Acute normovolaemic haemodilution – Is it a solution to reduce perioperative blood transfusions?

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ABSTRACT

Haemodilution is a technique used to reduce perioperative homologous blood transfusions. Haemodilution is a poorly investigated technique in veterinary medicine. This article reviews haemodilution as a potential technique to reduce perioperative homologous blood transfusions. The history of haemodilution is briefly reviewed followed by the mathematical basis to haemodilution. The issue of critical oxygen delivery and its implications for haemodilution are discussed. The effects of haemodilution on the patient, including the effects on oxygen transport, blood flow and coagulation are discussed as well as the use of colloids, fluids and blood components in haemodilution. The success and failure of haemodilution in human clinical trials and experimental evidence is discussed. Some guidelines are given for the use of haemodilution in small animal patients in the perioperative setting. It appears in all likelihood that haemodilution has a limited application in cats and other small patients. Haemodilution is most beneficial when the initial haematocrit is high, a low haemodiluted haematocrit is achieved, the patients circulating volume is large and a large amount of blood was lost. It is important to avoid haemoconcentration during surgery as this increases red blood cell loss. Haemodilution is not a substitute for poor surgical technique and inadequate haemostasis intra-operatively. Intravascular volume should be maintained throughout the procedure.

Key words: acute normovolaemic haemodilution, haemodilution, review, small animals.

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INTRODUCTION

During surgery blood is lost from the body and fluids are infused to maintain normovolaemia. As a result, the haemoglobin concentration drops and a corresponding drop in oxygen carrying capacity occurs. Surgical blood loss is well tolerated until a point where blood loss results in a reduction in oxygen delivery and tissue hypoxia occurs. In order to save red blood cells, a number of techniques have been employed. Preoperative blood donation, intra-operative blood salvage, pharmacological manipulation (haemostatics and haematinics), meticulous surgical haemostasis, and haemodilution have all been utilised. Cardiac bypass equipment was traditionally primed with heparinised blood and blood products and as a result homologous blood syndrome was commonly seen in these patients[45]. This prompted Panico and Neptune to prime the cardiac bypass circuit with saline in 1959, the beginnings of haemodilution[45]. Haemodilution has routinely been used in cardiac surgery since the early 1960s[27,45]. Acute normovolaemic haemodilution is performed by removing blood from the patient immediately prior to surgery and the replacement of blood with fluid to maintain normovolaemia. Haemodilution has been well utilised in healthy adults, children, and the elderly with good outcomes[45].

The research into haemodilution has been prompted by concerns raised with the transfusion of blood, namely the transmission of disease, septicaemia, transfusion reactions, hypocalcaemia, hypothermia, coagulation defects and vomition[8,45]. Haemodilution should be utilised in patients with a haematocrit greater than 34 % and who are expected to lose more than 1 litre of blood perioperatively[45].

THE CLASSIC ARGUMENT

Stehling and Zauder proposed that if a patient with a circulating blood volume of 5000 mℓ and a haematocrit of 45 %, lost 1000 mℓ of blood, a total of 450 mℓ of red blood cells were lost from the body[45]. On the other hand, if the same patient had a haematocrit of 25 % and the same blood loss occurred, a total of 250 mℓ of red blood cells were lost, representing a saving of 200 mℓ of red blood cells[45]. This has been the traditional impetus behind acute normovolaemic haemodilution (ANH). Brecher and Rosenfeld re-evaluated this model in light of the assumptions made in ANH models, namely that as blood is lost it is replaced with an equal volume of fluid resulting in a continually decreasing haematocrit[3]. Applying the integral equations developed, Bourke and Smith were able to show that the actual saving of red blood cells in Stehling and Zauder's model was only 181 mℓ and this occurred at the cost of removing 2939 mℓ of blood in order to achieve a haematocrit of 25 %[1,3]. If the autologous blood had been transfused after the 1000 mℓ of blood loss and the patient was still haemodiluted to a haematocrit of 25 %, the patient's final haematocrit would be 20.5 %[3]. Based on the same model of Stehling and Zauder, Weiskopf was able to show, using mathematical models, that a patient diluted to 25 % could lose 2500 mℓ of blood with normovolaemic haemodilution before a allogeneic blood transfusion was required[52]. The Weiskopf model differs from Brecher and Rosenfeld, in that they replace the surgically lost red blood cells with red blood cells and did not replace each millilitre of blood lost with blood[52]. When replacing red blood cells with red blood cells, savings are greatest when the haematocrit is diluted to the lowest possible safe clinical value[52]. Several clinical studies have only reported haemodilution with the removal of 1 or 2 units of blood and as a result have not demonstrated much benefit with haemodilution[52]. The allogeneic transfusion trigger point also plays an important role in showing the benefit of haemodilution. Weiskopf used a transfusion trigger of 15 % in his study[52].

