## Effect of Alcohol Intoxication on the Respiratory Exchange and Mortality Rate Associated with Acute Hemorrhage in Anesthetized Dogs [*]

DEAN T. GETTLER, M.D., FRANK F. ALLBRITTEN, JR., M.D.

From the University of Kansas Medical Center, Kansas City, Kansas

ALCOHOL intoxication, acute hemorrhage and trauma frequently are associated in patients seeking aid in the emergency ward. The clinical observation that intoxicated patients with superimposed mechanical trauma have more severe manifestations of shock than would seem to be warranted by the trauma or blood loss incurred has been recorded.[1, 6] There has been little experimental evidence to support this opinion. Moss and his associates have demonstrated that the acute loss of blood necessary to reduce the blood pressure to 60 mm. Hg in dogs which had ingested 3.0 Gm./kg. of ethyl alcohol one hour prior to bleeding was approximately two-thirds of the volume required in normal animals.[11]

The chief pharmacological action of alcohol is depression of function of the central nervous system. Death resulting from alcohol intoxication is due to depression of the respiratory center.[7] Loomis demonstrated in unanesthetized dogs that respira-

tory and cardiac depression occurred when at alcohol content of between 400 and 600 mg./100 ml. occurred in the blood and the fatal concentration was between 610 and 760 mg./100 ml.; when artificial respiration was maintained cardiac depression was not noted until the blood alcohol concentration was between 880 and 1,105 mg./100 ml.[9] Haag found an alcohol content in the blood between 400 and 680 mg./100 ml. was fatal in dogs.[4] The cardiovascular effect of sublethal doses of alcohol is primarily one of vasodilation of the cutaneous vessels.[2] Other demonstrable cardiovascular changes due to alcohol are not striking.

This study was undertaken to evaluate the effect of alcohol intoxication on mortality rate and respiratory exchange in dogs subjected to acute hemorrhage. The preparation utilized was one developed by Swan and his associates employing splenectomized dogs.[14] In this method, a certain part of the measured blood volume, depending on the mortality rate desired, is with-

drawn from the femoral artery in a single rapid hemorrhage; there was no mortality associated with a loss of 35 per cent of total blood volume but only three of 14 dogs survived a hemorrhage of 43 to 45 per cent of total blood volume. Artificial respiration did not influence mortality.[10]

## Materials and Methods

Thirty-four adult splenectomized mongrel dogs weighing between 7.8 and 16.8 kilograms were used for the experiments. The splenectomies had been performed through a midline abdominal incision at least 30 days before use of the animals in these experiments in order to allow full recovery.

Group I. Control Dogs with Alcohol Intoxication (Four Dogs). The animals were allowed only water for 18 hours before administration of intravenous sodium pentobarbital (30 mg./kg.) and intragastric ethyl alcohol (3.0 Gm./kg.) as a 25 per cent aqueous solution. Samples of blood were drawn from the jugular vein at one-half, one, two, three, four and six hours. Alcohol concentrations in the blood were determined by microdiffusion analysis as described by Feldstein and Klindsky.[3] The animals were returned to their cages and allowed to recover.

Group II. Control Dogs with Acute Hemorrhage (Ten Dogs). The animals were allowed only water for 18 hours before administration of intravenous sodium pentobarbital (30 mg./kg.) for anesthesia. They were then placed in a supine position on an animal table and water equivalent to fluid volume of the alcohol solution (12 ml./kg.) was given by gastric tube. An initial blood sample was taken, respiratory minute volume was determined with a gas flow meter, and a femoral artery was cannulated for monitoring systemic arterial blood pressure and for bleeding the animal. After blood pressure stabilization and immediately before bleeding the blood volume was determined using radioactive iodinated

human serum albumin (R.I.S.A.*), by counting the standard and single ten minute sample with a well-type scintillation detector, as described by Senn and Karlson.[13] Three hours after administration of water by gastric tube 35 per cent of the measured blood volume was removed from the femoral arterial cannula during a five-minute period. Blood pressure and respiration were monitored for at least three hours and the animal was returned to its cage without food or water until the following morning. Just prior to the hemorrhage and one hour after the hemorrhage, a blood sample adequate for pH determination, oxygen content and capacity, and carbon dioxide content measurements was drawn and respiratory minute volume was determined. Blood samples were replaced by an equal volume of homologous or autologous blood. Animals living seven days were considered to be survivors.

