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CRITICAL POINT IN PROGRESSIVE HEMODILUTION WITH HYDROXYETHYL STARCH

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Abstract

Anesthetized dogs were hemodiluted by serial blood withdrawals (10 ml/kg) and immediate infusion of equal volumes of hydroxyethyl starch solution every ten minutes until death. Serial determinations of circulatory and metabolic parameters were performed at approximately 20, 12, 8 and 5% hematocrit values.

"Complete compensation" was observed until Hb value reached approximately 5.5 g/100 ml. "Partial compensation" was observed at 5.5-4.0 g/100 ml Hb, where oxygen consumption started to decline. "Reversible decompensation" occurred at hemoglobin values of 4.0-3.0 g/100 ml for the following reasons: cardiac output declined from its maximal compensatory increase; heart rate and arterial pressure decreased; right ventricular end-diastolic pressure increased; venous hemogloblin oxygen saturation decreased sharply; pH declined and arterial lactate values rose; and reversibility of hemodilution proven by survival of 80% of 43 animals in the previous studies.

"Irreversible decompensation" occurred below 3.0 g/100 ml Hb. This is characterized by a dramatic decrease in cardiac output and venous hemoglobin oxygen saturation; and an increase in arteriovenous oxygen content difference. The lowest hemoglobin values measured (1.5-2.0 g/100 ml) were followed by another 3-7 blood exchanges before cardiac arrest occurred suddenly.

INTRODUCTION

In massive hemorrhage when cross-matched blood is unavailable,

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infusion of large amounts of a colloid plasma substitute is indicated. Although this restores circulating blood volume, it reduces oxygen-carrying capacity of blood. Dextran 75 (clinical) has been recommended for blood replacement during surgery either with or without additional blood transfusion[1].

Amberson replaced 97% of blood volume in cats, dogs, and rabbits with Ringer-Locke solution containing 13 to 14 g/100 ml of free hemoglobin[2]. The animals died when the hemoglobin content had dropped to 3 g/100 ml. Harris and associates[3] obtained similar results during lethal hemodilution with Dextran 75 in dogs. Avoiding hypovolemia, hemoglobin content in blood was reduced progressively. When it dropped to below 3 g/100 ml, asystole occurred. Takaori and Safar[4,5,6] diluted dogs to 10% hematocrit value, using a new experimental model. With colloids (Dextran 75, Dextran 40, hydroxyethyl starch) survival rate was 80% in 43 animals. Acute compensation would be supported by an increase in cardiac output and more efficient extraction of oxygen from blood. Chronic compensation seemed to be done by increased efficiency of oxygen extraction from blood in peripheral tissues and progressive increase of hemoglobin by erythropoiesis.

Most previous observations on circulatory dynamics and blood consituents following anemia acutely produced, dealt with hematocrit values above 10%[7-12]. Circulatory and metabolic changes were followed during acute lethal hemodilution with colloid plasma substitues for the following reasons.[1] Scarcity of serial observations or circulatory and metabolic changes in hemodilution below 10% hematocrit;[2] Lack of sufficient information about the limitations of acute hemodilution;[3] The necessity for delineating warning signs for monitoring subjects during progressive hemodilution.

Hydroxyethyl starch (HES)* in isotonic saline solution was used because of our familiarity with this substance[5,6]. Thompson and Walton[13,14] showed that 6% HES in isotonic saline solution has the same rheologic and biologic characteristics as 6% Dextran 75 (clinical, $\overline{MW}$ 75,000) in isotonic saline solution. Recently HES solution has been available commercially for clinical use and becomes useful to replace intraoperative blood loss less than 20 ml/kg.

* Hydroxyethyl starch is a derivative of waxy sorghum starch containing branched chains of glycoside molecules. It is made from corn powder. After gelatinization, hydroxyethylation is added on the 6th carbon atom in 90% of the glucose rings, which provides high resistance to amylase. The molecular weight is estimated to be 350,000-450,000.

