Effect of Aramine on the Survival of Dogs Subjected to Hemorrhagic Hypotension

By STANLEY J. SARNOFF, M.D., AND HERBERT E. KAUFMAN

One group of 19 control dogs and other group of 20 “treated” dogs were bled into hemorrhagic hypotension after Nembutal anesthesia and their arterial pressures controlled at 40 mm. Hg for an average period of one hour and fifteen minutes. Neither group had further blood depletion, or replacement, for an additional 1 hour and 39 minutes, but the treated group received Aramine. Reinfusion was performed after an oligemic period totaling 2 hours and 54 minutes. Of the dogs in the control group, 10.5 per cent survived; 50 per cent of the treated dogs survived.

T HIS COMMUNICATION will deal with the question of whether administration of an agent which increases myocardial contractility, peripheral vascular tone, arterial pressure and coronary artery flow can significantly alter the mortality rate of dogs in which hypotension is induced by hemorrhage.

METHOD

Thirty-nine mongrel dogs were divided into a control group of 19 dogs and an Aramine-treated group of 20 dogs. With three exceptions, these dogs were studied in pairs with side-by-side electrical recording of femoral arterial pressures. Mean pressures were obtained by the electrical integration of full pulse pressures. Intravenous Nembutal was the method of anesthesia used. Thirty-five mg. per kilogram of Treburon* was given intravenously to prevent clotting. In 34 dogs, reduction of mean arterial pressure to 40 mm. Hg† was accomplished by opening a tubing which connected the femoral artery cannula to a reservoir; in the remaining five dogs, hypotension was induced by withdrawing blood from a femoral artery by syringe. The reservoirs of the paired dogs were opened simultaneously and, after an average interval of one hour and 15 minutes, were closed simultaneously. Upon closing the reservoirs, the dog to be treated with Aramine‡ was selected by the flip of a coin. After a further period had elapsed (average of one hour and 39 minutes), both dogs were reinfused intravenously, receiving the reinfusion in about ten minutes. The average total period of oligemia was 2 hours and 54 minutes. After reinfusion, arterial pressures were observed for at least one hour, after which, if the dog was still alive, the wound was closed and it was returned to its cage for further observation. Dogs living 48 hours or longer were considered survivors; others were considered to have died as a result of the shock procedure.

Aramine, [Levo-l-(m-hydroxyphenyl)-2-amino-l-propanol], was administered in doses of 0.05 to 0.20 mg. per kilogram intravenously. In a few instances it was given intramuscularly. The frequency of the dosage of Aramine was adjusted in each case so that, where possible, a maintained pressor response was obtained. (See fig. 1.) The concentration of the administered Aramine solution was 0.5 mg. per cubic centimeter.

RESULTS

Comparability of the Control and the Treated Groups. Table 1 shows the average figures for the control and treated groups as regards body weight, anesthetic, hemorrhage volume, period of oligemia.

Survival. Two of the 19 control dogs survived (10.5 per cent). Ten of the treated dogs survived (50 per cent). Six of the 17 control dogs that died did so before reinfusion. None of the treated dogs died before reinfusion. Of those dogs that did not survive the procedure, the time from closing the blood reservoir to death was 8.2 hours in the control group and 13.4

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† The dog’s femoral artery was used as the zero reference baseline.
Fig. 1. Black bar at the top of each pair indicates period of controlled hypotension (open blood reservoir). Shaded bar represents total period of oligemia, that is, from the initiation of hemorrhage until reinfusion. The short arrows pointing upward indicate administration of 0.1 mg. Aramine per kilogram of body weight. The long arrows pointing upward indicate administration of 0.2 mg. per kilogram. Solid arrows indicate that Aramine was given intravenously; the broken arrows indicate the intramuscular route. In C, the downward pointed crossed arrows show where a secondary hemorrhage of 30 cc was performed in both dogs. The figures at the right indicate the dog's weight, bleeding volume expressed in percent of body weight, and whether the dog survived (+) or died (-). (See text.)

Table 1.—Comparison of Treated and Control Groups. Average Figures

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of dogs</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Weight in kilograms</td>
<td>12.1</td>
<td>13.6</td>
</tr>
<tr>
<td>Nembutal anesthesia in mg./Kg.</td>
<td>39.4</td>
<td>38.8</td>
</tr>
<tr>
<td>Volume of hemorrhage in % of body weight</td>
<td>5.12</td>
<td>5.05</td>
</tr>
<tr>
<td>Time in minutes of hypotension controlled at 40 mm. Hg by open reservoir*</td>
<td>74.8</td>
<td>75.1</td>
</tr>
<tr>
<td>Time in minutes from closing of reservoir until reinfusion</td>
<td>99.7</td>
<td>98.6</td>
</tr>
<tr>
<td>Time in minutes of total oligemic period†</td>
<td>174.5</td>
<td>173.7</td>
</tr>
<tr>
<td>Survival</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

*In five dogs (two controls and three treated dogs) hypotension was produced and maintained at 40 mm. Hg by syringe withdrawal of blood.
† When a control dog died prior to reinfusion the total oligemic time of the paired (treated) dog was assigned.

hours in the treated group. The former figure includes those control dogs that died prior to reinfusion.