Group III. Dogs with Alcohol Intoxication and Acute Hemorrhage (Ten Dogs). The same procedure as in Group II was used, except ethyl alcohol (3.0 Gm./kg.), as a 25 per cent aqueous solution, was given by gastric tube three hours before hemorrhage and a blood sample was taken at the time of the hemorrhage for determination of the blood alcohol concentration.

Group IV. Dogs with Alcohol Intoxication, Acute Hemorrhage and Assisted Respiration (Ten Dogs). The same procedure as in Group III was used, except room air intermittent positive pressure ventilatory assistance at a rate of 10 L./min. was given for the first hour after the hemorrhage.

Blood Samples and Chemical Methods. Blood specimens were collected in heparinized capped syringes containing a drop of mercury to aid in the mixing of the blood. PH determinations were made promptly after withdrawal of blood, using a Cam-
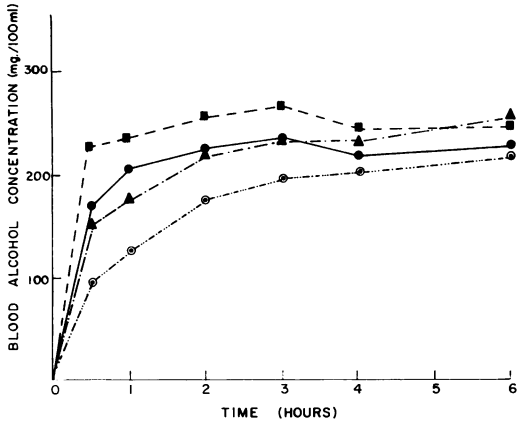
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* Abbott Laboratories.

FIG. 1. Concentration of alcohol in the blood of dogs receiving 3.0 Gm./kg. of ethyl alcohol.
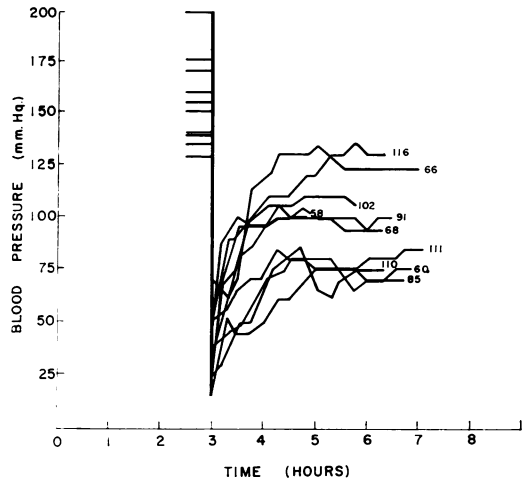


FIG. 2. Mean arterial blood pressure following a hemorrhage of 35 per cent of the total blood volume in control dogs.

bridge glass electrode pH meter. Oxygen content, oxygen capacity and carbon dioxide content of whole blood were then determined, using the technic of Van Slyke and Neill.[15] Plasma carbon dioxide content was obtained from the nomogram of Van Slyke and Sendroy [16] in volumes per cent and converted to millimols per liter by dividing by 2.226. Partial pressure of the carbon dioxide was then read from the nomogram of Van Slyke and Sendroy, using the calculated total plasma carbon dioxide in millimols per liter and the determined pH value. The nomogram was constructed from the Henderson-Hasselbach equation. Bicarbonate of the plasma was calculated

from the formula:

$$(^-HCO_3) \text{ plasma} = (\text{Total } CO_2) \text{ plasma} - 0.0301 \text{ pCO}_2.$$

Changes in fixed acid in the blood can be determined by the difference in bicarbonate value of blood specimens at a standard pH of 7.4. In order to correct for the difference in observed bicarbonate reading at 7.4, the buffer value of the blood must be known. Buffer value of a solution is the amount of acid which must be added to cause a change of one pH unit. In plasma which has been separated from red cells, buffer

