THE HEMODYNAMIC EFFECTS OF HEXAMETHONIUM BROMIDE IN THE DOG, WITH SPECIAL REFERENCE TO "SPLANCHNIC POOLING" ¹

By B. COMBES,² J. R. K. PREEDY,³ H. O. WHEELER,⁴ R. M. HAYS,⁵ and S. E. BRADLEY

(From the Department of Medicine, Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, New York, N. Y.)

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Arterial hypotension develops during the action of hexamethonium in man and the dog because cardiac output decreases in association with a fall in peripheral and central venous pressures (1-5). The drug does induce vasodilation in the skin, muscle, and brain; but vasoconstriction occurs in other areas so that the net total peripheral vascular resistance remains unchanged or actually rises. Since there is little evidence of myocardial dysfunction, diminished venous return of blood to the heart must be implicated as the cause for the fall in output. This response may be attributed 1) to a slight but widespread change in venous tone that results in a generalized retardation in venous flow, 2) to local "pooling" of blood in venous reservoirs or 3) to both. The increased distensibility of the digital veins in human subjects following intravenous administration of hexamethonium (6) gives some support to the first possibility, but the digital vasculature is highly specialized and may not faithfully reflect changes elsewhere. Moreover, a larger quantity of blood is held in other parts of the venous system where even limited changes in tone might be expected to have a correspondingly greater effect upon venous pressure and return. The splanchnic venous bed is particularly important in this respect because it accommodates as much as 20 per cent of the total blood volume at rest in both man and dog. Although hexamethonium does not seem to affect splanchnic vascular tone since splanchnic blood flow falls in proportion to the fall in arterial pressure (1, 7), it is possible that the splanchnic veins are influenced independently of arterioles so that venous distensibility and capacity are altered in the absence of a change in arteriolar resistance. To test this possibility, splanchnic blood flow and splanchnic blood volume were measured by indirect methods in dogs during the fall in cardiac output and arterial pressure produced by hexamethonium.

METHODS

Thirteen mongrel dogs (10.2 to 17.7 Kg.), five of which had been splenectomized at least two weeks previously, were studied under Nembutal[®] anesthesia (30 mg. per Kg.). Catheters were inserted by way of an internal jugular vein into a left hepatic vein and the right heart and left in place throughout the study. Both femoral arteries were cannulated, one for pressure measurement and the other for blood sampling. After control determinations of mean arterial blood pressure, cardiac output, splanchnic blood flow, total blood volume and circulating splanchnic blood volume were obtained, a single dose of hexamethonium bromide (0.6 to 0.8 mg. hexamethonium ion per Kg.) was given intravenously. All measurements, with the exception of total blood volume, were repeated following stabilization of the arterial pressure at a hypotensive level (60 to 95 millimeters of mercury). The cardiac output was determined approximately 15 to 20 minutes, and splanchnic blood flow and splanchnic blood volume 20 to 30 minutes after administration of the drug.

Mean arterial blood pressure was either measured directly with a mercury manometer or determined by planimetric integration of pulse wave tracings recorded photographically from a Statham pressure transducer. Cardiac output was measured by the direct Fick method on the basis of values for oxygen consumption (Benedict-Roth spirometer) and oxygen contents [Van Slyke and Neill (8)] of femoral arterial and right ventricular blood sampled simultaneously. Splanchnic blood flow (ESBF) was estimated by Bromsulfalein (BSP) extraction and clearance (9). Plasma volume was measured by dilution of I¹⁸¹-labelled human serum albumin (IHSA) and total blood volume calculated using the arterial hematocrit.

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² Post-doctoral Research Fellow, U. S. Public Health Service 1953–1955. Present address: Medical Unit, University College Hospital, London, England.

⁸ Visiting Fellow in Medicine, Fulbright Travel Award 1953–1954. Present address: Medical Unit, The London Hospital, London, England.

⁴ Life Insurance Medical Research Fund Fellow.

⁵ Present address : Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts.