The amount of blood saved by haemodilution is dependent on the patient's circulating blood volume, initial haematocrit, the diluted haematocrit, the allogeneic transfusion trigger point and surgical blood loss[13,21,22,52]. Haemodilution should be marked, the allogeneic trigger point set low and the blood loss marked

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for it to be most beneficial[22,52]. Acute normovolaemic haemodilution appears to be most beneficial in human patients in which more than 50 % of circulating volume is lost, who have a high initial haematocrit and can tolerate a marked dilution anaemia[13,22]. Using mathematical modelling, Feldman *et al.* showed that a patient with a haematocrit of 40 %, haemodiluted to 25 % and a loss of 2303 mℓ of blood did not necessarily benefit from haemodilution[13]. Feldman *et al.* also showed, that the same patient required the removal of 2250 mℓ of blood in order to achieve a maximum benefit from haemodilution[13]. This far exceeds the blood loss occurring during the procedure. If the haematocrit is less than 30 % it is not possible to save an appreciable amount of red blood cells even if the patient is haemodiluted to 15 %[13].

CALCULATING ALLOWABLE BLOOD LOSS

The allowable blood loss or blood to be removed for haemodilution can be calculated from the following equation after Bourke and Smith[1]:

$$L_t = V(\ln H_0 - \ln H_t)\,, \qquad (1)$$

where L_t = blood loss or removed, V = circulating blood volume, ln = natural logarithm, H_0 = initial haematocrit and H_t = final haematocrit.

The final haematocrit is taken as the lowest possible haematocrit that the patient can tolerate without affecting oxygen delivery and is usually a clinical judgement. This equation assumes that an equal volume of colloid or fluid replaces blood removed and that the changes in blood composition are instantaneously equalised within the circulating system[1]. This means that when initially calculating the maximum allowable blood loss from the above equations, it does take into account the fact that as blood is lost and replaced with fluid, the haematocrit decreases and hence the amount of haemoglobin lost from each successive millilitre of blood loss is less[17]. This was also not considered in the original model of Stehling and Zauder[45].

Bourke and Smith's equation[1] was simplified through Taylor series expansion, which introduces a small error in the calculation of haematocrit that is less than 1.2 % and usually over estimates the haematocrit[1]. The transformed equation is as follows:

$$L = V(H_0 - H_t)(3 - H_m)\,, \qquad (2)$$

where L = blood loss, V = circulating blood volume, H_0 = Initial haematocrit, H_t = final haematocrit and H_m = mean haematocrit ($(H_0 + H_t)/2$). The haematocrit value is entered as a decimal fraction.

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$$L = V \times ((H_0 - H_t)/H_m)\,, \qquad (3)$$

where L = blood loss, V = circulating blood volume, H_0 = initial haematocrit, H_t = final haematocrit and H_m = mean haematocrit ($(H_0 + H_t)/2$).

Gross's equation may have an error of up to 7.5 % but this equation is still considered to be clinically acceptable[17,45]. If blood loss is rapid and not replaced immediately with fluid, these equations may overestimate allowable blood loss[17]. By rearrangement the final haematocrit after haemodilution can be calculated:[3]

$$H_t = (H_0 \times V \times (1 - e^{-L/V}))/L\,, \qquad (4)$$

where H_t = final haematocrit, H_0 = initial haematocrit, V = circulating blood volume, L = blood loss, and H_m = mean haematocrit ($(H_0 + H_t)/2$).

EFFECTS OF HAEMATOCRIT ON BLOOD FLOW

The normal viscosity of plasma is 1.8 relative to water, with the addition of red blood cells the viscosity goes up to 3 or 4 times that of water. Viscosity of blood increases with increasing haemoglobin concentrations. Flow is inversely related to viscosity (Poiseuille's Law) and resistance increases with viscosity. As resistance increases myocardial work increases and hence an optimal viscosity (haemoglobin concentration) exists. Oxygen delivery does increase when haematocrit increases in spite of the drop in flow that is compensated for by an increase in myocardial work, up to a haematocrit of 55 %. After this, a drop in oxygen delivery occurs. Oxygen delivery increases as haematocrit drops as result of reduction in viscosity aiding forward flow. This occurs until the oxygen carrying capacity is too low, such that the increase in cardiac output does not compensate for the drop in oxygen carrying capacity. The optimal haematocrit for oxygen delivery has been shown to be about 30–32 %.

