The Effect of Hexamethonium Bromide Upon Coronary Flow, Cardiac Work and Cardiac Efficiency in Normotensive and Renal Hypertensive Dogs

By Charles W. Crumpton, M.D., George G. Rowe, M.D., George O'Brien, Ph.D., and Quillian R. Murphy, Jr., M.D., Ph.D.

Hexamethonium bromide in normotensive and renal hypertensive dogs resulted in significant reductions in arterial blood pressure, cardiac output and cardiac work. The decrease in cardiac output relative to that in blood pressure suggests that the blood pressure reduction was largely due to the decrease in cardiac output. There was a decrease in coronary flow accompanied by an increase in myocardial oxygen extraction of such degree that cardiac oxygen consumption remained unchanged. Since myocardial oxygen consumption remained unchanged despite the decrease in cardiac work the calculated cardiac efficiency was decreased.

Following the demonstration that hexamethonium is an effective autonomic blocking agent, considerable interest has centered on the effects of this drug in lowering blood pressure in hypertensive patients. The purpose of this report is to present the effect of hexamethonium upon coronary flow, cardiac work, and cardiac efficiency in normal and renal hypertensive anesthetized dogs.

METHOD

Dogs weighing 18 to 26 Kg. were given 3 mg. per kilogram morphine sulfate intramuscularly followed in one hour by 10 to 12 mg. per kilogram sodium pentobarbital intravenously. Experimental hypertension was produced by the perinephritis technic of Page. Coronary flow was measured by the nitrous oxide method as applied to the coronary circulation. Goodale-Lubin cardiac catheters (no. 7) were introduced through a small incision into the right external jugular vein and guided under fluoroscopic control into the coronary sinus and right ventricle respectively. An 18 gage needle connected to a short plastic tube was inserted into the femoral artery. The two cardiac catheters and femoral artery tubing were connected to individual manifolds through which blood samples were collected in oiled heparinized syringes. When arterial samples were not being collected, the femoral artery was connected to a damped mercury manometer or Statham strain gage for estimation of arterial blood pressure. The animals were connected to a low resistance flutter valve by an endotracheal tube supplied with an inflatable cuff. A three-way valve was utilized in the inhalation circuit to allow a rapid change from inhalation of room air to the nitrous oxide mixture (15 per cent N₂O, 64 per cent N₂, 21 per cent O₂). Expired air was collected at appropriate intervals in a Tissot spirometer. Lead II of the electrocardiogram was used to note cardiac rate and rhythm.

Observations were begun 60 to 80 minutes after the injection of sodium pentobarbital. Cardiac output determination consisted of a five-minute collection of expired air together with simultaneous blood samples from the coronary sinus, right ventricle, and femoral artery. Expired air was analyzed for oxygen and carbon dioxide content by the method of Scholander. Blood samples were analyzed for oxygen and carbon dioxide content by the manometric method of Van Slyke and Neill. Immediately after collection of expired air inspiration was changed from room air to the nitrous oxide mixture for a period of 10 minutes. Blood samples were obtained simultaneously from the coronary sinus and femoral artery at intervals previously described.

Two sets of observations were made 30 minutes apart on each of 36 normal and 7 renal hypertensive dogs.
CARDIAC EFFECTS OF HEXAMETHONIUM

TABLE 1.—Cardiovascular Effects of Hexamethonium Bromide 30 Minutes after Intravenous Administration (Mean Average Values 16 Dogs, 1 Mg. per Kilogram)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Drug</th>
<th>Mean Difference</th>
<th>S. D. of Individual Difference</th>
<th>S. E. of Individual Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.A.B.P. (mm. Hg)</td>
<td>123</td>
<td>107</td>
<td>-16</td>
<td>12.4</td>
<td>3.10</td>
</tr>
<tr>
<td>Coronary flow (cc./100 Gm./min.)</td>
<td>106</td>
<td>90†</td>
<td>-16</td>
<td>25.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Cardiac O₂ consumption (cc./100 Gm./min.)</td>
<td>11.4</td>
<td>11.6</td>
<td>+0.2</td>
<td>2.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiac output (L./min.)</td>
<td>3.9</td>
<td>2.20*</td>
<td>-0.99</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Cardiac work (Kg.M./min.)</td>
<td>5.40</td>
<td>3.24*</td>
<td>-2.16</td>
<td>1.06</td>
<td>0.27</td>
</tr>
<tr>
<td>Cardiac rate (/min.)</td>
<td>85</td>
<td>142*</td>
<td>+57</td>
<td>21.0</td>
<td>5.28</td>
</tr>
<tr>
<td>Calculated TPR (AU)</td>
<td>3105</td>
<td>4082*</td>
<td>+917</td>
<td>766</td>
<td>192</td>
</tr>
<tr>
<td>Coronary resistance (pressure/flow)</td>
<td>1.21</td>
<td>1.23</td>
<td>+0.02</td>
<td>0.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Δ art. O₂ — cor. sinus O₂ (vol. %)</td>
<td>10.8</td>
<td>12.9*</td>
<td>+2.1</td>
<td>2.2</td>
<td>0.54</td>
</tr>
<tr>
<td>Coronary sinus O₂ (vol. %)</td>
<td>5.6</td>
<td>2.7*</td>
<td>-2.9</td>
<td>1.7</td>
<td>0.43</td>
</tr>
<tr>
<td>Cardiac efficiency (%)</td>
<td>31</td>
<td>19*</td>
<td>-12</td>
<td>6.6</td>
<td>1.65</td>
</tr>
</tbody>
</table>