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Effect of hexamethonium on arterial pressure, cardiac output, total peripheral resistance, estimated splanchnic blood flow, splanchnic vascular resistance and circulating splanchnic blood notume in inter and splanchnic blood notumes in interformized doos *

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|------------|------------|------------------------|----------------------|-----------------|---|------------------------------|---------------------|---------------|-----------------------------|--------------------|----------------------|----------------------------|-------------------|----------------------|
| Dog No. | Wt. Kg. | Ca dose mg. ion | Hct % | MAP mm. Hg | O ₃ con- sumption ml./min. | A – MV Os diff. vol. % | CO L./min. | TPR A.U. | ESBF ml./10 Kg./ min. | SVR A.U. | SMCT sec. | SBV ml./10 Kg./ min. | TBV ml./10 Kg. | SBV/TBV X100 % |
| | | | | | | | A. Intact | | | | | | | |
| - | 13.2 | Control | 39.5 36.5 | 140 78 | 126 | | | | 373 276 | 17.8 12 8 | 30.2 60.0 | 188 276 | 1,233 | 15.2 |
| 2 | 16.4 | Control | 36.5 | 122 | 583 | 5.6 | 1.58 | 4.6 | 291 | 15.3 | 26.4 | 128 | 864 | 14.9 |
| 3 | 15.5 | Control | 37.0 | 117 | 322 | ø.0 | 5 . | 4.0 | 473 473 | 9.6 9.6 | 52.8 57.8 | 416 | 1,450 | 28.7 |
| 4 | 11.8 | Lo.U Control | 46.5 | 137 | 888 | 2.3 | 2.93 | 2.8 | 519 | 13.4 | 14.6 | 410 126 | 1,362 | 0.0 0.0 0.0 |
| ъ | 15.9 | Control | 45.5 37.5 | 113 | 80 <u>1</u> 8 | 0.00 0.00 0.00 | 2.65 | 2.6 | 608 470 227 | 9.1.0 | 31.6 | 247 | 1,654 | 15.0 |
| 9 | 14.1 | Lo.U Control | 52.0 55.0 | 114 | 152 | 11.1 | 1.37 | 2.0 | 383 | 12.7 | 33.2 33.2 | 212 | 1,167 | 18.2 |
| 7 | 15.6 | Lontrol | 55.0 44.5 | 0 <u>1</u> | 38; | 10.5T 6.3 | | 4.7. 0.7.0 | 209 | 21.9 21.9 | 82.0 42.3 | 147 | 1,665 | 20.0 8.0 9.0 |
| ø | 13.6 | Lou Control 10.0 | 44.5 39.5 44.0 | 08 129 68 | 43 62 8 | 5.3 5.3 | 1.19 1.54 .81 | 5.0 5.0 | 204 685 386 | 12.0 8.3 7.8 | 08.2 18.4 51.4 | 209 209 331 | 670 | 13.9 21.5 34.1 |
| | | | | | | B. | Splenectom | ized | | | | | | |
| 6 | 10.7 | Control | 51.5 42.5 | 83 10 | 67 58 | 3.9 | 1.72 | 2.9 0.8 | 540 | 8.6 | 20.0 | 179 | 1,187 | 15.1 |
| 01 | 17 5 | ontrol | 2 12 | 61 | | 0 6 | 1 3.4 | и | 232 | 14.7 | 76.0 37 8 | 294 203 | 1 160 | 24.7 17.5 |
| 2 | C.21 | 10.0 | 50.5 | 62 | 88 | 3.9 | 1.58 | 3.6 | 290 | 15.7 | 62.4 | 304 | 1,100 | 26.2 |
| 11 | 11.3 | Control | 42.0 41 0 | 84 84 | 47 | 3.6 | 2.04 | 2.5 2.5 | 476 401 | 9.4 7.4 | 41.5 44.5 | . 329 364 | 1,052 | 31.3 24 6 |
| 12 | 10.2 | Control | 32.5 | 825 | 51 | 5.7 | 68. 68. | 0.1.0 | 347 | 15.4 | 16.7 | 97 256 | 1,013 | 9.6 2 2 |
| 13 | 17.7 | Control 10.0 | 48.0 46.5 | 115 | 112 81 | 10.41 3.5 3.3 | 3.18 2.44 | 2.2 | 678 678 412 | 5.8 5.8 6.3 | 27.6 55.3 | 312 312 380 | 895 | 34.5 34.8 42.4 |
| Mean ± | : S.D. | Control | 43.1 14 6 | 116 | - 88 88 198 | 4.8 | 1.96 1.73 | 3.9 +1.3 | 447 + 140 | 12.6 | 29.9 + 11 | 215 01 | | 18.5 |
| | | ບັ | 王 41.3 土6.9 | ±17 ±12 | ±13 ±13 | ±2.5 €.1 | 王 1.38 土0.69 | ±1.7 ±1.7 | 王 343 土113 | 10.9 10.9 | 59.3 土18 | 317 317 土76 | | 王 27.3 王8.8 |
| Mean D | ifference | | -1.8 | -39 | - 14 | +1.3 | -0.58 | -0.3 | - 104 | -1.7 | +29.4 | +102 | | +8.8 |
| 4 | | | <0.02 | <0.01 | <0.05 | <0.05 | <0.01 | >0.5 | <0.01 | >0.1 | <0.01 | <0.01 | | <0.01 |
| | | | | | | | | | | | | | | |