Haematocrit and oxygen delivery are interrelated through cardiac output. As haematocrit falls the cardiac output needs to increase to maintain a constant delivery of oxygen. The converse would also be theoretically true, the higher the haematocrit the lower cardiac output has to be. This relationship is shown below.

$$DO_2 = CO \times CaO_2\,, \qquad (5)$$

where $CaO_2 = (Hb \times 1.34 \times SaO_2) + 0.003 \times PaO_2$.

$$DO_2 \approx CO \times (Hb \times SaO_2)\,, \qquad (6)$$

where DO2 = oxygen delivery, CO = cardiac output, CaO_2 = arterial oxygen content, Hb = haemoglobin, SaO_2 = arterial oxygen saturation, PaO_2 = arterial partial pressure of oxygen.

If DO_2 is to remain constant then CO changes to compensate for changes in Hb:

$DO_2 = 1$ & Hb = 1, therefore CO = 1
$DO_2 = 1$ & Hb = 1/2, therefore CO = 2
$DO_2 = 1$ & Hb = 1/4, therefore CO = 4.

A reduction in haematocrit by 40 % is correlated with a 26 % increase in cardiac output and a reduction in peripheral vascular resistance by 25 %[32,35]. An increase in haematocrit by 47 % results in a reduction in cardiac output by 51 % and an increase in peripheral vascular resistance by 50 %[32,35]. A rising haematocrit reduces cardiac output faster than what a reducing haematocrit increases cardiac output does[32,35]. The changes in peripheral vascular resistance is due to changes in blood viscosity[35]. Richardson and Guyton used the term 'cell flow' to define the delivery of oxygen. Cell flow is the product of cardiac output and haematocrit[35]. It gives an indication of the number of red cells available each minute per kilogram for the delivery of oxygen when the cardiac output is adjusted to body weight. The maximum cell flow occurs at a haematocrit of 40 %[35]. Several other workers have repeated these experiments with similar results[45]. During haemodilution, a reduction in blood viscosity aids the increase in cardiac output[45]. Haemoconcentrated patients benefit from haemodilution and blood flow usually improves[32].

HOW LOW CAN IT GO?

Haemoglobin is the major carrier of oxygen in blood and hence has the greatest influence over the oxygen carrying capacity of blood. It is important to realise that the binding of oxygen to haemoglobin is influenced by the arterial partial pressure of oxygen in the relationship defined by the oxygen dissociation curve. For arterial tensions higher than 120 mm Hg, the net increase in arterial oxygen content is small and mainly de-

rived from that portion dissolved in plasma. When arterial oxygen tension drops below 60 mm Hg, arterial oxygen content drops rapidly. This has important implications when performing haemodilution. It is well known that a healthy patient has considerable reserve for oxygen delivery[45]. Oxygen delivery is strictly defined as the amount of oxygen delivered per unit time. This usually then equates to function of body mass, either weight or body surface area. Oxygen delivery is then defined as mℓ O_2/kg/min or O_2/m^2/min. Oxygen delivery is usually calculated from Equation (5).

Usually the percentage of oxygen dissolved in plasma is small and this part of the oxygen carrying capacity equation is ignored. Cardiac output determines the work at which oxygen is delivered. Normal resting human adults consume approximately 250 mℓ O_2/min while the cardiovascular system delivers 1025 mℓ O_2/min[45]. This allows for considerable reserve and variation in the delivery of oxygen.

Critical oxygen delivery can be defined as the absolute minimum amount of oxygen that needs to be delivered, below which tissue hypoxia becomes evident and oxygen consumption becomes delivery dependent[26]. In humans, this value has been determined at less then 7.3 mℓ O_2/kg/min[26]. Maximal oxygen delivery can be defined as the highest oxygen delivery possible per unit time. Neither maximal nor critical oxygen delivery takes into account the work required to deliver oxygen. Optimal oxygen delivery occurs when the highest possible oxygen delivered at the lowest possible work rate occurs.

