
\]

where \(C\) equals the counts per second at the time \(t\) and \(t\) equals the time interval (in seconds) from the time of injection to the time at which concentration

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* We are indebted to Dr. Daniel Shaw of Wyeth & Company for the supply of pentolinium used in these studies.

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was measured. Using these figures, pulmonary blood volume was calculated from the formula,

\[ PBV = \frac{\text{Cardiac output (ml/min.)}}{60} \times MCT \]

as described by Hamilton and associates.\(^2\) Mean blood pressure at the time of the determination was calculated as the diastolic pressure plus \(1\frac{1}{3}\) of the pulse pressure. The reading represented the average of readings just before and just after injection of the tracer solution. Total peripheral resistance was calculated from the formula

\[ TPR \, \text{(dynes cm}^{-5}\text{sec.)} = \frac{MBP \times 1332 \times 60}{\text{Cardiac output (ml/sec.)}} \]

Cardiac index was calculated as

\[ \text{Cardiac output} \times \frac{1}{M^2} \text{Surface area} \]

Initial determinations, done 20 min. apart before therapy, gave an average variation in the cardiac output of \(\pm 3.29\) per cent with an upper limit of 6.75 per cent. The average value was 2.84 L./M\(^2\)/min. This is somewhat low, but the standing cardiac output was found to be decreased 33 per cent by McMichael and Sharpay-Schaper\(^2\) and a similar decrease would also be expected on sitting. Cardiopulmonary blood volume measurements varied up to \(\pm 7.1\) per cent with an average of \(\pm 4.1\) per cent. Although this measurement is considered rather inaccurate by Hamilton and others,\(^3\) a study by Doyle and co-workers\(^3\) gives figures on variation that are consistent with our data. Because precision is essential in obtaining reproducible results by this modified method for cardiac output, the following typical experiment is presented in some detail.

**Experiment**

E. L. P. was placed in the seated position, a 19-gage needle was inserted into the antecubital vein, and the arm elevated on pillows to heart level. An 18-gage Cournard arterial needle was inserted in the brachial artery of the opposite arm, and a Decholin circulation time was determined at 10.6 sec., which indicated the probable range of collection time for the subsequent arterial samples. After a few minutes to achieve a steady state, her brachial blood pressure, determined by an aneroid sphygmomanometer, was found to be 208/124. A known amount of RISA, approximately 10 microcuries in 2-3 ml., was injected in less than 1 sec, through the venous needle and was flushed rapidly into the central venous reservoir by the injection of 10 ml. of normal saline. A 3 sec. time lag (7 sec. less than the Decholin circulation time) was allowed and then collections were made from the Cournard needle through a \(1\frac{1}{16}\)" internal diameter siliconized plastic tubing and a special 3-way stopcock bored out to \(\frac{3}{32}\)". The flow was manually directed to a new tube every 2 sec. and a total of 24 samples were collected in tubes containing dried heparin. Individual samples averaged 1.2-2.0 ml. A specimen for blood volume was collected from the arterial needle 10 min. after the injection. The procedure was repeated 20 min. after the injection with the patient remaining in the same position and with a second dose of RISA containing the same amount of activity. The patient was then given 8 mg. of pentolinium bitartrate through the intravenous needle in divided doses over a period of 25 min. until her blood pressure had fallen to 106/70. The cardiac output was then repeated twice at 10 to 20 min. intervals; 2 and 4 times the radioactivity of the original sample were used to insure a new level significantly above background. The patient was then placed on oral pentolinium treatment and satisfactory blood pressure control was achieved. Ten days after the original determination, another set of duplicate determinations was done in the sitting position at the time of a significant blood pressure reduction. The method described delivered radiation of less than 0.1 milliure of \(^{131}\)I to the patient, a dose that is considered well within the safe range.