Response to Aramine. Figure 1A shows the data from one experiment representative of that type in which the administration of Aramine appeared to have exerted a significant influence on the outcome. The treated dog survived a total oligemic period of 3 hours and 25 minutes, during the last two hours of which a satisfactory arterial pressure was maintained following Aramine therapy. Figure 1B shows an experiment representative of the type in which the response to Aramine was poor. In general it was this type of dog in the treated group which did not survive. In three pairs of dogs a secondary hemorrhage was instituted after closing the reservoir. This was an attempt to simulate the field situation wherein a tourniquet slips or hemorrhage recurs for some other reason and is again con-
trolled. The results of one such experiment are shown in figure IC. Bleeding into the reservoir began at 12:54 p.m. and the reservoirs were closed at 1:54 p.m. The dog to be treated was selected by the flip of a coin and was given 0.1 mg. per kilogram of Aramine intravenously. This was followed by a satisfactory and well-maintained pressor response. At 3:03 p.m. "secondary hemorrhage" was instituted by the withdrawal of 30 cc. of blood from each dog, and both showed a fall in arterial pressure. The treated dog was then given an additional 0.1 mg. per kilogram intravenously, which restored his arterial pressure. Reinfusion was performed at 4:28 p.m. The total oligemic period was 3 hours and 34 minutes.

**Discussion**

In a previous publication from this laboratory experiments were described which indicated that myocardial failure consequent upon insufficient coronary flow may play an important role in late hemorrhagic shock. It was demonstrated that this myocardial failure could be reversed either by mechanical perfusion of the left main coronary artery or by the administration of Aramine. It was felt that if this depression of ventricular function could be reversed by Aramine, it might, if given prophylactically, appreciably increase the chance of survival. It appears to have done so in these experiments. The authors appreciate the fact that the results described above do not necessarily prove that the direct effect of Aramine on the myocardium was the sole factor in the higher survival rate of the treated group.

An analysis of the effects of Aramine on cardiac output, peripheral vascular resistance and tone, ventricular function curves (myocardial contractility), coronary flow, right and left atrial and pulmonary and aortic pressures is presented elsewhere. The results of its use in the hypotension and low cardiac output of experimental coronary insufficiency have also been presented. A review of the pharmacology and clinical experience with this compound is planned by K. H. Beyer.

The doses it was found necessary to use to produce a satisfactory pressor response in the experiments described above are larger than those which consistently produce similar effects in the normovolemic dog. In addition, whereas some of the oligemic dogs described above (fig. 1B) responded poorly to Aramine, the normal anesthetized dog always responds. The failure of some oligemic dogs to respond to sympathomimetic stimulation, in this case Aramine, appears to be characteristic of the later phase of shock as shown by Page who found the same to be true of epinephrine and angiotonin. The work of Fritz and Levine and Ramey, Goldstein and Levine suggests that unresponsiveness to sympathomimetic medication in shock may in some way be connected with a defect in the function of the adrenal cortex.

In spite of the attempt to control this study as completely as possible, one element in the conduct of the experiment might be construed as operating in favor of the treated group. That is, after the blood reservoirs were closed, one of the pair of dogs was selected for treatment with Aramine. If this dog's arterial pressure responded well (fig. 1A, and C), the reinfusion of both dogs was held off for a period that was appreciably longer than was the case if the treated dog responded poorly (fig. 1B). However, since the total oligemic period was the same for both the treated and control groups, it appears unlikely that this was the significant factor in the difference in mortality between the two groups. In all other ways the element of control was thought to be as thorough as shock experiments of this type permit. The application of the chi-square test indicates that the likelihood that these results occurred by chance was less than two in one hundred.

**Summary**

One group of 19 control and another of 20 treated dogs were subjected to hemorrhagic hypotension (40 mm. Hg) by bleeding into a reservoir which remained open for an average period of 1 hour and 15 minutes. The reservoir was then closed and the dogs to be treated received Aramine. A further period which aver-
aged 1 hour and 39 minutes was then permitted to pass before reinfusion. The average total period of oligemia was thus 2 hours and 54 minutes.

Two of the 19 control dogs survived (10.5 per cent). Ten of the 20 dogs receiving Aramine survived (50 per cent).

REFERENCES
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