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Impact of Acute Normovolemic Hemodilution in Organ and Cell Structure

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1. Introduction

Rigorous control procedures adopted presently by blood banks have reduced transfusion-associated risks, such as transmission of infectious diseases. Nevertheless, other complications related with blood-transfusions remain, such as transfusion-related acute lung injury (TRALI) and other immune disorders. In critically ill patients, transfusion has been associated with increase in morbidity and mortality, so that restrictive transfusion strategies have been proposed, which have reduced incidence of organ dysfunction as well as of other complications (Hajjar et al., 2010; Hebert et al., 1999).

In order to reduce or even avoid the need for transfusions in surgeries involving massive blood-loss, alternatives such as tolerance of lower hemoglobin levels or use of acute normovolemic hemodilution (ANH) have been considered. However, both strategies involve reduction of arterial oxygen content and alteration of rheological blood properties, which can affect oxygen delivery to organs and tissues. Acute anemia elicits a number of responses, such as decrease in vascular resistance and compensatory increases in heart rate and cardiac index (Ickx et al., 2000). These compensatory mechanisms provide maintenance of oxygen transport to tissues until a critical hemoglobin limit is reached.

When performing ANH, two important aspects that must be considered are the target hemoglobin level and the type of replacement fluid to maintain volemia. During acute anemia, oxygen content decreases and myocardial oxygen consumption increases because of increases in stroke work and heart rate (Ickx et al, 2000). Regarding the hemoglobin or hematocrit level, the main organs of concern are the heart and brain because of their high oxygen demand.

The objective of this review is to discuss the impact of acute normovolemic anemia on specific organs and tissues, focusing on experimental studies.

2. Heart tolerance to acute anemia

During acute anemia, the decrease in oxygen supply is compensated with increases in stroke index and heart rate. However, if a critical limit is reached, the heart may not be able to sustain the increased pumping requirement (Crystal et al., 1988). Although in normal conditions the heart is capable of tolerating extreme hemodilution, moderate anemia can

jeopardize myocardial oxygenation and contractility in specific patients, particularly in those with coronary artery disease. Therefore the detection of early signs of inadequate oxygen delivery is of paramount importance and, for this reason, cardiac tolerance to ANH has been extensively investigated. Cardiovascular function monitoring as well as systemic and regional markers of hypoxia have been used to identify critical oxygen delivery (Diebel et al., 2000; Mekontso-Dessap et al., 2002; Torres Filho et al., 2005). Conventional hemodynamic monitoring is a poor means to detect early cellular oxygen deprivation. Alterations in ECG, increases in lactate levels and hemodynamic instability occur only after tissue hypoxia has ensued. In healthy human volunteers, acute anemia (hemoglobin 5-7g/dL) promoted signs that were suggestive but not conclusive of myocardial ischemia, as evaluated by ECG ST-segment changes (Leung et al., 2000).

Few studies have addressed the effect of hemodilution in patients with cardiovascular diseases. A study demonstrated that ANH to a mean hemoglobin value of 8.6 g/dL was well tolerated in anesthetized patients with coronary artery disease who were receiving beta-blockers. These patients presented no ECG abnormalities or hemodynamic instability (Licker et al., 2004). A recent study comparing transfusion strategies in 512 patients, submitted to cardiac surgery, found that a restrictive strategy, defined as a transfusion performed when the hematocrit reached values of ≥ 24%, was as safe as the liberal strategy, defined as hematocrit ≥ 30%. The resulting mean hemoglobin values were 9.1 g/dL and 10.5 g/dL for the restrictive and liberal groups, respectively (Hajjar et al, 2010).

Except for few reports involving Jehovah's Witnesses patients (Gutierrez & Brotherton, 2011; Hashem & Dillard, 2004), data concerning use of exceedingly low hematocrit or hemoglobin thresholds derive from experimental studies. Such studies, performed with different species and various situations, demonstrated critical hematocrit levels between 10 and 15% (Fraga et al., 2005; Hiebl et al., 2010; van Bommel et al., 2002). In a study performed with dogs submitted to continuous hemodilution with lactated Ringer´s solution, a decrease in heart function (ejection fraction and fractional shortening) was observed when hemoglobin levels reached 3.5 g/dL. Also, at this hemoglobin level, oxygen delivery decreased to the point of impairing oxygen consumption (Fraga et al, 2005).