Using the isotope, one can perform multiple determinations without staining the skin as would occur if Evans-blue had been used as the tracer substance. Collecting specimens in tubes and using a well-type scintillation counter provided greater accuracy and a lower total radiation dose as well as avoiding the special equipment required by Pritchard's technic.\(^6\)

The acute effects of pentolinium bitartrate were studied in this manner in 5 severely hypertensive patients, 4 of whom were subsequently re-examined after 6 to 128 days on oral treatment. Two additional patients, G. Xa. and G. Be. were studied before and after chronic treatment but were not observed after acute intravenous injection of the drug. Finally, 1 patient, M. Po., who had been on therapy approximately 1 year, had the opposite procedure, i.e., a determination while on therapy and a second one after treatment was stopped and the blood pressure had risen to pretreatment levels (table 1, fig. 2).

**Results**

Reductions in blood pressure following acute therapy ranged from 54/17 to 145/63 mm. of Hg, or from 31 to 90.3 mm. of mean blood pressure. This change corresponds to an average blood pressure fall of 36.8 per cent with a range from 22 to 57 per cent. Chronic studies revealed blood pressure falls from 10/9 to 76/42. Expressed as per cent fall in mean blood pressure, the average was 24 per cent with a range from 6 to 45 per cent (table 1, fig. 1).

Values for cardiac index fell in all patients,
Table 1.—Hemodynamic Changes Following Acute Intravenous and Chronic Oral Pentolinium