METHOD

Eight adult, male mongrel dogs (11.2-14.2 kg) were anestheized with pentobarbital (25 mg/kg) intravenously and ventilated with a piston ventilator, using 30% O_2 and N_2 via a cuffed tracheal tube. The rate was constant at 12 per minute and tidal volumes were adjusted to maintain end-expiratory pCO_2 at approximately 40 mm Hg, as monitored with a Beckman LD-1 infrared CO_2 analyzer. The animals were maintained supine under light anesthesia with intermittent injections of pentobarbital (30 mg) and gallamine (10 mg) intravenously. Esophageal temperature was maintained at 38°C by a thermal pad.

A polyethylene catheter (I. D. 1.6 mm) was inserted through the right carotid artery into the aortic arch for measurement of arterial pressure with a Statham transducer and for withdrawal of blood for producing hemorrhage and sampling. Another catheter (I.D. 1.1 mm) was inserted through the right jugular vein into the right ventricle for administration of drugs and plasma substitutes and for measurement of pressure. The transducer was positioned at the level of the tricuspid value[15]. Cardiac output was measured by the indicator dilution with indocyanine green[16,17]. Central blood volume (right ventricle—aortic arch) was calculated with the Stewart Hamilton's equation from cardiac output and mean transit time, corrected by time delay for dye passage through the arterial catheter[18,19]. Pressures, electrocardiogram and dye dilution curves were recorded on a Grass polygraph.

Hemoglobin content (Hb) was measured by the cyanhematin method[20]. Microhematocrit was measured by centrifuging at 10,000 r.p.m. for five minutes. Arterial pH was measured potentiometrically with a glass electrode. Arterial and venous oxygen content and capacity were measured manometrically[21]. Oxygen consumption was calculated from cardiac output and arterio-venous oxygen content difference. Arterial lactate was measured enzymatically[22]. Body surface area was estimated from the Benedict formula[23].

After a steady state of anesthesia and ventilation, control measurements and sampling were proformed. Then, 10 ml/kg of arterial blood was withdrawn within 2 minutes, and immediately replaced by an equal volume of plasma substitute. The same amount of bleeding (whicn included sampled blood) and replacement by substitute were repeated every ten minutes until cardiac arrest occurred. It was attempted to time all circulatory measurements and blood sampling approximately at 20, 12, 8 and 5% hematocrit values. Although hematocrit vaule was determined

at each blood withdrawal, the various physiologic parameters were measured at the hemoglobin and hematocrit values listed in the Table and in Figures 1 to 4.

RESULTS

During progressive hemodilution, Hct decreased exponentially to 4–6 % and then rose to between 6 and 8% during the last 4 to 5 replacements just before arterial hypotension ensued. Finally, Hct showed a tendency to decrease again, but severe hypotension occurred. This was quickly followed by zero arterial pressure, with the electrocardiogram showing sinus arrest, leading to ventricular rhythm. Physiologic parameters in all 8 dogs are plotted against Hb content in scattergram (Figures 1-4). Response of each parameter to change in Hb could be separated into two phases, one above and one below 4 g/100 ml Hb value. Therefore, two regression lines were calculated. Their intersecting point would correspond to a flection point in an imaginary response curve, drawn through all data. Correlation coefficients, levels of significance and flection points are presented in the table.

Heart rate increased significantly at the flection point of 3.8 g/100 ml Hb (Figure 1). Thereafter, heart rate decreased sharply to approximately control values. Electrocardiographic changes were minimal to the point of sinus arrest, except for decreases of QRS vector in all leads.

Aortic mean pressure (Figure 1) decreased minimally but significantly at the flection point of 3.3 g/100 ml Hb. Below this it dropped sharply but to a variable degree. It was sustained above 70 mm Hg until sinus arrest occurred at which time the pressure dropped to zero within 1 minute.

Right ventricular end-diastolic pressure (Figure 1) following hemodilution remained unchanged until Hb of 3.8 g/100 ml; and thereafter increased sharply.

Cardiac index (Figure 2) increased significantly from 3.69 ± 0.49 L/min/m^2 to approximately 6.29 L/min/m^2 until the flection point of 3.8 g/100 ml Hb. Then it decreased sharply to control levels at the lowest Hb level obtained before death. *Central blood volume* remained essentially unchanged but diminished slightly at Hb level mostly below 5 g/100 ml.