* p < .01; † p < .02.

The mean average values obtained for 16 normotensive animals during the control period and 30 minutes after intravenous hexamethonium bromide are summarized in table 1. Mean arterial blood pressure fell from 123 to 71 mm. Hg within 1 to 2 minutes following injection and stabilized at a mean of 107 mm. Hg at the time the second flow determination was made. There was a reduction in cardiac work which resulted from a significant decrease in both mean arterial blood pressure and cardiac output. These changes occurred in spite of a sinus tachycardia of 142 beats per minute. Since there was a greater percentage reduction in cardiac output than in arterial blood pressure, the calculated total peripheral resistance increased.

Coronary blood flow decreased from 106 to 90 cc. per 100 Gm. per minute (p < 0.02). Cardiac oxygen consumption did not change following hexamethonium. Apparently this was accomplished by an increase in oxygen extraction from 10.8 to 12.9 volumes per cent (p < 0.01) since coronary sinus oxygen content fell from 5.6 to 2.7 volumes per cent (p < 0.01). Total oxygen consumption was significantly reduced from 120 to 106 cc per minute.

The 10 minutes required by the nitrous oxide method does not permit valid measurement of coronary flow at the time of lowest blood pressure reduction. However, in five dogs coronary flow was measured when the hypotensive action of hexamethonium was most marked, that is, immediately following a single injection. The changes observed in these experiments (table 2) were similar to those observed after blood pressure stabilization (table 1).
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Table 3.—Cardiovascular Effects of Hexamethonium in Normotensive and Renal Hypertensive Dogs. Per Cent Change from Control Observations

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th>Hyper- tensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (%)</td>
<td>Drug (%)</td>
</tr>
<tr>
<td>M.A.B.P. (mm. Hg)</td>
<td>+3</td>
<td>-13*</td>
</tr>
<tr>
<td>Coronary flow (cc./100 Gm./min.)</td>
<td>-8</td>
<td>-15*</td>
</tr>
<tr>
<td>Cardiac O2 consumption (cc./100 Gm./min.)</td>
<td>+4</td>
<td>+2</td>
</tr>
<tr>
<td>Cardiac output (Lit./min.)</td>
<td>-9</td>
<td>-31*</td>
</tr>
<tr>
<td>Cardiac work (Kg.M./min.)</td>
<td>-6</td>
<td>-40*</td>
</tr>
<tr>
<td>Cardiac rate (/min.)</td>
<td>-3</td>
<td>+67*</td>
</tr>
<tr>
<td>Calculated TPR (AU)</td>
<td>+10</td>
<td>+28*</td>
</tr>
<tr>
<td>A art. O2—cor. sinus O2 (vol.)%</td>
<td>+13*</td>
<td>+19*</td>
</tr>
<tr>
<td>Coronary sinus O2 (vol.%)</td>
<td>-14*</td>
<td>-52*</td>
</tr>
</tbody>
</table>

* Denotes statistically significant change.

Results obtained in seven hypertensive dogs were not analyzed statistically due to the small number of animals. Table 3 shows the percentage change from the control observation for comparison with the normotensive group. Following 1 mg. per kilogram hexamethonium, blood pressure fell in the hypertensive dogs an average of 26 per cent. Calculated total peripheral resistance increased 7 per cent. In other respects the changes observed were similar to those of the normal animals.

As an over-all control observations were obtained in 15 normal dogs before and 30 minutes after intravenous injection of 1 cc. physiologic saline solution. Coronary blood flow decreased 8 per cent (p < 0.2) as compared with a statistically significant reduction 15 per cent (p < 0.02) one-half hour following hexamethonium. Except for a 13 per cent increase in myocardial oxygen extraction and 15 per cent decrease in coronary sinus oxygen at the time of the second flow determination, there were no significant differences in the mean averages of the two determinations.

DISCUSSION

It is well documented that hexamethonium in sufficient dosage is capable of producing a marked and sustained blood pressure reduction, in these studies, however, interest was not directed toward the cardiovascular adjustments during a period of marked hypotension but rather toward such adjustments as occur during a period of moderate blood pressure reduction.