<table>
<thead>
<tr>
<th>Patient</th>
<th>Observation</th>
<th>Blood pressure</th>
<th>Mean circulation time</th>
<th>Cardiac index</th>
<th>Stroke volume</th>
<th>Peripheral resistance</th>
<th>Pulmonary volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic/diastolic mm. Hg</td>
<td>Mean</td>
<td>% Δ</td>
<td>L./M./min.</td>
<td>% Δ</td>
<td>ml.</td>
</tr>
<tr>
<td>L. Ke.</td>
<td>Initial</td>
<td>204/121</td>
<td>145</td>
<td>19</td>
<td>2.94</td>
<td>52.4</td>
<td>2631</td>
</tr>
<tr>
<td></td>
<td>Acute-1</td>
<td>110/80</td>
<td>90</td>
<td>-38</td>
<td>21</td>
<td>1.65</td>
<td>-44</td>
</tr>
<tr>
<td></td>
<td>Acute-2</td>
<td>128/84</td>
<td>99</td>
<td>-32</td>
<td>21</td>
<td>2.03</td>
<td>-31</td>
</tr>
<tr>
<td></td>
<td>Chronic-1</td>
<td>180/106</td>
<td>131</td>
<td>-10</td>
<td>20</td>
<td>2.30</td>
<td>-22</td>
</tr>
<tr>
<td></td>
<td>Chronic-2</td>
<td>176/110</td>
<td>132</td>
<td>-9</td>
<td>18</td>
<td>2.29</td>
<td>-22</td>
</tr>
<tr>
<td>La. P.</td>
<td>Initial</td>
<td>200/117</td>
<td>148</td>
<td>19</td>
<td>3.24</td>
<td>63.4</td>
<td>1943</td>
</tr>
<tr>
<td></td>
<td>Acute-1</td>
<td>106/70</td>
<td>82</td>
<td>-48</td>
<td>28</td>
<td>1.57</td>
<td>-51</td>
</tr>
<tr>
<td></td>
<td>Acute-2</td>
<td>146/100</td>
<td>115</td>
<td>-22</td>
<td>22</td>
<td>2.32</td>
<td>-28</td>
</tr>
<tr>
<td></td>
<td>Chronic-1</td>
<td>152/96</td>
<td>115</td>
<td>-22</td>
<td>22</td>
<td>2.27</td>
<td>-30</td>
</tr>
<tr>
<td></td>
<td>Chronic-2</td>
<td>150/92</td>
<td>111</td>
<td>-25</td>
<td>21</td>
<td>2.43</td>
<td>-25</td>
</tr>
<tr>
<td>C. Na.</td>
<td>Initial</td>
<td>211/119</td>
<td>150</td>
<td>24</td>
<td>2.97</td>
<td>79.1</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Rx 6 days</td>
<td>152/96</td>
<td>105</td>
<td>-30</td>
<td>39</td>
<td>1.86</td>
<td>-37</td>
</tr>
<tr>
<td></td>
<td>Acute-1</td>
<td>142/98</td>
<td>113</td>
<td>-29</td>
<td>25</td>
<td>2.31</td>
<td>-32</td>
</tr>
<tr>
<td></td>
<td>Acute-2</td>
<td>135/90</td>
<td>106</td>
<td>-33</td>
<td>26</td>
<td>2.30</td>
<td>-33</td>
</tr>
<tr>
<td></td>
<td>Chronic-1</td>
<td>150/108</td>
<td>122</td>
<td>-23</td>
<td>27</td>
<td>1.80</td>
<td>-47</td>
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<tr>
<td></td>
<td>Chronic-2</td>
<td>160/106</td>
<td>124</td>
<td>-21</td>
<td>26</td>
<td>2.50</td>
<td>-27</td>
</tr>
<tr>
<td>H.v A.</td>
<td>Initial</td>
<td>186/119</td>
<td>141</td>
<td>38</td>
<td>2.25</td>
<td>54.8</td>
<td>2572</td>
</tr>
<tr>
<td></td>
<td>Acute-1</td>
<td>130/96</td>
<td>110</td>
<td>-22</td>
<td>34</td>
<td>1.84</td>
<td>-18</td>
</tr>
<tr>
<td></td>
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<td>176/110</td>
<td>132</td>
<td>-6</td>
<td>28</td>
<td>2.16</td>
<td>-4</td>
</tr>
<tr>
<td></td>
<td>Chronic-2</td>
<td>174/110</td>
<td>132</td>
<td>-7</td>
<td>32</td>
<td>2.00</td>
<td>-11</td>
</tr>
<tr>
<td>G. Be.</td>
<td>Initial</td>
<td>196/124</td>
<td>148</td>
<td>16</td>
<td>3.28</td>
<td>47.3</td>
<td>2502</td>
</tr>
<tr>
<td></td>
<td>Chronic-1</td>
<td>100/72</td>
<td>81</td>
<td>-45</td>
<td>25</td>
<td>2.07</td>
<td>-37</td>
</tr>
<tr>
<td></td>
<td>Chronic-2</td>
<td>108/74</td>
<td>85</td>
<td>-42</td>
<td>32</td>
<td>1.94</td>
<td>-41</td>
</tr>
<tr>
<td></td>
<td>Chronic-3</td>
<td>120/82</td>
<td>95</td>
<td>-36</td>
<td>25</td>
<td>2.79</td>
<td>-15</td>
</tr>
<tr>
<td></td>
<td>Chronic-4</td>
<td>120/82</td>
<td>95</td>
<td>-36</td>
<td>27</td>
<td>2.98</td>
<td>-9</td>
</tr>
<tr>
<td>G. Go.</td>
<td>Initial</td>
<td>225/123</td>
<td>157</td>
<td>24</td>
<td>2.12</td>
<td>39.7</td>
<td>3626</td>
</tr>
<tr>
<td></td>
<td>Acute-1</td>
<td>95/62</td>
<td>74</td>
<td>-53</td>
<td>40</td>
<td>1.03</td>
<td>-51</td>
</tr>
<tr>
<td></td>
<td>Acute-2</td>
<td>80/60</td>
<td>67</td>
<td>-57</td>
<td>30</td>
<td>1.31</td>
<td>-38</td>
</tr>
<tr>
<td>M. Po.*</td>
<td>Chronic</td>
<td>157/106</td>
<td>123</td>
<td>31</td>
<td>2.00</td>
<td>53.5</td>
<td>2665</td>
</tr>
<tr>
<td></td>
<td>Off Rx.</td>
<td>200/122</td>
<td>148</td>
<td>17</td>
<td>35</td>
<td>2.89</td>
<td>44</td>
</tr>
</tbody>
</table>

* M. Po. was first tested while on chronic treatment. Three days after withholding the drug, the observation was repeated.