Mixed venous hemoglobin oxygen saturation (SvO_2) decreased from $71 \pm 2.7\%$ to approximately 62% at the flection point of 3.5 g/100 ml Hb (Figure 3). Below this point, venous Hb oxygen saturation decreased markedly.

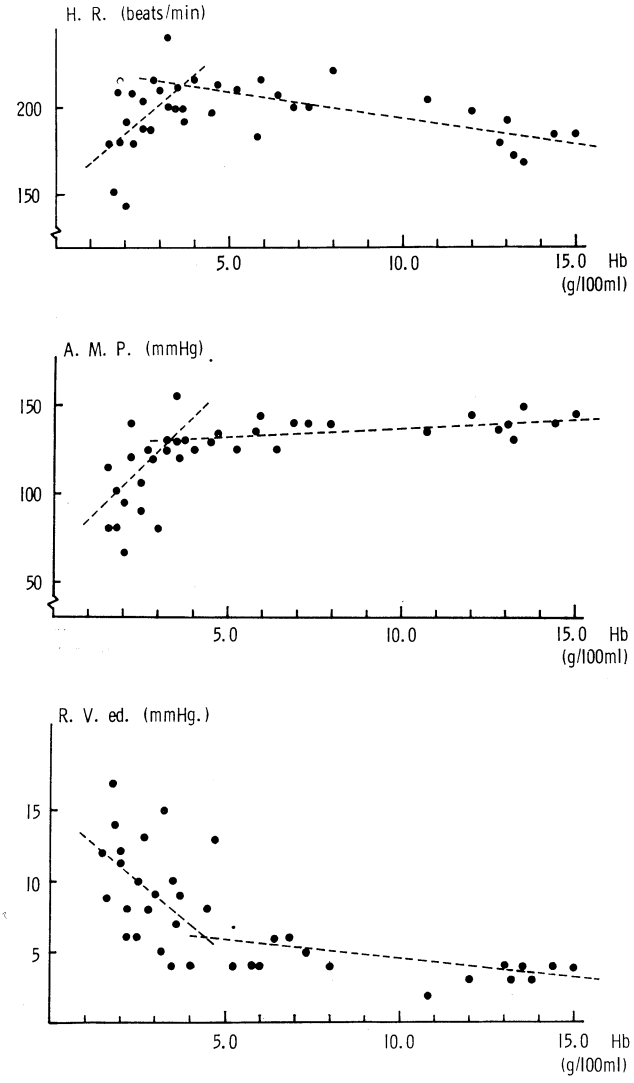

Fig. 1. Changes in heart rate (top), mean arterial pressure (center), and right ventricular end-diastolic pressure (bottom), caused by various degrees of reduction in Hb content. Progress of hemodilution is read from right to left. Individual data of 8 experiments plotted (see data) and regression lines. Note flection points of regression lines.

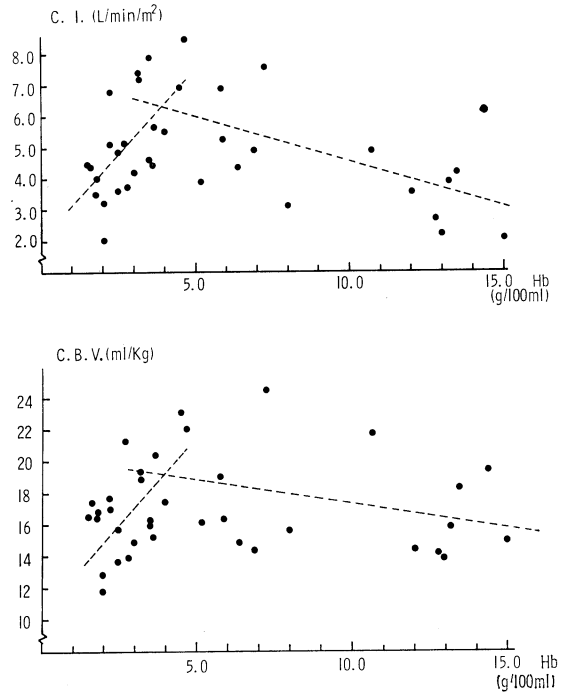

Fig. 2. Cardiac index (top) and central blood volume (bottom) during various degrees of reduction in Hb content. Note flection points of regression lines.

