Oxygen Transport and Consumption during Acute Hemodilution

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REPLACEMENT of blood loss with buffered saline solutions results in hemodilution. The consequences of rapid reduction of blood oxygen-carrying capacity associated with dilution are frequently overlooked in studies that focus on blood flow, peripheral resistance and reduction in cardiac work. In surgical care the ability of the circulation to deliver adequate amounts of oxygen to the tissues continues to be of paramount importance and must be taken into account in any effort to define safe limits of acute hemodilution. Quantitative examination of the alterations in oxygen transport and consumption in the course of hemodilution are urgently needed since the reserve oxygen carrying capacity of the normal circulation may be limited by heart disease or metabolic abnormalities in some patients. While recent studies [15, 18] have attempted to fix the limits of non-colloid administration in hemorrhagic shock, certain physiologic changes associated with sudden reduction in blood oxygen content may be of clinical importance long before lethal limits of hemodilution are approached.

In the present experiment circulatory and metabolic responses to acute hemodilution were studied in anesthetized dogs. A stepwise hemodilution sequence was designed to obtain hematocrit ratios of 20 to 35%. These values are commonly encountered in clinical care and not considered lethal *per se*. Significant changes in oxygen metabolism were evident in this study despite the fact that extremes of hemodilution were avoided and mean aortic pressure remained constant.

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Methods

Ten mongrel dogs each weighing between 9.5 and 16.0 Kg. were anesthetized with pentobarbitol sodium, 25 mg./Kg., which was supplemented as necessary. A cuffed endotracheal tube was inserted. Rectal temperature was monitored and maintained between 37 and 38° C. A flexible catheter was flow guided into the right ventricle via the external jugular vein for mixed venous blood samples. The other jugular vein was cannulated in order to measure central venous pressure. One femoral artery was catheterized for arterial pressure measurement with a Statham transducer while the other vessel was used to withdraw blood and inject Ringer's lactate solution. The right heart catheter was also used to inject green dye and dye dilution curves were recorded from femoral artery blood in order to calculate cardiac output. Arterial blood was also sampled for pH, and oxygen content.[7] Identical determinations were made on mixed venous blood.

The endotracheal tube was attached to a respirator through a non-rebreathing valve

and minute volume adjusted until pCO_2 values fell between 30 and 40 mm. Hg. This was accomplished during the control period after which no further changes in minute ventilation were made. The animals were ventilated with room air and expired air was collected in Mylar coated aluminum foil bags [6] from the expiratory port of the non-rebreathing valve. Oxygen concentration was determined with a Beckman paramagnetic analyzer and oxygen consumption calculated after temperature and barometric pressure corrections.

Blood lactate was determined enzymatically on arterial blood and blood was drawn for duplicate microhematocrits at precise times in the hemodilution sequence.

After control studies were complete the animals were bled 12 ml./Kg. This blood was discarded and replaced by Ringer's lactate solution using three times the volume of shed blood. The Ringer's solution was a commercially available preparation (Abbott Laboratories) containing Na-130 mEq./l., K-4 mEq./l., Ca 3 mEq./l., Cl-109 mEq./l. and lactate 28 mEq./l. with a pH of 6.5. For comparison in two additional dogs isotonic saline was used in order to observe serum lactate levels during hemodilution performed without the addition of exogenous lactate.

The experiment consisted of three 30-minute study periods as shown in Figure 1. Time is indicated on the horizontal axis. There is no vertical scale other than the indication that blood was replaced by three times as much Ringer's solution. The time required to withdraw blood and reinfuse Ringer's solution varied from 5 to 10 minutes. However, hematocrits were always determined exactly 5 minutes after the completion of hemodilution and 10-minute expired air collections were always initiated 15 minutes after the start of bleeding. Cardiac outputs were recorded in triplicate with reinfusion of the blood drawn through the cuvette after each determination. Blood was withdrawn for dye calibration after