The critical level of haemodilution is the point at which critical oxygen delivery occurs[51]. In a Jehovah's Witness undergoing massive surgery, cardiac output (5.8 ℓ/min) was decreasing but still raised above preoperative levels and blood pressure (MAP 56 mm Hg) was reduced at a haematocrit of 8 %[51]. The critical point of oxygen delivery determined by van Woerkens *et al.* was 4.9 mℓ/kg/min and this occurred at a haemoglobin concentration of 4 g/dℓ[51]. Several animal studies have indicated that at a haematocrit of 10–15 % tissue oxygenation is maintained[52]. In humans, haemoglobin levels of 6 g/dℓ are well tolerated[52] and 8.8 g/dℓ is safely tolerated in geriatric patients[44]. In primates, a haematocrit of 10 % is well tolerated[45]. Extreme haemodilution to a haematocrit of 9 % has been performed safely in children[22]. The critical value of haemoglobin at which oxygen delivery is equal to oxygen utilisation has been shown to occur at 3.5–4.0 g/dℓ (haematocrit of ±10 %)[50]. Total oxygen extraction at this point is approximately 60 %, which correlates with values recorded during haemorrhagic shock[50]. At a haematocrit of less than 25 % (Hb < 7.5 g/dℓ) evidence of myocardial ischaemia has been found in human patients with coronary heart disease[2]. Oxygen delivery to organs remains unchanged at a haematocrit between 20 % and 25 %[18]. Children diluted to a haematocrit of 9 %, showed no signs of global hypoxia or impairment of cardiac function[14]. In dogs, haemodilution has been safely performed at a haematocrit of 10 %[32]. In patients with cardiac disease the critical point of oxygen delivery has been shown to be approximately 300 mℓ/m^2/min[51]. Human critical care has defined the limits of oxygen delivery as a mean blood pressure of 60 mm Hg, a cardiac index of 2.2 ℓ/min/m^2 and a mixed venous saturation of 60 %[14]. In dogs, a critical point of oxygen delivery has been found at 10 mℓ/kg/min and 7.9 mℓ/kg/min[51]. In another study in pigs, critical oxygen delivery has been found to occur at a haemoglobin concentration of 3.9 g/dℓ[51]. The critical level of oxygen delivery in rabbits has been found to be between 8.4 and 10.9 mℓ/kg/min and in pigs at 10.4 mℓ/kg/min[31,41]. All of these studies have been performed on anaesthetised animals and the level of critical oxygen delivery in conscious patients is most probably a lot higher. Measurement of tissue oxygen tension in the liver, brain, heart, kidneys, intestines and muscle in research animals has shown that it is well maintained at a haematocrit of 20 %[45]. Critical levels in mixed venous saturation at which hypoxia becomes present have been identified between 32% and 44 %[40,49]. It is important to realise that mixed venous saturation is not as important as mixed venous oxygen tension[40]. When mixed venous oxygen tension is below 3.5 kPa, tissue hypoxia becomes evident[43]. Any reading of mixed venous saturation should be interrupted in light of the current disposition of oxygen dissociation curve[40]. A critical mixed venous oxygen tension of 29.9 mm Hg has been determined in hypovolaemic dogs[49]. In haemodiluted normovolaemic dogs critical oxygen delivery occurs at a mixed venous saturation of 32.3 mm Hg[49]. Under anaesthetic conditions cardiac output does not always increase in response to hypoxia[50]. Anaemic hypoxia is a potential complication of haemodilution if careful attention is not paid to oxygen delivery (haemoglobin concentration)[34].

Haemodilution has traditionally been performed to a haematocrit of 30 % based on the fact that optimal oxygen delivery occurs at this haematocrit[22,32]. During cardiac surgery, the haematocrit is reduced to 15–20 % while on the bypass circuits[28,29]. Fontana *et al.* showed that haemodilution can be safely performed when the haematocrit is lower than 20 %[14,30]. At a haematocrit of 10 % there is very little room for error and a target haematocrit of 20 % allows us a fair margin of safety[30].

Below levels of critical oxygen delivery, signs of circulatory collapse and shock develop. Signs of shock include a reduction in cardiac output, an increase in central venous pressure, bradycardia, a decrease in mixed venous saturation, an increase in arterial lactate concentration and a decreased arterial blood pressure[39,41]. Hypoxia is not well tolerated during haemodilution[41]. Every patient has a minimally tolerable haematocrit, but this is seldom clinically known and the degree of haemodilution is usually performed on the basis of an educated guess.

WHEN TO REPLACE LOST BLOOD WITH BLOOD

There is as of yet no consensus when to replace surgical blood lost with blood. Blood has been replaced at the end of surgery, below a certain haematocrit (transfusion trigger), after a certain volume of blood has been lost or as soon as surgical blood loss occurs[13]. The timing of autologous blood transfusion may have an impact on the effectiveness of haemodilution to save red blood cells. If blood loss is not compensated for with adequate fluids and colloids, shock may rapidly ensue. When haemodiluted (Ht 11 %), all pigs that lost 40 mℓ/kg of blood died due to cardiovascular collapse[39]. The control group of non-haemodiluted pigs (Ht 33 %) tolerated this blood loss with only 1 death in 6 pigs[39]. It is concluded from this study that hypovolaemia during haemodilution is not tolerated and adequate fluids should be given intra-operatively as blood loss occurs[39].