Arterio-venous oxygen content difference ($Ca\text{-}vO_2$) decreased at the flection point of 2.8 g/100 ml Hb (Figure 3).

Oxygen consumption showed a minimal decrease at about 5.5 g/100 ml Hb and decreased relatively sharply below that point (Figure 4).

Lactate values remained unchanged at approximately 7.7 mg/100 ml prior to the flection point at 4.1 g/100 ml of Hb. Later, it increased above the normal range (10-20 mg/100 ml) in all animals but one (Figure 4).

Arterial pH at first decreased slightly from 7.39 ± 0.01 to 7.33 at the flection point of 3.7 g/100 ml of Hb and decreased relatively sharply (Figure 4).

In general the flection points for the metabolic parameters were in the higher hemoglobin levels (3.7-5.5 g/100 ml) than those of the circulatory parameters (3.3-4.0 g/100 ml).

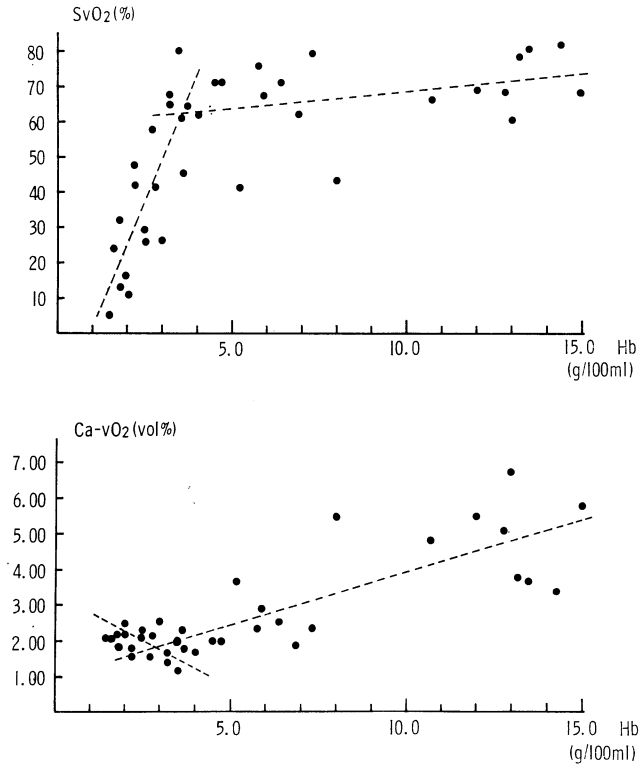

Fig. 3. Mixed venous oxygen saturation (top), and arterio-venous oxygen content difference (bottom) during various degrees of reduction in Hb content. Progress of hemodilution is read from right to left. Individual data of 8 experiments plotted (see data) and regression lines. Note flection points of regression lines.

DISCUSSION

Progressive hemodilution leads to a progressive decrease in Hb, with the exception of a peculiar rise from about 1.7 to 2.3 g/100 ml Hb (5% to 7% Hct), in spite of continuing blood exchanges. We may explain the latter as follows:[1] leakage of plasma from the vascular space due to increased venous pressure from hypervolemia and hypoxic capillary damage;[2] preterminal mobilization of red cells from storage organs. These possibilities will be supported by a similar rise of Hct observed with massive hemodilution by lactated Ringer's solution[25].