* Abbreviations: C₆-Hexamethonium bromide; Hct-Arterial hematocrit; MAP-Mean arterial pressure; A-MV O₂ diff.-Arterial-mixed venous oxygen difference; CO-Cardiac output; TPR-Total peripheral resistance; A.U.-Arbitrary unit = MAP/CO (ml. per sec.); ESBF-Estimated splanchnic blood flow; SVR-Splanchnic vascular resistance; SMCT-Splanchnic mean circulation time; SBV-Circulating splanchnic blood volume; TBV-Total blood volume; S.D. = Standard Deviation.

S.D. = Standard Deviation.
A The unusually high values for arterial-mixed venous oxygen difference and low values for cardiac output in these dogs are possibly attributable to circulatory inadequacy arising from inapparent infection. Elimination of these figures does not affect the results and does not seem justifiable in any case.

Circulating splanchnic blood volume was determined by the regional dilution technique (10). After rapid injection of approximately 10 to 20 microcuries of IHSA into an external jugular vein, samples of blood were withdrawn simultaneously from the femoral artery and hepatic vein, three times in succession, the first at a slow constant rate of 1 ml. per 30 seconds over a period of two minutes, the second and third at a rate of 2 ml. per 30 seconds during two succeeding 30-second intervals. Approximately 75 ml. of blood was removed from each animal during the entire study. Aliquots of plasma (0.5 ml.) were pipetted onto aluminum planchettes and dried under an infra-red lamp. A commercial detergent (Haemosol[®]) was used to insure even spreading and to prevent sublimation of iodine. Radioactivity was assayed by means of a Geiger-Muller end-window tube and conventional scaler. Splanchnic blood volume was calculated by dividing the amount of IHSA activity dispersed in the splanchnic vasculature at equilibrium by the equilibrium concentration as follows:

$$\text{SBV} = \frac{(\overline{A} - \overline{V}) \cdot t}{[\text{Eq}]} \times \text{ESPF} \times \frac{1}{1 - \text{Hct.}}$$

SBV = Splanchnic blood volume (ml.)

- A = Mean arterial plasma activity during equilibration (counts per ml.)
- $\overline{\mathbf{V}}$ = Mean hepatic venous plasma activity during equilibration (counts per ml.)

t = Equilibration time in seconds

ESPF = Splanchnic plasma flow (ml. per sec.)

[Eq] = Plasma activity at equilibrium (counts per ml.) Hct. = Arterial hematocrit

When equilibrium (or agreement between radioactivity in the arterial and hepatic venous samples within the analytical error) was achieved in the second sampling period, mean arterial activity was calculated as follows: $\overline{A} = (A_1 \times t_1) + (A_2 \times t_2) \div t_1 + t_2$ where A_1 and A_2 are the activities of the first and second samples, respectively, and t_1 and t_2 are the respective time intervals

TABLE II

Effect of hexamethonium on mean arterial, splenic venous, wedged hepatic venous and right auricular pressures in dogs *

| | the second | | | | |
|------------|---|---------------|---|---|--|
| Dog No. | | MAP mm. Hg | Splenic venous pressure mm. Hg | Wedged hepatic venous pressure mm. Hg | Right auricular pressure mm. Hg |
| 14 | Control | 127 | 8.0 | 8.9 | 1.3 |
| | C6 | 85 | 8.5 | 7.9 | 2.0 |
| 15 | Control | 128 | 12.4 | 8.5 | 1.6 |
| | C6 | 92 | 7.9 | 7.7 | 1.7 |
| 16 | Control | 120 | 11.8 | 8.4 | 3.2 |
| | C6 | 90 | 9.4 | 8.3 | 3.4 |
| 17 | Control | 145 | 11.6 | 13.3 | -0.4 |
| | C6 | 109 | 11.8 | 12.6 | -4.6 |

* MAP-Mean Arterial Pressure ; C₆-Following administration of hexamethonium bromide. during which blood was withdrawn. With equilibrium in the third period, the values for A and t for that sample were also incorporated in the calculations. The values for mean hepatic venous activity (\overline{V}) were computed similarly. Mean splanchnic circulation time was calculated from the values for SBV and ESPF. In four additional anesthetized dogs (9.1 to 15.9 Kg.) pressure tracings (Statham pressure transducer) were obtained successively (within 30 seconds) from the right atrium, an occluded hepatic vein (11, 12), the portal vein, and femoral artery, before and after administration of hexamethonium (0.6 to 0.8 mg. ion per Kg.). Portal venous pressures were measured by means of a polyethylene catheter passed after laparotomy through one of the splenic vein radicles approximately 10 cm. towards the portal vein. All values for venous pressure were measured from a zero reference point located halfway between the dog's back and xiphoid process.