Blood removed and stored at room temperature should be used within 6 hours of removal[45]. Storing at room temperature has been shown to preserve platelet function[45]. Platelet aggregation and inhibition of coagulation factors are 2 problems associated with the use of heparin for blood collection[8].

EFFECTS ON CARDIORESPIRATORY FUNCTION

In uncompensated haemorrhage (haemorrhagic shock), cardiac output and stroke volume decrease rapidly[4]. As a result of this cardiac output, stroke volume and central circulating volume are integrally related (Frank Starlings Law)[4]. In haemodilution, central circulating volume is maintained by the infusion

of fluids and colloids. Haemodilution results in an increase in cardiac output and myocardial and coronary blood flow which is coupled to the central circulating volume (preload of the left ventricle)[2,4,32,49]. Blood pressure usually remains essentially unchanged during haemodilution but the pulse pressure widens[9,16,32,53]. As a compensatory effect to the reduced arterial oxygen content, cardiac output increases to maintain oxygen delivery[2,5]. Cardiac output may increase as a result of changes in heart rate or stroke volume or both[12,48,49]. The increase in cardiac output in dogs appears to be due to an increase in heart rate and a reduction in peripheral vascular resistance[12,20,45]. Other workers have shown that stroke volume and contractility are also increased[14,18,20]. In cats it appears that the primary increase in cardiac output is the result of an increase in stroke volume, which is different to what has been reported in dogs[47]. Stroke volume increases as a result of an increase in venous return indicated by a rise in central venous pressure and pulmonary capillary wedge pressure[14,30,49]. The decrease in peripheral vascular resistance is the result of changes in blood rheology[45]. Accompanying the reduction in blood viscosity is an increase in peripheral vascular bed area (vasodilatation), resulting in further reduction in peripheral vascular resistance[15]. After the administration of colloids during haemodilution blood viscosity is reduced, and this may in part explain the increase in cardiac output seen during haemodilution[4,5]. The reduction in peripheral vascular resistance is mediated through the release of nitrous oxide[9]. The stimulus for nitrous oxide release from the endothelial cells is in response to changes in blood flow and shear stress[9]. Alternatively, the reduction in red cell mass may also reduce the bodies ability to scavenge nitrous oxide[9]. Some authors have suggested that systemic vasoconstriction does occur[16]. No electrocardiographic or ST segment changes have been reported during haemodilution[16]. If this compensatory effect is not maintained then tissue hypoxia may occur[2].

Some evidence has been presented that the increase in cardiac output may not be maintained for longer than an hour[2]. In a study on dogs, Bowens *et al.* showed that cardiac output, coronary blood flow, stroke volume and plasma noradrenalin concentration increased during progressive haemodilution[2]. No changes were observed in adrenalin, arterial blood pressure, pulmonary blood pressure, systemic vascular resistance and pulmonary vascular resistance[2]. The target haemodilution in this study was a Hb of 7.5 g/dℓ and this was maintained for 4 hours[2]. During this period of haemodilution, no changes in cardiovascular parameters were reported with the exception of a rise in left ventricular pressure that decreased in the 4th hour[2]. It was concluded from this study that extended periods of moderate haemodilution were well tolerated and the compensatory reflexes were maintained[2].

Carey has suggested that haemodilution should not be undertaken in patients with a reduced ability to increase cardiac output as total systemic available oxygen (cardiac output and arterial oxygen content) is reduced and not compensated for during haemodilution[5]. Geriatric patients have a reduced cardiovascular functional reserve at maximum cardiac effort[44].

Talwar *et al.* reported on the effects of adrenalin, acetylcholine and sodium nitroprusside on cats undergoing haemodilution to a haematocrit of 14 % (Hb 4.0 g/dℓ)[47]. They were able to show that cardiac output, stroke volume and heart rate increased and total peripheral vascular resistance decreased during haemodilution[47]. The increase in mean arterial blood blood pressure, heart rate, left ventricular systolic pressure and left ventricular pressure rise (dP/dt) induced by adrenalin was reduced during haemodilution[47]. Haemodilution also decreased the cardiovascular responses to acetylcholine and sodium nitroprusside[47]. The haemodynamic response to dobutamine is altered during haemodilution[42]. Higher doses of dobutamine are required to increase cardiac output and little effect is seen on peripheral vascular resistance and left ventricular end diastolic pressure compared with normal subjects[42]. The increase in contractility caused by dobutamine is reduced although it still exerts a positive effect[42]. The failure of dobutamine to affect systemic vascular resistance and left ventricular end diastolic pressure are most probably related to the cardiovascular effects of haemodilution itself[42]. These results suggested that the cardiovascular system's responses to cardiovascular drugs are altered under conditions of haemodilution[42,47].