All procedures were done in seated posture. "Initial" determinations are the average of 2 determinations done in the pretreatment state. "Acute" observations were done 20 min. after the blood pressure had fallen significantly following intravenous injection. "Chronic" were also paired observations after varying periods of oral therapy.

Both in the acute and chronic studies. In the acute studies, the cardiac indices fell from 0.41 to 1.67 L./min., giving an average percentage fall of 37.3 per cent. After prolonged treatment an average decrease of 25.2 per cent was observed. In all but 1 instance, G. Be., the reduction in cardiac index paralleled the reduction in blood pressure. Since pulse rate did not change markedly, it follows that there was a comparable decrease in stroke volume. In the acute observations, the average reduction was 35 per cent and ranged from 22 to 52 per cent. In chronic studies the average reduction was 15.1 per cent with a range from +8 to -43 per cent.

Calculation of peripheral resistance gave figures averaging 2,553 dynes/cm.² before treatment. After acute blood pressure reduction, the average peripheral resistance was 2,492 dynes/cm² or a fall of 2.4 per cent. In the chronic studies, there was an average rise in peripheral resistance of 4.9 per cent. It will be
noted that only 2 patients in the acute study and 1 in the chronic study (G. Be.) experienced any significant fall in peripheral resistance. The latter was examined on 2 occasions while under therapy with similar findings each time (table 1, fig. 2).

Changes in mean circulation time could be compared in acute studies, but the difference in injection sites in the acute and chronic studies makes comparison questionable. Initial mean circulation times varied from 18 to 38 sec. After treatment with pentolinium bitartrate, the mean circulation time was increased in all but 1 patient, H.v A., and ranged from 21 to 40 sec. (table 1).

Pulmonary blood volumes were compared only in the acute experiments. Initial volumes varied from 1,365 to 2,795 ml. Reduction in blood pressure with pentolinium resulted in a reduction of pulmonary volume from 188 to 750 ml, which gives a percentage reduction of 9.0 to 38 percent. The average reduction was 21.7 percent (table 1).

In studies of total blood volume, no consistent or significant variation was noted under conditions of acute or continued pentolinium treatment.

The patient studied after discontinuing long-term therapy had a rise of 17 percent in mean blood pressure. This was accompanied by a 44 percent rise in cardiac index. There was a 31 percent increase in stroke volume. There was a 15 percent decrease in peripheral resistance as the blood pressure rose.
DISCUSSION

The reductions in cardiac output and stroke volume noted in the sitting position after acute or chronic ganglionic blockade confirm the clinical impression of increased fatigue and weakness associated with this form of blood pressure depression. Failure of cardiac output to improve after long intervals of treatment is also confirmed by clinical experience; the patient who had been under treatment for 14 months noted improved strength when the drug was discontinued and the cardiac output and blood pressure rose. Despite these observations, we believe that pentolinium and other ganglionic-blocking agents perform a useful role in severe hypertension, both by reducing the arterial lesions that may follow sustained arterial hypertension but also by their effects on the heart, which undergoes a great reduction in work load, and on the lungs, which lose blood volume to the systemic circulation, as is shown by the regular reduction in pulmonary blood volume noted in these studies. A shift of 300 ml. of blood from lung to periphery could be very advantageous if pulmonary edema were incipient. Werko also noted reductions in pulmonary blood volume in the recumbent position after ganglionic blockade. We are unable to explain the contrary observations of Gilmore and associates, although they used a different method of calculating pulmonary blood volume.

The reduction in cardiac output in the seated posture appears to account entirely for the decline in blood pressure that is seen acutely or chronically. As stated previously, there are no comparable studies on the effects of chronic administration of ganglionic-blocking agents on cardiac output, and only a few observations of the acute effects of these agents in the orthostatic position. These latter are difficult to compare with our own observations. The studies of Gilmore and associates in 4 patients using the direct Fick procedure showed "no accentuation of the usual reduction in cardiac output after tilting when the patient had been given C-6." Hickam and Pryor, studying the cardiac output of 12 patients with postural hypotensive disease, recorded a reduction in output when they were tilted to 60°, which was usually no greater than that observed in the normal subject. When a large amount of albumin in saline solution was infused, the cardiac output increased and the blood pressure in some cases was maintained after tilting. This suggested "that these large output falls resulted from an inadequate venous return to the heart." It is to be noted that these 2 studies quoted are not strictly comparable to our own, since the patients were not studied in the sitting or tilted position both before and after ablation of neurogenic tone.