RESULTS

Comparison of the results obtained in splenectomized and intact dogs failed to show statistically significant differences with the exception of the control mean arterial blood pressure which was significantly lower on the average in the splenectomized animals (102 mm. Hg) (p = 0.02) than in the intact dogs (125 mm. Hg). Consequently, the data for all the animals have been combined, and the mean figures, differences between means, and significance of the differences for the group as a whole are presented in Table I.

Arterial and venous pressures

The values for mean arterial blood pressures (MAP) presented in Table I are those obtained at or close to the time of measurement of splanchnic blood flow and cardiac output. The pressures were identical at the time of both measurements throughout each study, save in Dog 9, in which the value was 61 mm. Hg during the determination of splanchnic blood flow and 10 mm. Hg during the measurement of cardiac output following administration of hexamethonium. Mean arterial pressure fell in all dogs by 39 mm. Hg on the average (p < 0.01) or 34 per cent. Right atrial, wedged hepatic venous and splenic (or portal) venous pressures did not change significantly (Table II—four animals only).

Cardiac output (CO—Table I)

Cardiac output fell in the 11 dogs in which the measurement could be made. The fall was associated with a decrease in total oxygen consumption (by 14 ml. per min. on the average, p < 0.05) and an increase in arteriovenous oxygen difference (by 1.3 ml. per cent on the average, p < 0.05). The average decrease of 0.58 liters per minute (or 30 per cent) was statistically significant (p < 0.01).

Total peripheral resistance (TPR—Table I)

Total peripheral resistance was calculated in arbitrary units (A. U.) by dividing the mean arterial blood pressure by the cardiac output in ml. per second. Total peripheral resistance did not change on the average (p > 0.5) since cardiac output and mean arterial blood pressure decreased to approximately the same extent. It is possible that the marked reduction in TPR which was observed in Dog 9 may be accounted for at least in part by the failure to obtain a value for mean arterial pressure at precisely the time of the measurement of cardiac output.

Estimated splanchnic blood flow and resistance (ESBF and SVR—Table I)

Splanchnic blood flow decreased in 10 dogs, remained unchanged in one (Dog 7), and rose in two (Dogs 4 and 11). The average decrease in ESBF per 10 Kg. body weight was 104 ml. per min., a significant reduction (p < 0.01). The splanchnic vascular resistance (SVR—Table I) was computed in arbitrary units (A. U.) by dividing the mean arterial pressure by the splanchnic blood flow (ml. per second). Splanchnic resistance decreased in 7 dogs (Dogs 1, 2, 4, 6, 7, 10 and 11), increased in 2 (Dogs 9 and 12) and remained unchanged in 4 (Dogs 3, 5, 8 and 13). The average reduction in resistance (1.7 A. U.) was not statistically significant (p > 0.1).

Splanchnic blood volume (SBV—Table I)

Splanchnic blood volume averaged 215 ml. per 10 Kg. body weight during the control periods, amounting to 18.5 per cent of the total blood volume (SBV/TBV—Table I). After hexamethonium, SBV increased in 12 dogs and remained unchanged in one (Dog 3). The average increment of 102 ml. per 10 Kg. body weight (48 per cent) was highly significant (p < 0.01). This change was reflected in an increase in the mean splanchnic circulation time (SMCT—Table I) from 29.9 seconds on the average during the control periods to 59.3 seconds following hexamethonium (p < 0.01). The tendency for the hematocrit to fall (Hct.—Table I) could be explained largely on the basis of the withdrawal of blood samples, and it was therefore assumed that total blood volume remained unchanged. On this assumption, the splanchnic vasculature appeared to contain 27.3 per cent of the blood volume during the hypotensive phase.

DISCUSSION

Autonomic blockade following the intravenous administration of hexamethonium produced a fall in blood pressure in dogs that could be ascribed solely to a reduction in cardiac output, in agreement with the results of other workers (1-4). The splanchnic blood flow tended to decrease in proportion to arterial pressure, whereas circulating splanchnic blood volume appeared to rise. The seemingly paradoxical expansion of the splanchnic bed to accommodate a larger volume of blood without significant simultaneous vasodilatation to permit a relatively larger minute flow could be construed as evidence that hexamethonium reduces splanchnic venous tone without affecting the arterioles. Retarded venous return as a result of "pooling" in the splanchnic reservoir-and presumably also in veins elsewhere in the bodycould therefore play an independent role in reducing cardiac output and arterial pressure. Further analysis of the data, however, does not sustain the validity of these inferences nor of the conclusion to which they tend-that the major site of action of hexamethonium lies upon the venous side of the circulation.