Much debate has existed as to the physiological control of compensatory mechanisms of haemodilution. In a carefully designed trial, Fahim *et al.* showed that the increase in cardiac output was the result of a reduced vagal outflow but they were also able to show that part of the response was mediated by the normal autoregulatory mechanisms of the heart independent of the autonomic nervous system[12]. Aortic chemoreceptors in cats appear to be sensitive to 'anaemia' and result in a large increase in cardiac output when stimulated[45].

Total body oxygen consumption remains unchanged during haemodilution[18,20]. The partial pressure of oxygen in arterial blood is not affected by haemodilution[12,49]. The oxygen extraction fraction increases during haemodilution and this is accompanied by a decrease in mixed venous saturation and in a widening of the difference in arterial-venous oxygen contents[6,16,18,40,44,45,49]. During moderate and extreme haemodilution, blood pH and base excess is well maintained[28,32,49]. There are no significant changes in blood lactate during haemodilution[32]. With a decreasing haematocrit, the oxygen dissociation curve shifts to the right[48,51]. An acute right shift in the oxygen dissociation curve can occur at a haematocrit below 10 % over and above the expected changes due to changes in pH and $PaCO_2$[51]. Blood pH has been shown to decrease during haemodilution[4]. A right shift has been associated with a decrease in mixed venous saturation[51]. Changes in the oxygen dissociation curve may play an important role in oxygen delivery during haemodilution[51]. Although the right shift affects oxygen loading in the lungs, due to the high inspired percentage of oxygen used under anaesthesia this is seldom a clinical problem[30]. There is no evidence to indicate that a change in 2.3 DPG takes place during haemodilution in man, but in dogs an increase has been demonstrated[45]. Total lung water has been shown to increase during haemodilution with Ringer's lactate[25]. No changes in pulmonary function have been recorded as a result of haemodilution[45].

As the heart extracts the most amount of oxygen of all organ systems within the body, a lot of research into the effects of haemodilution on cardiac blood flow has followed[45]. Myocardial blood flow increases sufficiently to compensate for the drop in oxygen content during haemodilution[16,18,45]. The increase in coronary blood flow is greater than the increase in aortic blood flow[45]. Myocardial oxygen extraction does not increase during haemodilution[18,45]. Even at a haematocrit of 20 %, the heart continues to metabolise lactate despite a significant increase in myocardial work[18]. Severe haemodilution may well affect the regional distribution of blood flow in the myocardium[45]. The changes in regional blood flow were accompanied by ST segment changes in the ECG, an indicator of myocardial hypoxia[45]. Coronary artery disease reflected as a 50 % reduction in coronary artery diameter has a similar effects on the heart as haemodilution to a haematocrit of 20 %[45]. At a haematocrit of less than

10 %, the coronary blood vessels are fully dilated and further increase in coronary blood flow is not possible[45]. Cardiac blood flow is regulated by myocardial work[36]. At a haematocrit of 20 %, coronary blood vessel reserve is severely compromised and this may predispose patients with myocardial disease to hypoxia[16].

The increase in coronary blood flow is accompanied by an increase in cerebral blood flow and cerebral autoregulation becomes narrower[45]. The effect of blood flow on other organ systems is not conclusive but splenic, renal, duodenal, and pancreatic blood flow remains constant or increases slightly and skeletal, muscle and skin blood flow increases[32,36,45]. Microvascular blood flow is increased and better distributed due to reduced viscosity and Rouleaux formation[20,45].

HAEMOSTASIS

It is important to realise that dilution and platelet dysfunction are causes of post-operative bleeding tendencies[23]. Colloids and lactated Ringer's are known to significantly affect coagulation[23]. Fibrinogen, factor V, factor VII and platelets have been shown to decrease during haemodilution[7,45]. This has resulted in a prolongation of prothrombin and partial thromboplastin time[23,45]. Dale *et al.* failed to show any statistical difference in platelet count between moderate (Ht 27.4 %) and extreme haemodilution (Ht 16.5 %)[7]. Reaction time for clot formation is delayed while the rate of clot formation and clot strength were reduced with hetastarch, gelatine and albumin[11]. Surgical bleeding time has not been found to increase[45]. These values have been found to return towards normal in a short space of time[45]. Hobisch-Hagen *et al.* showed no statistical difference in prothrombin time and activated partial thromboplastin time between a haemodiluted group and a control group[19]. This group also studied fibrinolysis and concluded that there was no statistical difference between groups[19]. However, other workers have shown that hetastarch, gelatine and albumin promote clot lysis[11]. Hobisch-Hagen *et al.* could conclude that the degree of coagulation and fibrinolytic disturbances were correlated to the invasiveness of surgery[19]. Fresh autologous blood is richer in clotting factors than stored blood[27].