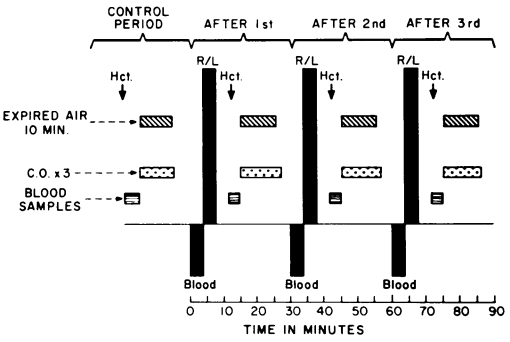

FIG. 1. After control measurements blood was withdrawn and replaced by three times the volume of R/L. Then the same measurements were repeated; the time scale shows onset and duration of the measurements.

each dilution step. After 30 minutes the entire procedure was repeated and finally a third hemodilution completed the protocol. In this way progressive hemodilution was produced in three stages and observations were made after each step. It is obvious that blood removed in the second and third steps was diluted by previously administered Ringer's lactate solution so that less than 12 mg./Kg. of the animal's blood was removed. This was not considered important since the sole purpose of the hemodilution sequence was to achieve a stepwise reduction in hematocrit.

The dogs were sacrificed and autopsied at the completion of the experiment.

Results

Table 1 shows the mean values of all parameters measured during the control period followed by the values after each of the three hemodilution steps. It is evident that central venous pressure and blood pressure did not change. The serum lactate concentration approached control values plus the concentration of 25.2 mg.% lactate in the Ringer's solution infused. The two additional dogs given isotonic saline without lactate confirmed the fact that endogenous lactate levels remained stable. The decreasing Hct values are shown in Figure 2. It was not thought worthwhile to continue

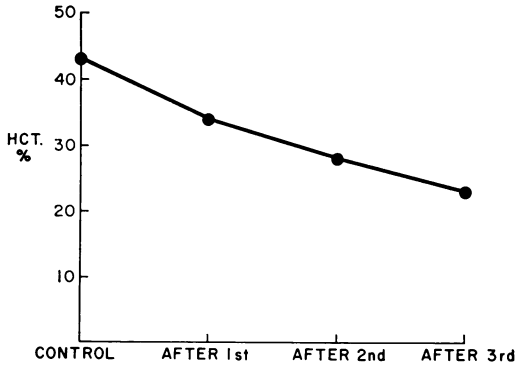

FIG. 2. Mean hematocrit values during the course of stepwise hemodilution. Standard deviations are shown in Table 1.

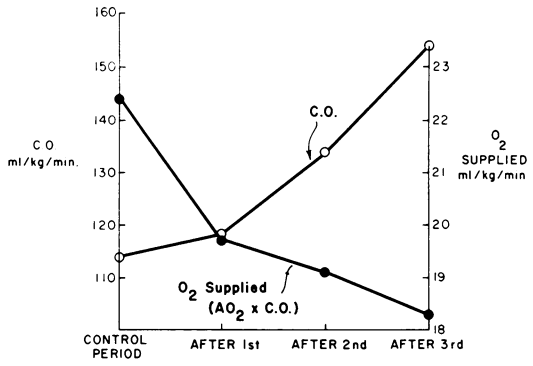

FIG. 3. Mean values for cardiac output and oxygen supplied ($AO_2 \times$ C.O.) for the ten dogs during progressive hemodilution.

hemodilution beyond ranges that might be encountered clinically. In the course of diluton with Ringer's solution a mild fall in pH took place. Since this was not due to lactate accumulation, it may reflect dilution of plasma protein and red cell mass with resultant decrease in circulating buffers. The actual acid load resulting from infusion of commercial Ringer's solution (pH 6.5) is quite small since neutralization of one liter requires only 4.46 mEq. of base.