In the present study it is difficult to escape the conclusion that ganglionic blockade did not reduce arteriolar tone but acted upon the cardiac output through a reduction in venous return to the heart, as suggested for some of Hickam's cases. This theory would best explain the observations of Restall and Smirk that immersion in water exactly cancels the effect of ganglionic blockade. The increase in tissue pressure so produced would hardly be of sufficient magnitude to reduce the lumen of arterioles, which normally maintain pressures greatly in excess of the pressure in the water bath, but such external pressure would be expected to correct exactly that decrement in peripheral venous pressure gradient brought about by the imposition of the force of gravity, and thus to "set" venous return, blood flow, and cardiac output at a new level. The decline of pulmonary blood volume noted in this study and in that of Werko and associates can be explained on the basis of a peripheral shift of blood as a result of a new balance between pulmonary and peripheral arterial blood pressures.

If this conception of a dynamic change in venous flow rather than a static one can be accepted, other physiologic phenomena can be more easily explained. The normal reduction in cardiac output on standing may be explained as a failure of peripheral venoconstrictors to overcome the increased gravitational load. This change is nearly instantaneous and can be accomplished with minimal peripheral pooling or decrease in central venous pressure. Ganglionic blockade only serves to accentuate this normal tendency. Idiopathic or postsympathe-
tomy postural hypotension would lower blood pressure by a decrease in cardiac output mediated through a failure of normal peripheral venoconstriction as postulated by Hickam and Pryor. 11

Although the studies reported here do not necessarily apply to the effect of ganglionic-blocking agents on the circulation in the recumbent patient, the importance of this subject in assessing “neurogenic” and “humoral” factors in hypertension 13, 14 justifies an attempt to extend the present theory to the action of these agents in the resting recumbent subject. As reviewed by Doyle and Smirk, 14 observations on cardiac output in the recumbent subject are in conflict, but a number of authors did not observe a change in the calculated peripheral arteriolar resistance when the drug was given intravenously to the recumbent hypertensive patient not in cardiac failure. 16-20 Crosley and co-workers 20 demonstrated a consistent decrease in cardiac output and right atrial pressure with no change or an increase in total peripheral resistance when pentolinium was given intravenously to the recumbent hypertensive subject. Their experiments would conform with the observation that, except for the hands and feet, no vascular bed in the hypertensive subject can be demonstrated to have an increased blood flow after ganglionic blockade. 21-23 and while vascular resistance falls in some of these areas, this occurs equally and pari passu with the blood pressure as if the vasodilatation were compensatory to the blood pressure fall rather than the primary factor in causing the reduction in blood pressure.

If we accept the fact that blood pressure reduction, even in recumbency, reflects chiefly a decreased cardiac output, it should be expected that decreased peripheral venous pressures and increased venous pooling should follow ganglionic blockade. Reductions in pressure in an isolated peripheral venous segment have been noted by Duggan, Love, and Lyons, 24 and, even in recumbency, Restall and Smirk 12 have shown that the blood pressure may be partially elevated by immersion in a water bath. 13 While venous pooling has not been demonstrated in the extremities, a considerable sequestration of blood in the liver has been noted by Bradley 25 after hexamethonium. These observations suggest that the major site of action of ganglionic blockade is on venoconstrictor tone, perhaps by reducing the peripheral-to-central venous pressure gradient and thus causing a decrease in cardiac output and systemic blood pressure. This gradient, which maintains venous return to the heart, is reduced still further in the orthostatic position, and is improved by returning to the recumbent posture, by infusion of norepinephrine or angiotonin, which actively constricts peripheral veins, or by increasing tissue pressure with steroids or salt infusions; all procedures that have been claimed to introduce a “humoral factor” into the maintenance of the blood pressure. 13, 14 If neurogenic tone is considered to include particularly peripheral veins and venules, then we should agree with Doyle and Smirk 14 that the over-all blood pressure response to ganglionic blockade is a measure of pre-existing neurogenic tone. Since “neurogenic tone” is usually considered to apply chiefly to the arterioles, which regulate peripheral resistance, we wish to emphasize that ganglionic-blocking agents may also affect blood pressure simply by altering neurogenic venous tone, and thus reduce blood pressure by reducing cardiac output. Such seems to be the mechanism of action in the patient with orthostatic hypotension induced by these agents.