The changes observed in severe lethal hemodilution and artificial ventilation with 30% oxygen under conditions of this experiment suggest a classification of the deterioration of physiologic parameters into four

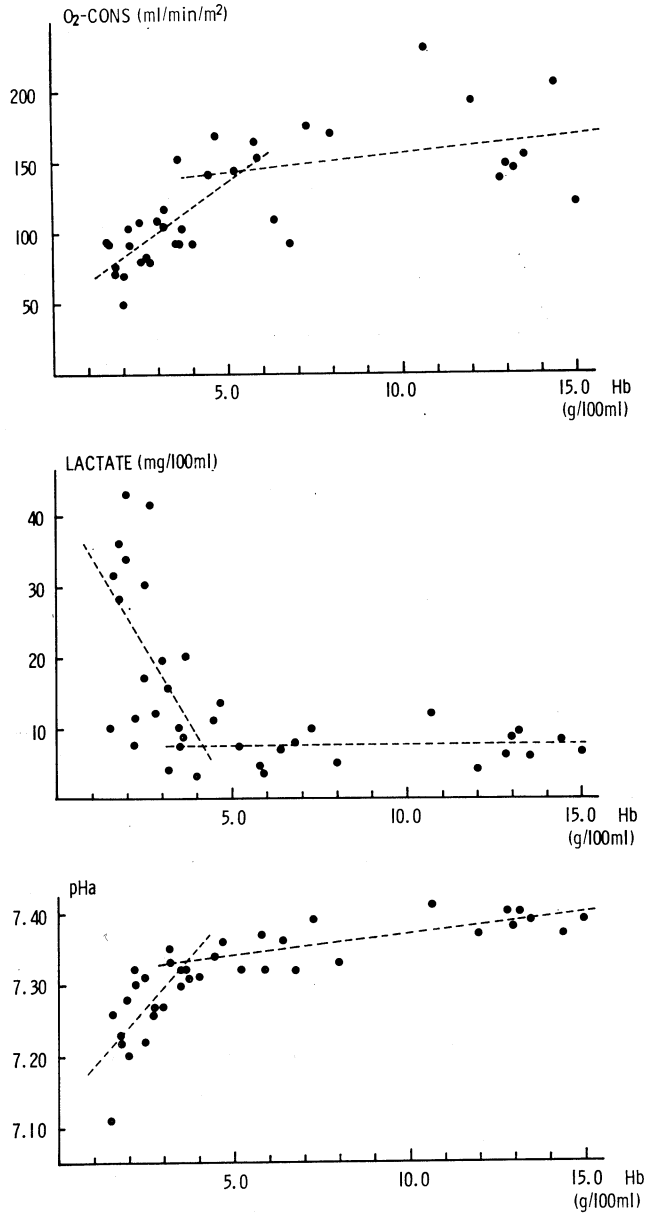

Fig. 4. Oxygen consumption (top), arterial lactate values (center), and arterial pH (bottom) caused by various degrees of reduction in Hb content. Progress of hemodilution is read from right to left. Individual data of 8 experiments plotted (see data) and regression lines. Note flection points of regression lines.

stages: (1) *complete compensation*, to 5.5 g/100 ml Hb; (2) *partial compensation*, between 5.5 and 4.0 g/100 ml Hb; (3) *reversible decompensation*, between 4.0 and 3.0 g/100 ml Hb; and (4) *irreversible decompensation*, below 3.0 g/100 ml Hb.

The flection point of deterioration appeared earlier for the metabolic than for the circulatory parameters. A decrease in oxygen consumption occurred before all of other parameters started to change. Although inadequate oxygen delivery to tissues results in decreased oxygen consumption, this parameter remains unchanged under mild or moderate hemorrhage[26]. There was no decrease in body temperature which could have explained the reduction in oxygen consumption. Even if the infused colloid per se would have suppressed oxygen comsumption, this would have been observed at higher Hct levels. There is no reason to believe that oxidative enzymes were inhibited under these experimental conditions. Therefore, the gradual decrease in oxygen consumption is best explained by a relative decrease in oxygen supply.