The 31 per cent reduction in cardiac output associated with a 13 per cent fall in blood pressure resulted in a significant increase in calculated total peripheral resistance. These findings are contrary to what would be expected following a potent ganglionic blocking agent and suggest that the blood pressure reduction one-half hour after hexamethonium is the result of a reduced cardiac output. Moyer7 gave 5 mg. per kilogram hexamethonium intravenously and measured cardiac output by the pulse contour method. He reported an initial transitory increase in cardiac output and a fall in total peripheral resistance immediately following hexamethonium. At the end of 30 minutes the total peripheral resistance had returned almost to the control value while the blood pressure was still below its original level, indicating that heart output had been reduced. We observed a similar relationship between cardiac output and total peripheral resistance one-half hour after a smaller dose of hexamethonium and a more moderate blood pressure fall. Our studies do not permit conclusions as to whether the reduction in output is due entirely to a decrease in venous return or is associated with a specific action of the drug upon the myocardium.

The effect of cardiac work on coronary flow and myocardial oxygen utilization has been investigated under various experimental conditions. Gregg and Shipley8,9 observed that augmented work resulted in an increased coronary flow and oxygen utilization. Eckenhoff and co-workers10 reported reductions in work, flow, and oxygen consumption during hypotension. These investigators pointed out, however, that the oxygen content of coronary sinus blood in their experiments was so low in the control period that a decrease in the volume of blood flow could not be effectively compensated by any increase in the arterial-coronary sinus oxygen difference.

Our studies demonstrated that the decreased
cardiac work following hexamethonium was not associated with any significant change in myocardial oxygen consumption. This resulted in a reduction in calculated cardiac efficiency. Contrary to the experiments of Eckenhoff, the control coronary sinus oxygen content was sufficiently high to allow for a greater oxygen extraction. Thus, the myocardial oxygen consumption remained unchanged at the time of reduced coronary flow.

These observations suggest that a satisfactory metabolic adjustment may have occurred following a moderate reduction in blood pressure after intravenous hexamethonium. Since these experiments were performed on dogs without objective evidence of myocardial damage, one cannot state whether such adjustments would take place in an abnormal myocardium.

SUMMARY AND CONCLUSIONS

In 16 normotensive dogs, studies were made, before and one-half hour after hexamethonium bromide (1 mg. per kilogram) intravenously. Within 1 to 2 minutes after hexamethonium blood pressure fell from a mean average of 123 to 71 mm. Hg and stabilized at 107 mm. Hg at the time the second set of observations was obtained. Heart rate increased from a mean average of 85 to 142 beats per minute. Cardiac work was significantly decreased as a result of a 31 per cent reduction in cardiac output and 13 per cent reduction in mean arterial blood pressure. Since the percentage reduction in cardiac output was greater than that of the mean arterial blood pressure, the calculated total peripheral resistance (TPR) was observed to increase. This would suggest that under the conditions of these studies the blood pressure reduction one-half hour after hexamethonium was the result of a reduced cardiac output.

Coronary blood flow fell from 106 to 90 cc. per 100 Gm. per minute (p < 0.02). Myocardial oxygen consumption did not change in spite of a significant reduction in cardiac work. This resulted in a decrease in calculated cardiac efficiency. A significant reduction in total oxygen consumption was observed following hexamethonium.

Except for a greater blood pressure reduction (26 per cent) and less increase in calculated total peripheral resistance (7 per cent) the changes observed in seven renal hypertensive dogs 30 minutes after hexamethonium (1 mg. per kilogram intravenously) were similar to those of the normal animal.

Measurements obtained in five normotensive dogs during the period of greatest blood pressure change gave results similar to those obtained after blood pressure stabilization.

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REFERENCES

1 PATON, W. D. M., and ZAIMIS, E. J.: Clinical poten-
tialities of certain bisquaternary salts caus-
3 ECKENHOFF, J. E., HAFKENSCHIEL, J. H., HARMEL, M. H., GOODALE, W. T., LUBIN, M., BING, R. J., and KETY, S. S.: Measurement of coro-
4 GOODALE, W. T., LUBIN, M., ECKENHOFF, J. E., HAFKENSCHIEL, J. H., and BANFIELD, W. G., Jr.: Coronary sinus catheterization for study-
ing coronary blood flow and myocardial me-
6 HERKMAN, G. R.: Experimental heart disease. I. Methods of dividing hearts; with sectional and proportional weights and ratios for two hun-
8 Gregg, D. E., and Shipley, R. E.: Augmentation of left coronary inflow with elevation of left ventricular pressure and observations on the mechanism for increased coronary inflow with increased cardiac load. Am. J. Physiol. 142: 44, 1944.


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