TABLE 1. *Group II. Control Hemorrhage*

| Dog No. | Wt. (kg.) | Blood Vol. (ml.) | 35% Bl. Vol. (ml.) | Initial Hgb. (Gm. %) | Initial Hematocrit (%) | Result |
|---|---|---|---|---|---|---|
| 58 | 11.5 | 903 | 316 | 14.0 | 43 | Survival |
| 60 | 11.5 | 890 | 312 | 12.0 | 39 | Survival |
| 66 | 13.8 | 1,165 | 407 | 13.6 | 41 | Survival |
| 68 | 13.8 | 1,380 | 483 | 13.4 | 42 | Survival |
| 85 | 16.3 | 1,577 | 552 | 12.2 | 41 | Survival |
| 91 | 10.9 | 1,028 | 360 | 16.1 | 50 | Survival |
| 101 | 10.2 | 925 | 324 | 16.1 | 51 | Survival |
| 102 | 11.0 | 828 | 290 | 14.7 | 42 | Survival |
| 111 | 11.8 | 1,071 | 375 | 12.8 | 45 | Survival |
| 116 | 16.8 | 1,357 | 475 | 14.0 | 47 | Survival |

TABLE 2. *Changes in Blood Chemistry and Respiration Following Hemorrhage*

| Group | Source of Blood | No. Dogs | pH Control | pH 1 Hr.* | pCO$_2$ (mm. Hg) Control | pCO$_2$ (mm. Hg) 1 Hr. | Plasma Bicarbonate (mM./L.) Control | Plasma Bicarbonate (mM./L.) 1 Hr. | O$_2$ Saturation (%) Control 1 Hr. | O$_2$ Saturation (%) 1 Hr. | Minute Respiratory Volume (L.) Control | Minute Respiratory Volume (L.) 1 Hr. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| II | Venous | 3 | 7.27 | 7.12 | 53.0 | 66.5 | 23.9 | 20.7 | 58 | 20 | — | — |
| II | Arterial | 7 | 7.39 | 7.38 | 32.2 | 28.8 | 19.3 | 16.2 | 95 | 90 | 5.2 | 6.1 |
| III | Venous | 4 | 7.11 | 7.01 | 75.3 | 83.5 | 23.1 | 20.5 | 63 | 30 | — | — |
| III | Arterial | 6 | 7.23 | 7.14 | 51.9 | 51.0 | 20.7 | 17.0 | 79 | 88 | 2.1 | 2.0 |
| IV | Arterial | 10 | 7.31 | 7.28 | 41.7 | 32.5 | 21.7 | 15.6 | 98 | 99 | 2.4 | 10.0** |

* 1 Hr. = 1 Hr. after hemorrhage.
** With intermittent positive respiratory assistance.

value can be measured by the change in bicarbonate concentration when it is titrated with carbon dioxide, and the buffer value (B) can be calculated by dividing the change in bicarbonate by the change in pH. This value in normal plasma alone is approximately 8.6. However, in the presence of red cells an additional buffering effect is noted, and this has been found to be about 2.3 times the hemoglobin expressed in millimols per liter. The value of the plasma bicarbonate at pH 7.4 may be calculated:

(1)  $Hb.\ mM./L./ = \dfrac{Hb.\ in\ Gm.\ per\ 100\ cc.\ \times\ 10}{16.7}$

(2)  $B = 8.6 + 2.3\ (Hb.\ in\ mM./L.)$

(3)  $[^-HCO_3]$ plasma corrected $= {}^-HCO_3$
$\qquad\qquad\qquad\qquad + B\ (observed\ pH - 7.4)$

## Results

**Group I.** Blood alcohol concentrations for four dogs over a six-hour period are shown in Figure 1. With three Gm./kg. of ethyl alcohol given by gastric tube, the maximum blood concentration occurred three hours after administration. No deaths occurred in this group.