The expected fall in oxygen content of arterial blood (AO_2) was accompanied by a rise in cardiac output (C.O.) as shown in Figure 3. It is evident that the amount of oxygen delivered to the tissues ($AO_2 \times$ C.O.), declines despite the increase in cardiac output because of the rapid decrease in blood oxygen carrying capacity associated with hemodilution. The oxygen content of venous blood (VO_2) also falls as is shown in Figure 4. However, the more rapid decrease in AO_2 leads to a decreasing A-V oxygen difference as hemodilution progresses.

Oxygen consumption is shown in Figure 5. Direct measurements from analysis of expired air are shown in the lower portion of the figure. An alternative expression shows oxygen consumption as the difference between oxygen delivered to the tissues ($AO_2 \times$ C.O.) and that returned in venous blood ($VO_2 \times$ C.O.). Decreased oxygen consumption is evident both by direct measurement and indirect calculations. The amount of oxygen returned in the venous circulation does not change appreciably. Oxygen consumption appears to fall primarily because of the decreased supply of oxygen so that under these conditions consumption may depend on the amount of oxygen available. The per cent utilization of oxygen is defined as the oxygen consumed divided by the oxygen supplied per 100 ml. of blood times 100. The 30% figure recorded during the control period did not change after the first hemodilution. Following the second and third hemodilutions there was a slight fall but the final figure of 24% is still considered normal.

Discussion

The ability of non-colloidal solutions in proper volumes to support the circulation following hemorrhage has been established. Furthermore, hemodilution is well tolerated as long as the oxygen carrying capacity of the blood is sufficient to provide proper tissue oxygenation. Therefore, the transport and utilization of oxygen under conditions of rapid hemodilution are of obvious concern in the continuing debate over the proper role of balanced salt solutions in resuscitation after the blood loss.

In previous studies, oxygen consumption, measured by means of a spirometer, was

TABLE 1. *Results (Means ± 1 S.D.)*

	Control	1	2	3
Hct %	43 ± 1.9	34 ± 1.9	28 ± 3.3	23 ± 3.8
pH	7.46 ± 0.06	7.41 ± 0.05	7.36 ± 0.04	7.31 ± 0.04
CVP (cm.)	4.6 ± 0.80	4.8 ± 1.25	5.0 ± 1.10	4.7 ± 0.90
Mean BP (mm. Hg)	142 ± 5.5	143 ± 2.4	142 ± 5.4	140 ± 5.4
Lactate (mg.%)	16 ± 1.3	21 ± 3.5	27 ± 2.4	32 ± 2.0
C.O. (ml./Kg./min.)	114 ± 16	118 ± 24	134 ± 28	154 ± 20
Oxygen Consumption (ml./Kg./min.)	6.9 ± 1.2	6.1 ± 1.4	5.1 ± 0.8	4.4 ± 1.3
A-V diff. (ml./100 ml. blood)	6.5 ± 1.4	4.9 ± 1.6	3.6 ± 1.3	2.9 ± 1.3

utilized to calculate cardiac output by the Fick principle.[1, 13, 15, 17, 20] Others have determined cardiac output by dye dilution methods [19] and calculated oxygen consumption from cardiac output and the A-V oxygen difference. In the present experiments both cardiac output and oxygen consumption were measured independently so that one value was not dependent on the other. Animals were ventilated with room air rather than high oxygen spirometer mixtures in order to conduct the experiment with normal levels of dissolved oxygen. Furthermore, it has been shown that oxygen transport can approach normal levels despite severe anemia when breathing 100% oxygen [9] provided there is an increase in cardiac output and a decrease in A-V oxygen difference.

This study confirms the fact that cardiac output increases in response to acute anemia. However, the magnitude of this response and whether it is adequate to maintain normal delivery of oxygen to the tissues must be considered in evaluating the effects of hemodilution. Although the cause of increased cardiac output following hemodilution is not entirely clear there are a number of mechanisms involved. It has been suggested that decreased blood viscosity and concomitant lowering of peripheral resistance is a major factor.[14] The decrease in oxygen carrying capacity has also been shown to play a role although evidence suggests that Hct values must first fall to 50% of control values.[17, 20] An important determinant of cardiac output is blood volume and it has been shown that cardiac outputs are significantly higher in hypervolemic than in normovolemic hemodilution.[11] It is clear that if compensatory increases in cardiac output are to take place administration of non-colloid solutions must be at a rate that will maintain plasma volume. Further limitations on the ability to increase cardiac output may appear in clinical situations in patients with heart disease.

