# Hemodynamics in Hemorrhage: Influences of Sympathetic Nerves and Pentobarbital Anesthesia (35244)

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In experiments reported previously (1), chronically splenectomized dogs and sympathectomized dogs were anesthetized with sodium pentobarbital and subjected to various degrees of hemorrhage. The hemodynamic changes (pressure–flow–volume relations) were compared between these two groups of anesthetized dogs for an evaluation of the role of posthemorrhage sympathetic activity. Since general anesthesia is known to exert profound circulatory and autonomic influences in normal states (2) and in shock (3), such studies should also be performed in the unanesthetized state. Although cardiac output and arterial pressure have been measured in unanesthetized dogs subjected to hemorrhagic shock (4), there is a lack of information on the relation between these parameters and blood volume reduction in sub-shocking hemorrhage. In the present experiments, such pressure–flow–volume relations were studied in unanesthetized splenectomized dogs. A comparison on these data with those previously obtained on unanesthetized, sympathectomized-splenectomized dogs (5) permits an analysis of the role of the sympathetic nervous system in the absence of general anesthesia.

*Methods.* Healthy mongrel dogs were board-trained and splenectomized at least 1 month before the hemorrhage experiment, which was performed in the postabsorptive state without the use of any general anesthesia. The femoral region was exposed under local anesthesia (lidocaine) and the femoral artery was cannulated. A catheter was introduced into the right ventricle via the femoral vein. The cardiac output was determined by the dye dilution technique using indocyanine green (6). In some experiments cardiac output was simultaneously measured with the direct Fick method, and there was no significant difference between the results. Plasma volume and cell volume were determined with the use of T-1824 and RBC-$^{51}$Cr respectively, and the sum gave the blood volume (7). Hematocrit values were determined in Wintrobe tubes centrifuged at 1500*g* for 30 min and corrected for plasma trapping (7). The plasma protein concentration was determined by the refractometric method (8). The various measurements were made in the control period and at intervals following a single hemorrhage which varied from 3 to 59% of the control blood volume in different experiments.

*Results.* The control data on the unanesthetized, splenectomized dogs (referred to as normal dogs in this paper) are given in Table I.

Following the removal of more than 20% of the control blood volume, the arterial pressure and cardiac output decreased sharply (Fig. 1). In approximately 1 hr, however, these measurements gradually increased to reach new steady levels which were below

TABLE I. Control Hemodynamic Data in 22 Unanesthetized Dogs.[a]

| | |
|---|---|
| Body wt (kg) | 11.2 ± 0.4 |
| Total blood vol (ml/10 kg) | 799 ± 26 |
| Hematocrit (%) | 40.6 ± 0.8 |
| Plasma protein conc (g/100 ml) | 6.10 ± 0.14 |
| Mean arterial pressure (mm Hg) | 136 ± 2 |
| Cardiac output (liters/min/10 kg) | 1.92 ± 0.13 |
| Total peripheral resistance (PRU—10 kg) | 4.7 ± 0.3 |
| Heart rate (per min) | 90 ± 4 |
| Stroke vol (ml/10 kg) | 23.4 ± 2.0 |

[a] Values given are means ± SEM.

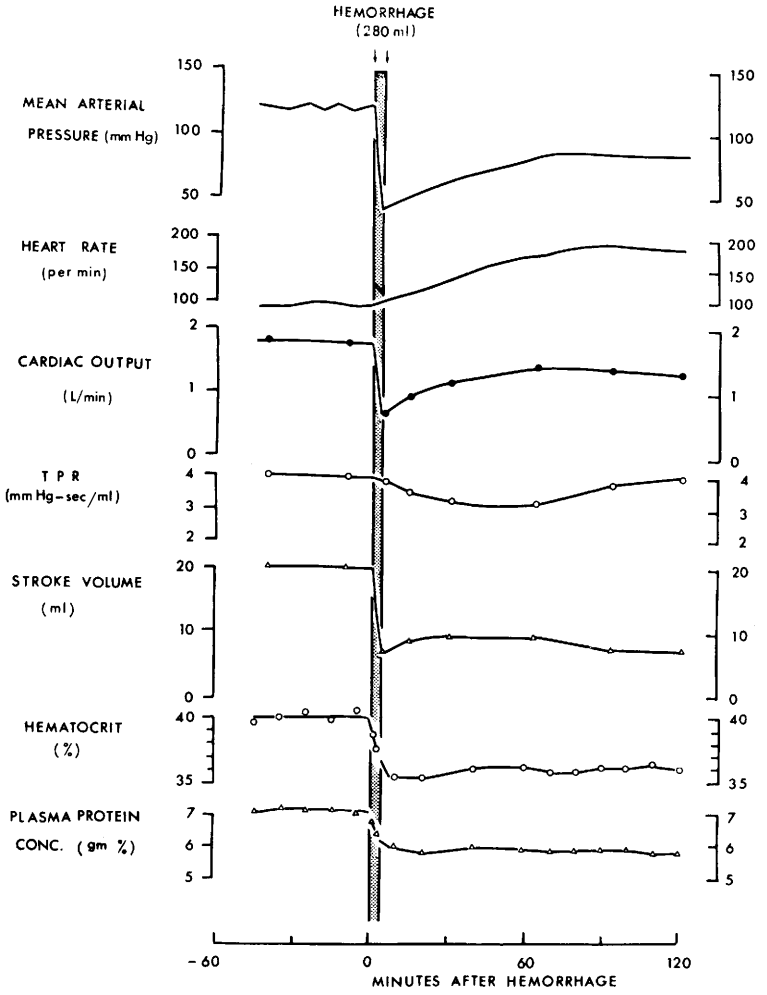


FIG. 1. Time course of hemodynamic changes in an unanesthetized splenectomized dog after the removal of 23% of blood volume.