The slight and gradual decrease in oxygen consumption was followed at approximately 4.0 g/100 ml Hb by an increase in arterial lactate values, which in turn was followed by a sharp decrease in pH. At lower Hb levels, lactate values increased above the normal ranges. Cain[27] reported a marked increase in lactate values after acute anemia to 3 g/100 ml Hb. In contrast, Jervell[28] described an increase in lactate in most patients with chronic anemia, unrelated to hemoglobin content. In our previous studies, lactate values increased in some of the dogs hemodiluted to 3 g/100 ml Hb, but most values remained within the normal range[4,5]. The mild decrease in pH observed prior to reaching 3 g/100 ml Hb was found previously to be due primarily to a reduction in buffer base[4,5]

Between 5.5 and 4.0 g/100 ml Hb, circulatory parameters were well compensated and oxygen transport was well-maintained. The flection point of all circulatory parameters was between 4.0 and 3.0 g/100 ml Hb. Previous experiments proved changes at 3.0 g/100 ml Hb to be reversible most instances[4,5,6,24].

Many investigators have found that anemia without hypovolemia is accompanied by an increase in cardiac output[8–12,23,25,29]. Halmagyi and his associates demonstrated a logarithmic correlation between Hb content and cardiac index in anesthetized sheep during acute anemia[12]. All these observations were made at Hb values above 3-4 g/100 ml. In our studies, the greatest increase in cardiac index was reached at approxi-

mately 4.0 g/100 ml Hb, when it started to diminish. At the same time, right ventricular end- diastolic pressure increased sharply and heart rate decreased, suggesting depression at this point of myocardial function, presumably due to hypoxia. Case and associates[30] documented that the depression of ventricular function in severe anemia is caused by inadequate oxygen supply to the myocardium, due to a limited compensatory increase in coronary blood flow.

It is well-known that reduction in hemoglobin is paralleled by a reduction in venuos oxygen saturation. In *chronic* anemia increased oxygen extraction without increased cardiac output compensated well during rest, until hemoglobin values reached 5 g/100 ml[31]. In contrast, in *acute* anemia the increase in cardiac output occurs early at higher hemoglobin values. The cause of this difference in response between acute and chronic anemia is unknown. Wise[9] found progressive decrease in SvO_2 at hemoglobin levels below 6-9 g/100 ml. Murry[32] reported no significant reduction in SvO_2 in dogs at Hb levels of approximately 3-7 g/100 ml. A review of his data reveals a small but definite decrease in SvO_2 at Hb levels below approximately 5.5 g/100 ml. In our study, a reduction in Hb levels was not associated with a reduction in SvO_2 above approximately 3.5 g/100 ml Hb, at which point SvO_2 was 62%, only slightly lower than control. Below this point, SvO_2 decreased sharply. These observations correlate well with those of Murray[32].

Arterio-venous oxygen content difference decreased with progressive hemodilution and did not change or increased slightly at lower Hb levels (2.8 g/100 ml). This may be explained by the decline in cardiac output[26,33-35].

Hemodilution with equal volumes of colloid solutions within 100 minutes to approximately 3 g/100 ml Hb resulted in survival of 80% of 33 animals[4-6]. Expansion of plasma volume was essential. Hemodilution with lactated Ringer's solution in equal or 2.5 times the volumes withdrawn resulted in progressive hypovolemia and death[25]. Hemodilution with colloids below 3 g/100 ml Hb is unlikely to result in survival since all vital signs started to deteriorate at or below this level. The same critical hemoglobin level was suggested by Amberson[2].

The plasma substitutes used in these experiments draw fluid from the extravascular into the intravascular space. Comparable hemodilution with dextren 40 increased total blood volume to 150% of control and with HES to 130%[24]. In this study, there was an earlier rise in right ventricular end- diastolic pressure presumably due to a increase in total

blood volume. There was no evidence of pulmonary edema in spite of increase in total blood volume and cardiac decompensation. Actually, there was a tendency for central blood volume to decrease before death.

We may assume that the data observed in these healthy dogs are applicable also to healthy humans in whom massive hemorrhage treated with equal volumes of colloid solutions without hemoglobin would be reversible to 5 g/100 ml of Hb. However, in most clinical emergencies, patients may have impaired cardiac reserve or pre-existing metabolic disturbances. Under such circumstances, using hematocrit or hemoglobin values alone for determining the safe level of hemodilution may be insufficient. Our data indicate that in such cases central venous pressure and mixed venous oxygen saturation or tension would be useful additional parameters for monitoring.

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