**Group II.** No deaths occurred in this group of ten dogs, after acute hemorrhage of 35 per cent of their blood volume (Table 1). The average blood vol./kg. body weight was 86.9 ml. Mean femoral arterial blood pressures for each animal during the period of observation, are shown in Figure 2. Blood pressure readings had to be discontinued before the end of the three-hour observation period on two animals because of insufficient sedation. Average pH, pCO$_2$ and plasma $^-HCO_3$ changes (Table 2) in the venous blood of three animals, following hemorrhage, represent an uncompensated metabolic acidosis, characterized by a decreased pH, increased pCO$_2$ and decreased plasma $^-HCO_3$. In the arterial blood of seven animals there are findings of respiratory compensation of a metabolic acidosis, indicated by a normal

TABLE 3

| | No. Dogs | Change in Fixed Acid (mM./L.) |
|---|---|---|
| Anesthesia | 7 | +1.9 |
| Anesthesia Intoxication | 10 | +3.3 |
| Anesthesia Hemorrhage | 6 | +3.3 |
| Anesthesia Intoxication Hemorrhage | 10 | +5.2 |
| Anesthesia Intoxication Hemorrhage Ventilation | 10 | +6.5 |



FIG. 3. Mean arterial blood pressure following a hemorrhage of 35 per cent of the total blood volume in intoxicated dogs.

pH, decreased $pCO_2$, decreased plasma $^-HCO_3$ and an increase in fixed acid of 3.3 mM./L. (Table 3). The average arterial blood oxygen saturation preceding bleeding was 95 per cent. Following hemorrhage it was 90 per cent. Average respiratory minute volume increased from 5.2 liters to 6.1 liters after hemorrhage (Table 2).

Group III. There were three deaths in this group of ten dogs. One death occurred before the entire 35 per cent of the blood volume was withdrawn, one in one-half hour and one in less than 16 hours after hemorrhage (Table 4). Blood alcohol concentrations of these animals were 246, 136, and 227 mg./100 ml., respectively. For the entire group, average blood volume/kg.
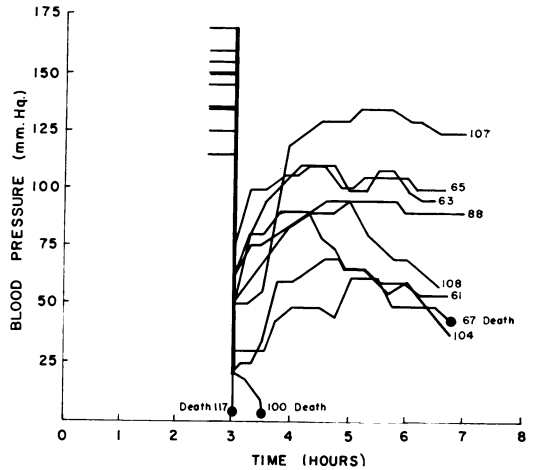
body weight was 86.6 ml. Blood alcohol concentrations at the time of the hemorrhage were between 136 and 251 mg./100 ml., with a mean of 225 mg./100 ml. Mean femoral arterial blood pressure for each animal, during the period of observation, is shown in Figure 3. The average pH, $pCO_2$ and plasma $^-HCO_3$ changes (Table 2) in the venous blood of four animals and the arterial blood of six animals following a hemorrhage shows an uncompensated metabolic acidosis. There was an average increase in fixed acid of 5.2 mM./L. (Table 3) which indicates a slightly greater metabolic acidosis than observed in the control