Summary

A method is presented for determining cardiac output with radioactive iodinated serum albumin that permits multiple serial determinations and involves relatively simple apparatus. The intravenous injection of depressor doses of pentolinium bitartrate to hypertensive patients in the sitting position resulted in a decline in cardiac output and no change in total peripheral resistance. Blood was shifted from the pulmonary to the peripheral circulation. Continued effective oral treatment with this agent over a period of 6 to 128 days did not result in any long-term decline in peripheral resistance, the cardiac output in the sitting position remaining depressed over this time interval. When ganglionic blocking agents lower blood pressure in hypertension, they do so primarily
by reducing venomotor tone, decreasing venous return, and lowering cardiac output. Their effect on neurogenic arteriolar tone is minor.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Dr. Alberto Agrest, University of Buenos Aires, Argentina, for his assistance, while a research fellow in the Hypertension Unit, in setting up the procedure for cardiac output.

SUMMARIO IN INTERLINGUA

Es presentate un methodo pro determinar le rendimento cardiac per medio del etiquettage de albumina serial con iodo radioactive. Le methodo permette determinaciones in serie e require un relativamente simple apparatura.

Le injection intravenose de doses depressori de bitartrato de pentolium in patientes hypertensive in position sedente resultava in un declino del rendimento cardiac e in nulle alteration del total resistentia peripheric. Sanguine esseva transferite ab le circulation pulmonar verso le circulation peripheric. Le continue efficace tractamento oral con iste agentes durante periodos de inter 6 e 128 dies non resultava in un declino tardive del resistentia peripheric, durante que le rendimento cardiac in position sedente remaneva de-primite. Quando agentes de bloqueo ganglionic reduce le pression sanguine in hypertension, illos effectua iste resultato primarmente per reducir le tono venomotori, per reducir le retorno venose, e per reducir le rendimento cardiac. Lor effecto super le neurogene tono arteriolar es minime.

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Two patients are described in whom cardiovascular manifestations accompanied metastasizing carcinoid. In 1, a 53-year-old man, diarrhea, “asthma,” flushing attacks, and congestive heart failure accompanied biopsy-proven hepatic metastases whose origin was not identified. In the second patient, a 68-year-old woman, autopsy revealed extensive scarring and deformity of the valves of the heart in the following order of descending severity: pulmonic, tricuspid, mitral, aortic. An unusual feature that was thought to account for involvement of the valves on the left side was patent of the foramen ovale and right-to-left shunt. The presence of the last was attested to by the cyanosis and polycythemia present in life. These circumstances are consonant with the theory that the endocardial changes are produced directly by noxious substance(s) elaborated by the tumor, secreted into the blood stream, and partially destroyed in the lungs. The necessity for the presence of liver metastases suggests that the liver likewise destroys the noxious material. Another circumstance of the second case is the presence of only insignificant liver metastases, but of a huge metastasis to the ovary (which has its venous drainage directly to the vena cava) supports the view that the liver ordinarily destroys the noxious material, in part at least. In general, the behavior observed is that of serotonin, and a direct influence in the production of valvular lesions is suggested. Histologically, there were, in addition to chronic inflammatory changes, lesions with the appearance of platelet thrombi. Observations on a number of circulating patients are not available; the thrombocytosis observed in animals with injection of serotonin and in man with carcinoid tumor may have been present.

McKusick
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