control but higher than the early posthemorrhage values. At the same time, the heart rate also increased to reach a steady level. In the analysis to follow, the measurements in the steady state (*i.e.*, 1–2 hr after hemorrhage) are used.

The posthemorrhage measurements on circulatory functions are calculated as percentage of control values and tabulated in Table II. The posthemorrhage blood volume was generally greater than that expected from the percentage bled. The volume of transcapillary fluid replacement, represented by the difference between the measured and expected posthemorrhage blood volume, tended to become greater as the percentage of hemorrhage increased. This is also reflected in the decreases in hematocrit and plasma protein concentrations (Table II).

When the posthemorrhage blood volume (measured) was reduced by more than 10%, there was a progressive decrease in arterial pressure (Fig. 2). The regression equation between mean arterial pressure (MAP, % of control) and volume reduction ($V_r$, as percent of prehemorrhage blood volume) is:

$$\text{MAP} = 114 - 1.27\,V_r,$$

with a standard error of estimate of 10.8. The coefficient of correlation is 0.853 ($p<0.001$). The cardiac output decreases almost linearly

TABLE II. Effects of Hemorrhage on the Circulation of Unanesthetized Dogs.[a]

| Expt. no. | % BV bled | % of control value | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | BV | H | PP | MAP | CO | HR | TPR | SV |
| 1 | 3 | 98 | 96 | 94 | 94 | 93 | 100 | 101 | 93 |
| 2 | 5 | 95 | 101 | 99 | 94 | 81 | 93 | 116 | 87 |
| 3 | 8 | 94 | 100 | 100 | 95 | 80 | 93 | 121 | 86 |
| 4 | 9 | 94 | 98 | 94 | 96 | 96 | 108 | 100 | 89 |
| 5 | 12 | 93 | 93 | 99 | 102 | 103 | 93 | 99 | 111 |
| 6 | 16 | 84 | 97 | 99 | 94 | 75 | 120 | 127 | 58 |
| 7 | 18 | 84 | 96 | 98 | 79 | 73 | 200 | 108 | 37 |
| 8 | 23 | 86 | 82 | 79 | 88 | 89 | 180 | 99 | 49 |
| 9 | 26 | 84 | 92 | 92 | 99 | 75 | 136 | 133 | 55 |
| 10 | 28 | 84 | 89 | 86 | 83 | 64 | 148 | 133 | 32 |
| 11 | 28 | 82 | 91 | 82 | 70 | 76 | 194 | 93 | 39 |
| 12 | 29 | 74 | 89 | 92 | 64 | 58 | 200 | 110 | 29 |
| 13 | 33 | 78 | 90 | 90 | 90 | 73 | 132 | 123 | 55 |
| 14 | 40 | 68 | 88 | 84 | 62 | 62 | 326 | 100 | 19 |
| 15 | 43 | 66 | 84 | 89 | 49 | 46 | 235 | 107 | 20 |
| 16 | 44 | 70 | 71 | 76 | 58 | 57 | 246 | 102 | 23 |
| 17 | 45 | 65 | 83 | 88 | 60 | 36 | 310 | 167 | 12 |
| 18 | 46 | 68 | 80 | 74 | 52 | 32 | 246 | 165 | 13 |
| 19 | 47 | 61 | 76 | 79 | 68 | 50 | 234 | 138 | 21 |
| 20 | 55 | 59 | 72 | 76 | 29 | 28 | 209 | 102 | 13 |
| 21 | 58 | 60 | 72 | 73 | 58 | 46 | 172 | 126 | 27 |
| 22 | 59 | 60 | 61 | 74 | 33 | 43 | 210 | 77 | 20 |

[a] BV, total blood volume; H, hematocrit; PP, plasma protein concentration; MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; TPR, total peripheral resistance; SV, stroke volume.