TABLE 4. Group III. Alcohol Intoxication and Hemorrhage

| Dog No. | Wt. (kg.) | Bl. Vol. (ml.) | 35% Bl. Vol. (ml.) | Initial Hgb. (Gm. %) | Initial Hematocrit (%) | Blood Alcohol Concentr. (mg. %) | Result |
|---|---|---|---|---|---|---|---|
| 61 | 8.9 | 700 | 245 | 13.6 | 48 | 238 | Survival |
| 63 | 10.3 | 978 | 342 | 14.6 | 48 | 241 | Survival |
| 65 | 11.9 | 1,180 | 413 | 17.5 | 54 | 235 | Survival |
| 67 | 12.2 | 1,200 | 420 | 12.6 | 41 | 227 | Death |
| 88 | 11.3 | 995 | 348 | 15.0 | 35 | 223 | Survival |
| 100 | 15.0 | 1,260 | 442 | 13.3 | 42 | 136 | Death |
| 104 | 10.4 | 835 | 292 | 14.2 | 41 | 251 | Survival |
| 107 | 12.5 | 970 | 340 | 12.2 | 42 | 201 | Survival |
| 108 | 10.7 | 960 | 336 | 10.3 | 30 | 250 | Survival |
| 117 | 13.2 | 992 | 347 | 13.8 | 45 | 246 | Death |

TABLE 5. *Group IV. Alcohol Intoxication, Acute Hemorrhage and Assisted Respiration*

| Dog No. | Wt. (kg.) | Bl. Vol. (ml.) | 35% Bl. Vol. (ml.) | Initial Hgb. (Gm. %) | Initial Hematocrit (%) | Blood Alcohol Concentr. (mg. %) | Result |
|---|---|---|---|---|---|---|---|
| 8 | 13.5 | 995 | 340 | 16.6 | 51.5 | 282 | Survival |
| 9 | 11.1 | 858 | 300 | 15.0 | 48.0 | 276 | Survival |
| 21 | 14.6 | 1,215 | 425 | 12.4 | 38.5 | 225 | Death |
| 31 | 14.2 | 1,140 | 439 | 13.8 | 51.0 | 284 | Survival |
| 33 | 12.5 | 963 | 337 | 16.2 | 51.0 | 259 | Survival |
| 85 | 10.9 | 843 | 295 | 15.0 | 50.0 | 283 | Survival |
| 87 | 13.6 | 1,158 | 405 | 13.4 | 42.0 | 233 | Survival |
| 88 | 13.6 | 1,112 | 390 | 13.4 | 43.5 | 269 | Survival |
| 91 | 14.1 | 1,017 | 356 | 15.0 | 49.5 | 227 | Death |
| 93 | 13.9 | 1,077 | 376 | 16.0 | 51.5 | 196 | Death |

group. There was gross arterial blood oxygen desaturation preceding the hemorrhage (79%). Following bleeding arterial oxygen saturation increased to 88 per cent in the surviving dogs. Determinations were not done in animals that died before the first hour after hemorrhage had elapsed. The average respiratory minute volume was essentially unchanged; 2.1 liters before and 2.0 liters after hemorrhage.

Group IV. There were three deaths in this group of ten dogs (Table 5). Deaths occurred at 1½ hours, 2½ hours and less than 21 hours. Concentrations of alcohol in the blood in these animals were 225, 196 and 227 mg./100 ml., respectively. For the entire group, average blood volume/kg. body weight was 78.6 ml. Alcohol concentrations in the blood at the time of hemorrhage were between 196 and 284 mg./100 ml., with a mean of 253 mg./100 ml. The mean femoral arterial blood pressure for each animal, during the period of observation, is shown in Figure 4. Average pH, $pCO_2$ and plasma $^-HCO_3$ changes (Table 2) in the arterial blood following hemorrhage, indicated respiratory compensation of the metabolic acidosis. Increase in the fixed acid of 6.5 mM./L. (Table 3) was approximately the same change observed without ventilation (5.2 mM./L. Ventilatory volume from spontaneous respiration was grossly diminished. There was no ar-

terial blood oxygen desaturation before or after hemorrhage.

## Discussion

A mortality rate of 30 per cent in the intoxicated dogs subjected to acute hemorrhage helps to confirm the clinical impression that the intoxicated animal does not tolerate trauma and hemorrhage as well as the nonintoxicated subject.