Even though cardiac output did increase in the presence of anemia, it is evident that normal oxygen delivery was not maintained because the modest increase in cardiac output was not enough to compensate for the decreased oxygen carrying capacity of diluted blood.

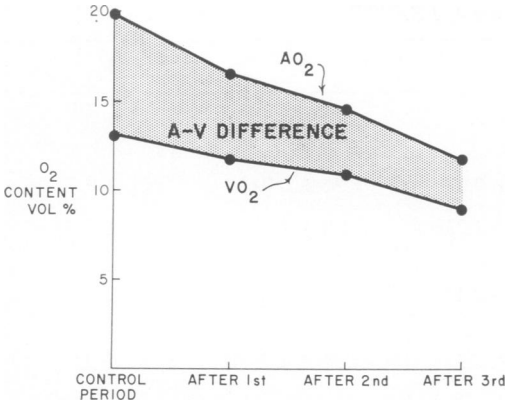

FIG. 4. Mean arterial and venous oxygen content during hemodilution. The decreasing A-V difference is evident.

These results confirm previous work in which normovolemic dilution was produced by Dextran.[10] Furthermore, falling oxygen transport in association with hemodilution has been reported both in hypervolemic [11] and hypovolemic states.[2] Oxygen delivery calculated by multiplying cardiac output by arterial oxygen content, represents the maximum oxygen available for utilization. It is therefore a limiting factor for sustained metabolism of an animal.

The consequences of decreased oxygen transport in anemic states are not well understood except at extremes of hemodilution where obvious hypoxic changes take place. While careful studies show no changes in resting oxygen consumption in chronic anemia,[4] observations in acute hemodilution have resulted in conflicting reports. It is important to determine the level of inspired oxygen in all such experiments since oxygen consumption is frequently measured by breathing 100% oxygen from a spirometer. The decreased oxygen transport associated with rapid hemodilution can be largely prevented by inhalation of oxygen, effectively masking any fall in oxygen consumption resulting from reduced transport of oxygen.

In the present study, employing ventilation with room air, oxygen consumption decreased during the course of progressive hemodilution. This decrease is difficult to interpret since there was no evidence of anaerobic metabolism and percent utilization of oxygen remained in the normal range. One aspect of treatment with lactate solutions that has received little attention is the effect of giving a racemic mixture (commercial preparations contain equal parts of the D&L forms of lactic acid) on oxygen consumption. It is known that the body can metabolize the natural L form much more readily and that at similar blood levels the stimulating effect of D lactic acid on oxygen consumption is reported to be about four times less than that of L lactic acid.[8] Serum lactate levels doubled in the study being reported as the result of administering about 250 mg. of D-L lactic acid during hemodilution. When hemodilution was carried out without addition of exogenous lactate (2 dogs infused with saline) lactate levels remained constant. Calculations showed that approximately ⅓ of the administered lactate was metabolized during the 90-minute experiment and this would require 60 ml. of oxygen assuming complete oxidation to CO_2 and water. If we concede that twice as much lactic acid would be metabolized if only the L form were administered it would still add only a little more than one ml./min. to total oxygen consumption which averaged 69 ml/min. for a 10-Kg. dog. Although it is evident that racemic mixtures of lactic acid are not a factor in the decreased oxygen consumption in the present experiment large quantities of D lactic acid may occasionally be important clinically because this form is metabolized so slowly.