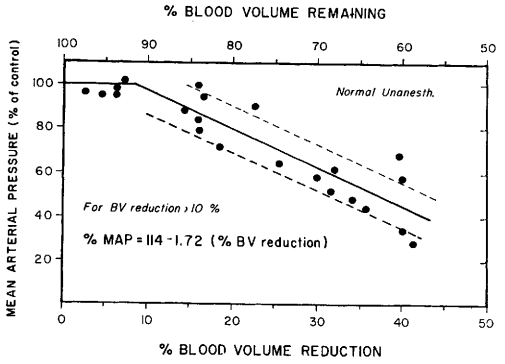


FIG. 2. Relationship between arterial pressure and blood volume in unanesthetized splenectomized dogs with intact sympathetics: (--) standard errors of estimate for the regression line.

with increasing degrees of blood loss (Fig. 3). The data can be fitted by the regression equation:

$$CO = 99 - 1.50\,V_r$$

*i.e.*, the cardiac output (CO, % of control) decreases by 1.5% for each 1.0% reduction in blood volume. The standard error of estimate is 9.0 and the coefficient of correlation is 0.913 ($p<0.001$). The total peripheral resis-

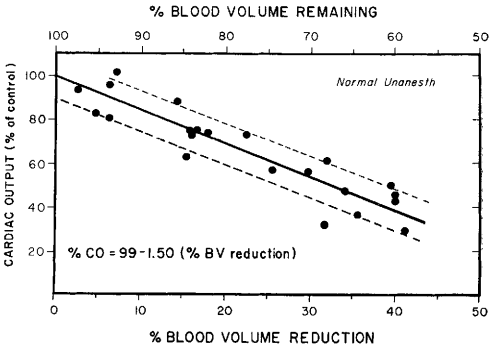


FIG. 3. Relationship between cardiac output and blood volume in unanesthetized splenectomized dogs with intact sympathetics: (--) standard errors of estimate for the regression line.

tance showed only slight elevations after hemorrhage (Table II).

When the blood volume was reduced by less than 10%, there was no significant change in heart rate. Greater losses of blood caused cardioacceleration, and the percentage decrease in stroke volume was then greater than that of the cardiac output (Table II).

*Discussion. A. Comparison between sympathectomized and normal dogs (unanesthetized).* The effects of hemorrhage in the unanesthetized, normal dogs with intact sympathetics can be compared with those found in the unanesthetized, sympathectomized (sympx) dogs (5). For each 1.0% reduction in blood volume, the cardiac output decreases by only 1.5% in normal dogs (Fig. 3), but by 2.5% in sympx dogs (5). The lesser decrease in cardiac output in normal dogs is attributable mainly to a greater increase in heart rate. With a given percentage volume reduction, although the arterial pressure and cardiac output are both higher in normal dogs than in sympx dogs, the pressure/output ratio (total peripheral resistance) is not significantly different. In both, the total peripheral resistance tends to increase slightly after hemorrhage. As the blood viscosity is probably reduced by the decreases in hematocrit and plasma protein concentration (Table II), the rise in resistance may be considered as vascular in origin. Since the rise in vascular resistance is present also in the sympx dogs, it is most likely due to a passive reduction in vascular size secondary to the decrease in distending pressure.

*B. Influence of pentobarbital anesthesia on posthemorrhage adjustments.* For a given percentage reduction in blood volume, the percentage decreases in arterial pressure and cardiac output are much greater in the anesthetized dogs (1) than in the present unanesthetized dogs. In the unanesthetized normal dogs, hemorrhage causes cardioacceleration by the activation of the sympathetic nerves and a reduction of vagal impulses (9), and hence the percentage reduction of cardiac output is less than that of the stroke volume. In the anesthetized normal dogs, hemorrhage does not cause any significant increase in heart rate, which has already been elevated by the prehemorrhage autonomic responses to the anesthesia (1), and hence the cardiac output falls in proportion to the stroke volume. The detrimental effects of pentobarbital on the posthemorrhage maintenance of cardiac output is at least partially attributable to the direct cardiovascular actions of the anesthesia independent of the sympathetic system, for even in the sympx dogs, the decreases of cardiac output are greater when pentobarbital is used (1, 5).

When under pentobarbital anesthesia, a comparison between the pressure–output relations of the normal dogs and the sympx dogs indicates the occurrence of sympathetically induced vasoconstriction in the former (1). In the unanesthetized dogs, however, the pressure–output relations are essentially the same whether or not the sympathetics are intact.

The above discussions indicate that pentobarbital alters the posthemorrhage activation of the sympathetic system. In the absence of anesthesia, hemorrhage activates mainly the cardiac sympathetics (and possibly also the sympathetics innervating the capacitance vessels) with little sympathetic modifications of the overall vascular resistance. Under pentobarbital, however, hemorrhage cannot further increase the discharge of the cardiac sympathetics and the major sympathetic response is to elicit constriction of the resistance vessels.

*Summary.* In the unanesthetized splenectomized dogs, hemorrhage causes 1.5% decrease in cardiac output for each 1.0% reduction in blood volume. The posthemorrhage decreases in arterial pressure and cardiac output in these unanesthetized dogs with sympathetics intact are less than those seen in the unanesthetized sympathectomized dogs, but the pressure–output relations are essentially the same in these two groups. Therefore in the unanesthetized state, the sympathetic system aids in the maintenance of the circulation primarily by its cardiac influence with little action on the overall vascular resistance. In contrast, with the use of pentobarbital anesthesia, hemorrhage cannot further increase the discharge of the cardiac sympathetics and the major sympathetic response is to cause constriction of the resistance vessels.

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