SELECTION OF COLLOIDS

Owing to the rapid redistribution of crystalloid solutions, 3–5 times the volume of blood withdrawn must be replaced[45]. The use of less than 3 times the volume results in a decrease in cardiac output and blood pressure as a result of hypovolaemia[45]. Saline maintains circulating volume for less than 2 hours[4]. Larger molecules including dextran-70 are expected to maintain circulating volume for longer[5]. A solution of 2.5 % dextran-40 has been found to support circulating volume for approximately 2 hours[4,5]. Albumin has been used for haemodilution, but is associated with some risk of disease transmission and serum hepatitis[6]. Low molecular weight dextrans or small-sized molecules are excreted by the kidney, pass more rapidly through the capillary walls and are more rapidly metabolised than high molecular weight colloids[47]. Dextran-based solutions are known to induce allergic reactions[33].

Dextran-40 may promote a haemorrhagic diathesis at a dose greater than 1 mg/kg[5]. Hetastarch may affect coagulation by inhibiting platelets, reducing Factor VIII function and volume dilution of clotting factors[38]. Hetastarch and gelatine significantly delay activated clotting time and reduce clot formation[23]. Ringer's lactate appears to have the least effect on clotting parameters[23]. Saline tends to create a hypercoagulatable state and reduce clot lysis[11]. Synthetic colloids exert an oncotic pressure and counteract the drop in protein oncotic pressure due to haemodilution[38]. Hetastarch 6 % may be used on a volume-to-volume basis to replace blood withdrawn. Hetastarch 10 % is hypertonic and additional fluid may be required. Hetastarch 10 % results in a volume expansion of a 140 % of the infused volume such that 500 mℓ of hetastarch will increase plasma volume by 700 mℓ[38]. The maximum recommended dose of hetastarch is 20 mℓ/kg[38]. Haemodilution with dextran-60 maintains oncotic pressure[32]. Ionised Ca^{++} concentrations are well maintained with hetastarch and gelatine and decrease when albumin and saline are used, but all values remained within the physiological range[11].

Bovine haemoglobin has been shown to add to the carrying capacity of oxygen in blood and has been shown to be a suitable substance for exchange of red blood cells[24]. Haemoglobin substitutes decrease cardiac output and may reduce oxygen delivery in spite of raised oxygen carrying capacity[24]. The net effect is that a haemoglobin substitute does not improve oxygen delivery[24]. The role of haemoglobin substitutes needs to be further evaluated before recommendation for haemodilution can be made.

Current recommendations indicate that each millilitre of blood removed is replaced with 1 mℓ of colloid and 0.5–1 mℓ of crystalloid solution[45]. Crystalloids may be advantageous in that diuretics can be administered prior to the infusion of autologous blood to prevent a volume overload[45]. Peripheral oedema is not uncommon during haemodilution and must not be equated to pulmonary oedema[45]. The use of crystalloid solutions and other solutions with high sodium content may cause a total body sodium overload requiring excretion in the post-operative period[29].

CONTRAINDICATIONS

In humans, haemodilution is contraindicated in patients with a haemoglobin concentration of less than 11 g/dℓ, patients with renal failure, in cardiac disease when an increase in cardiac output is required Haemodilution is contraindicated in patients with lung disease with an associated desaturation of haemoglobin, increased oxygen consumption as occurs with sepsis and fever, myocardial and valvular disease, impairment of oxygen loading and in patients with chronic anaemia[34].

IS IT WORTH IT?

The volume of blood lost by patients undergoing aortic valve replacement was reduced by 47 % by extreme haemodilution (Ht 18 %)[27]. This resulted in less homologous blood being transfused[27]. It is important to realise that in this study the extreme haemodiluted group had a final haematocrit of 10 % lower than the moderately haemodiluted group[27]. Haemodilution has reduced the need for homologous blood transfusion[33]. Cohn *et al.* reported that preoperative phlebotomy and autologous blood transfusion reduced post-operative homologous blood transfusion requirements (4.3–3.9 units per patient) in patients undergoing cardiac bypass for cardiac surgery compared with 8 units per patient when haemodilution was not performed[6]. In another study by Lilleaasen and Stokke similar results were obtained when evaluating blood loss in patients undergoing aortic valve replacement on bypass[28].