There is evidence that acidosis may interfere with oxygen utilization.[12] However, the mild acidosis noted in the present study would not be expected to exert a significant metabolic effect. Furthermore, oxygen consumption was maintained in other studies despite pH values below those reported here.[15]

Interstitial edema from infusion of large amounts of crystalloid solutions may form a barrier to tissue oxygenation and play a role in decreased oxygen consumption. Since blood loss was replaced with three times its volume it is obvious that weight gain must follow hemodilution under these circumstances. The effect of this extra fluid load depends in part on the degree of interstitial fluid depletion associated with hemorrhage. If there is no marked depletion of the extracellular space then edema may result from the additional fluid required to support intravascular volume. Autopsy did reveal slight macroscopic edema in all dogs involving especially the mesentery. Intracellular edema is also possible under these circumstances and suppression of enzymatic activity with decreased oxygen consumption may follow.[3]

The question of whether decreased oxygen consumption in these dogs is the result of a metabolic injury related to rapid hemodilution is of great interest. Although a number of possible explanations have been considered above, the precise mechanism remains uncertain. Furthermore, total body oxygen consumption measurements may have to be supplemented by determinations of oxygen consumption in individual organs. There is evidence that the increased cardiac output associated with hemodilution is not evenly distributed since hemodilution results in dissimilar changes in venous oxygen tension from blood draining different regions.[9] Under these circumstances significant decreases in oxygen consumption in important organs might be hidden by continued normal levels of oxygen uptake in larger but less critical vascular beds. Some support for this statement is provided by recent studies showing decreased oxygen consumption of the myocardium[16] and kidney[5] following acute hemodilution.

Additional evidence of metabolic damage in the course of significant hemodilution

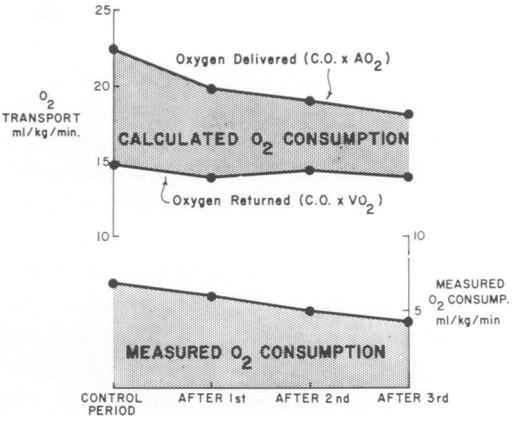

FIG. 5. O_2 consumption can be calculated by subtracting O_2 returned from O_2 delivered to the tissues. Expired air collection will also allow calculation of O_2 consumption; the two methods can be compared in this illustration.

can be found by examination of survival data. Takaori and Safar[18] found that all five of their dogs diluted to a Hct of 10% died within 2 hours. However, five dogs diluted with Ringer's lactate to a final Hct of 20% survived for longer periods. Although one dog died in 3 hours the others lived for 13 hours, 2 days and 5 days after hemodilution while the fifth dog was still alive at 8 days. Rush and Eiseman[15] also found late deaths in eight dogs with 50% hemorrhages (final Hct 16%). While all dogs survived the immediate posthemorrhage period three of the eight died within 7 days. Delayed deaths in dogs acutely hemodiluted to Hcts of 15–20% suggest cellular injury at the time of hemodilution that subsequently proves to be lethal for some of the animals. The decreased oxygen consumption noted in the present study may be an indication of cellular injury and emphasizes the importance of oxygen transport and utilization studies in the continuing efforts to define safe limits of hemodilution.

Summary and Conclusion

Stepwise hemodilution with Ringer's lactate was carried out in order to study the response of ten dogs to sudden decrease in

blood oxygen carrying capacity. The experiment was designed to examine adaptive mechanisms in the range of hemodilution that might be encountered clinically. Despite a compensatory increase in cardiac output the amount of oxygen delivered to the tissues decreased in the course of hemodilution indicating that hemodynamic adjustments did not completely compensate for acute decreases in blood oxygen content. A moderate fall in oxygen consumption was also observed in this study without evidence of anaerobic metabolism. The possible significance of decreased oxygen uptake in these animals has been discussed.

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