Acidosis produced following hemorrhage and partial respiratory compensation has been described previously. Hertzman and Gesell demonstrated the higher pH of venous blood as compared to arterial blood by simultaneous measurement during acute hemorrhage.[5] According to Wiggers, when a state of posthemorrhage hypotension is sustained more than 45 minutes, evidences usually begin to appear that the nutrient flow does not equal requirements of the body at rest.[17] In extensive studies by Root, it was found that with hemorrhage or trauma to muscle there are decreases in pH and arterial $CO_2$ content and progressive increases in pyruvate and sulfate.[12] Root also states that the metabolic acidosis is partly compensated by reduction in arterial $CO_2$ tension secondary to respiratory activity.

Alcohol intoxication followed by acute hemorrhage appears to ablate respiratory compensation of metabolic acidosis. The

average posthemorrhagic respiratory minute volume of intoxicated animals was not increased from the prehemorrhagic level and was only one-third that of controls (Table 2). Without respiratory depression produced by alcohol, there was an increase in respiratory minute volume and metabolic acidosis in controls was corrected by a compensatory respiratory alkalosis. In intoxicated animals there was a failure to correct the acidosis and the arterial blood pH remained low. When artificial respiration was administered for one hour before posthemorrhagic blood samples were taken, there was respiratory compensation of the metabolic acidosis, demonstrating the ability of hyperventilation alone to restore pH to near prehemorrhagic levels. Increase in the prehemorrhagic oxygen desaturation found in the intoxicated animals when compared to the controls, presumably represented additive effect of alcohol to respiratory depression produced by the anesthetic.

Blood pressure recovery following hemorrhage was generally better in the control group than in the group intoxicated with alcohol (Fig. 2, 3). In all control animals mean blood pressure, after three hours, had returned to 70 mm. Hg or higher, whereas only half of the intoxicated animals had a blood pressure of this level or higher after the same period of time. However, in intoxicated animals with ventilatory assistance, all survivors (70%) had a blood pressure above 70 mm. Hg after three hours.

These studies imply that there is need for increased alertness to the cardiovascular status and necessity of blood volume replacement in acutely intoxicated patients entering the emergency ward with evidence of recent or continued blood loss. The effect of uncompensated metabolic acidosis on mortality in intoxicated dogs was not determined in this study, but Levine came to the conclusion that acidosis is an important factor in determining the reversibility of far advanced shock.[8]

## Summary

The effect of alcohol intoxication on tolerance to acute hemorrhage in dogs has been investigated. There was a mortality rate of 30 per cent in the group intoxicated with alcohol subjected to hemorrhage of 35 per cent of the blood volume. There were no deaths in the control group subjected to hemorrhage. Mean arterial blood pressure response was significantly lower in intoxicated animals than in controls. Acute hemorrhage produced a metabolic acidosis which was compensated by respiratory elimination of carbon dioxide in control animals, but remained uncompensated in intoxicated animals, due to respiratory depression. Acidosis in intoxicated animals was partially corrected by intermittent positive pressure ventilatory assistance, but no change in mortality rate was observed.

It was concluded that moderate alcohol intoxication did increase mortality rate in dogs subjected to hemorrhage and could be a deciding factor between survival and death following acute hemorrhage or trauma.
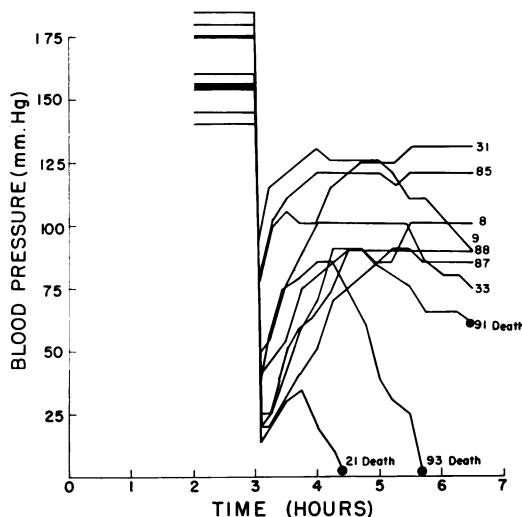


FIG. 4. Mean arterial blood pressure following a hemorrhage of 35 per cent of the total blood volume in intoxicated dogs which were given intermittent positive pressure respiratory assistance for one hour immediately after hemorrhage.

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