As a matter of fact, interference with arteriolar activity by hexamethonium is evident in the absence of the usual change (13) in the peripheral vascular resistance during the development of arterial hypotension. The tendency for maintenance of arteriolar cross-section by so-called "basal tone" (14) in vascular beds that have been completely denervated by surgical methods may account for the apparent absence of peripheral arteriolar vasodilation. The difference between the arteriolar and venous responses may actually reflect differences in the distending forces exerted by intraluminal pressures which are inversely related to diameter and are consequently much more powerful in the veins than in the arterioles and capillaries. In this view, the splanchnic arterioles and veins are more or less equally affected by hexamethonium; but in the latter the "basal tone" [as defined by Folkow (14)] is not sufficient to resist distention.

The anatomic evidence (15) suggests that the hepatic and portal venous systems contain the bulk of the circulating blood in the splanchnic bed. If the splanchnic vascular reservoir simply serves as a passive elastic receptacle, its volume would be a function of the distending pressure The fact that SBV increased without alone. change (or with a fall) in the portal venous pressure seems to point to an active role of the venous musculature in determining capacity. Splanchnic blood flow and splanchnic venous pressures decrease similarly in dogs following hemorrhage, but with a reduction, rather than an increase, in circulating splanchnic blood volume (16). The quantity of blood within the splanchnic vasculature therefore appears to vary independently of local pressure differences and blood flow. It seems reasonable to conclude that change in capacity is determined largely by an active dimensional change presumably arising from contraction or relaxation of the smooth muscles in the walls of hepatic and portal venous radicles under the control of the autonomic nervous system.

Estimation of the splanchnic blood volume by the regional dilution technique requires the assumption that I¹³¹-labelled human serum albumin is evenly dispersed throughout the bed during an equilibration period of a minute or less. The tracer has little time to find its way into blood not actively a part of the circulating volume and the blood in the splenic pulp is thus not readily accessible to measurement. The change observed following administration of hexamethonium was therefore the same in intact and splenectomized animals.

Owing to the uncertainties regarding the relationships between venous and atrial pressures and cardiac output, it is difficult to evaluate the cardiac effect of hexamethonium or to define with precision the part played by "splanchnic pooling." Unfortunately, the methods currently available are too crude to permit quantitative appraisal of the course of events during the brief interval required for circulatory adjustment. When measurements could be made, a *quasi* steady-state had developed in which cardiac output was persistently depressed in association with a right atrial pressure which had apparently been stabilized at the control level. Changes in pressure too small for measurement may have been implicated as the basis for the continued reduction in output, but the possibility that hexamethonium actually interfered with cardiac function cannot be eliminated.

SUMMARY

The systemic and splanchnic hemodynamic effects of hexamethonium (0.6 to 0.8 mg. hexamethonium ion per Kg. body weight) were studied in thirteen anesthetized dogs—in five at least two weeks following splenectomy. Cardiac output was measured in 11 dogs by the direct Fick method, splanchnic blood flow by the Bromsulfalein method, and the circulating splanchnic blood volume by the regional dilution technique. Femoral arterial, right atrial, wedged hepatic venous, and portal venous pressures were measured directly in four animals.

Arterial pressure decreased in all the animals, by 39 mm. Hg on the average; whereas atrial, hepatic venous, and portal venous pressures did not change. Cardiac output fell, by 30 per cent on the average, to approximately the same extent as the arterial pressure. Estimated splanchnic blood flow decreased in 10 dogs, remained unchanged in one and rose in two; on the average falling significantly (p < 0.01) by 104 ml. per min. per Kg. Splanchnic vascular resistance was not significantly affected on the average, but the circulating splanchnic blood volume increased in twelve dogs and remained unchanged in one, rising on the average by 102 ml. per 10 Kg. body weight or 48 per cent.

These findings may be interpreted as evidence for the view that autonomic blockade by hexamethonium causes a fall in arterial pressure by simultaneously reducing cardiac output and interfering with compensatory peripheral arteriolar adjustments. The fall in cardiac output may be attributed to a decrease in venous return as a result, in part at least, of "pooling" in the splanchnic vasculature secondary to diminished venous "tone." Autonomic blockade therefore appears to affect both arteriolar and venous activity.

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