Brecher and Rosenfeld showed in a mathematical model that acute normovolaemic haemodilution did not save more than 540 mℓ of blood when 2500 mℓ of blood was lost from a circulating volume of 5000 mℓ and the transfusion was started when a haematocrit of 18 % was reached[3]. Similarly, only 270 mℓ was saved when the transfusion was started at a haematocrit of 25 %[3]. Brecher and Rosenfeld's study calls into question the efficiency of saving red blood cells[3]. It is important to bear in mind that as red blood cells are diluted so are white blood cells, clotting factors, platelets and all the other components of blood. Most mathematical models do not adjust for potential

increases in haemorrhage associated with the dilution of clotting factors and platelets[3]. Clinically though the mathematical assumption appears to be valid, as no increase in intra-operative or postoperative bleeding has been reported[3]. Very little work has been performed on the potential saving of clotting factors, platelets and other components of blood that haemodilution may have[13].

Several clinical studies have demonstrated dramatic savings of red blood cells from haemodilution[13,45]. A closer study of these trials will reveal several design flaws in these studies[13]. Very few carefully controlled, prospective, double-blind studies have been performed with haemodilution[13,45]. Failure to apply the same methods to control groups and haemodiluted groups in several studies has resulted in erroneous results[13]. Some of the clinical studies used historical or sicker patients in the control groups resulting in unfair comparisons being made[3]. The results of several mathematical models concur and show less dramatic savings in red blood cells[13]. Some clinical trials have supported this with minor saving in red blood cell mass[13]. Very often the clinical trial showing benefit fails to take note of the mathematical modelling of haemodilution and do not utilise the principles which allow for the greatest saving of red blood cells[21].

Haemodilution is not a benign procedure and may be associated with the retransfusion of contaminated blood, accidental transfusion of another patient's blood and haemodilution predisposes the patient to a blood transfusion should the removed blood become unusable[3,13]. Each unit of blood withdrawn from the patient should be appropriately labelled. Haemodilution may add an additional 40 minutes onto the procedure time[33].

MONITORING

Appropriate monitoring is indicated according to the clinical status of the patient and the degree to which the patient is haemodiluted. An ECG should be used to evaluate heart rate and rhythm and to observe for changes in the ST segment, an indicator of myocardial hypoxia. Fluid load should be monitored through central venous pressure or pulmonary capillary wedge pressure. Urine output (2 mℓ/kg/hr) is also a useful guide to intravascular volume status. Serial determinations of haematocrit are essential to follow changes in haematocrit during the procedure. Invasive blood pressure monitoring, pulse oximetry and capnography provide important and useful information and are imperative[41]. A continual record of blood loss should be kept and fluids, colloids or blood administered appropriately. Blood gas analysis of both arterial and mixed venous blood is useful. A good correlation between mixed venous saturation and central venous saturation during haemodilution has been found and central venous blood may be used[40]. The mixed venous saturation should be maintained above 60 %[14]. Lactate, standard bicarbonate, base excess and SvO_2 are better indicators of inadequate systemic oxygenation than cardiovascular parameters[41]. Global measures of oxygen delivery and other indicators of global hypoxia may mask hypoxia of individual organs or systems[46].

CONCLUSIONS

Haemodilution is not without risk. Haemoconcentration due to fluid deficits from fasting, 3rd space losses, dehydration, diarrhoea and vomition should be corrected before surgery starts. Haemoconcentrated patients will lose more haemoglobin than normal patients and should be avoided in all surgical patients. Any technique used to save red blood cells cannot compensate for poor surgical technique and inadequate intra-operative haemostasis. ANH is an option to preserve the patient's own red blood cells. Adequate fluids, colloids and blood should be administered to maintain normovolaemia and the haemoglobin concentration above minimum levels.

The circulating volume of a cat is approximately 66.7 mℓ/kg while that of a dog is 92.5 mℓ/kg[37]. The normal haematocrits of cats and dogs are 30–45 % and 37–55 %, respectively[10]. In view of the small mass, low circulating volume and generally lower haematocrits of cats, haemodilution is unlikely to be as useful in cats as it is in dogs. From mathematical modelling it is known that a high initial haematocrit, a low diluted haematocrit, the patient's circulating volume and a large amount of blood loss are required to obtain the maximum benefit from haemodilution. Dogs are more likely to benefit from haemodilution. Very few clinical trials have been performed in veterinary medicine and thus the value of haemodilution is not known. Increasing the patient's red blood cell mass with erythropoietin, prior to haemodilution may show potential advantages but at this stage is largely experimental[13].

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