In a recent study, a critical hematocrit of 10% was determined for the pig myocardium. Lower levels resulted in insufficient myocardial partial oxygen pressure and circulatory collapse (Hiebl et al , 2010). In all of these studies, the critical hematocrit was identified only after the observation of signs of global hypoxia, as represented by hemodynamic instability, cardiac arrhythmias and/or increase in lactate levels. However, in another experimental study, hemoglobin levels of 4-5 g/dL were associated with changes in heart rate variability (HRV), obtained by time- and frequency-domain analysis of ECG data, but ST-segment changes were not observed until a mean hemoglobin level of 3 g/dL, at which point oxygen consumption also decreased (Lauscher et al., 2011) . Other ECG changes not related to the ST-segment were observed in another experimental study by the same group, in which ANH induced gradual prolongation of the QT and QTc interval and reduction in the amplitude of the T wave (Scheller et al., 2011). In both studies, early ECG alterations were observed in the absence of traditional transfusion triggers, such as increase in serum lactate levels, elevation of the ST-segment or arrhythmias. The determination of early indicators of tissue hypoxia is very important to help establish safe limits for ANH.

In spite of these results, it is necessary to consider that most studies involving ANH were performed in young, healthy and anesthetized animals. Anesthesia may induce changes in tolerance to anemia by lowering oxygen comsumption and the critical hematocrit or suppressing compensatory mechanisms (Fantoni et al., 2005; Tircoveanu & Van der Linden, 2008).

The effect of anesthesia depth on hemodilution was shown in a study performed with dogs, in which increase of anesthesia depth either with halothane (from 1.0 to 1.5 MAC) or ketamine (from 0.2 to 0.4 mg/kg/min) resulted in decreased tolerance to acute anemia, with significant increase in critical hemoglobin concentration (from 2.3 to 4.1 g/dL with halothane and 2.5 to 3.7 g/dL with ketamine) (Van der Linden et al., 2003). As previously stated, decreases in arterial oxygen content caused by ANH are compensated by increases in cardiac output. This compensatory response may be blunted depending on the anesthetic protocol. High doses of negative inotropic agents may also blunt the cardiac output response by direct depression of the myocardial function. (Van der Linden et al, 2003). Cardiac output also depends on heart rate which may be affected by drugs such as opioids, which induce vagal stimulation, or β-adrenergic antagonists, which impair the expected cardiac response (Clarke et al., 1980; Ickx, 2000; Ragoonanan et al., 2009; Spahn et al., 1997). Even equipotent MACs of different inhalational anesthetics may induce different hemodynamic responses to ANH. Hemodilution performed in dogs anesthetized with 1 MAC of halothane, isoflurane or sevoflurane had the same pattern of hemodynamic response, though differences in oxygen consumption and oxygen extraction rate were observed among groups (Fantoni et al, 2005).

Ventilation and oxygenation also impact tolerance to anemia. A simple example involves hyperoxic ventilation. Ventilation with 21% oxygen induced ECG changes associated with ischemia at hemoglobin levels of 2.3 ± 0.2g/dL. When increased to 100% oxygen, ECG readings improved until hemoglobin levels of 1.2 ± 0.4 g/dL were reached (Meier et al., 2005).

3. Impact of ANH on brain

Reduction in oxygen transport may lead to tissue hypoxia, and this may bear important consequences to the brain, including cognitive dysfunction. Available data regarding safe hematocrit levels for the nervous system derive mostly from experimental studies and a few clinical studies that associate anemia with neurological outcome after cardiopulmonary bypass (Hare et al., 2007). In healthy young human subjects, ANH to hemoglobin of 5.7 g/dL elicited subtle cognitive dysfunction and memory deficits that were reversible with erythrocyte transfusion or increase in oxygen concentration (Weiskopf et al., 2002). Such effects seem to be worse in aged patients, given the greater incidence of cognitive dysfunction in this population (Moller et al., 1998). This hypothesis was demonstrated in an experimental study by Li et al (2010), who showed the association between acute anemia (i.e. hemoglobin 5 g/dL) and age-dependent visual-spatial working memory and learning impairment in rats. They also showed an increase in hypoxia-inducible factor (HIF) and related molecular markers of cellular hypoxia, in the presence of normal systemic and local cerebral tissue oxygenation, which was more evident in older animals (Li et al., 2010).

In an ongoing experimental study with healthy pigs, cerebral cortex and hippocampus neuronal apoptosis proteins Bax and Bcl-x, as well as caspase-3 and -9 activities, presented

no alterations during ANH to hematocrit 15% or 10%. However, a slight increase in cerebral nuclear and mitochondrial DNA fragmentation was observed, indicating possible cellular hypoxia (Frazilio et al., 2011).

The disagreement among results regarding different molecular markers of cellular hypoxia and global or even tissue oxygen parameters point out the difficulty in diagnosing hypoxia during hemodilution. Hemodilution may lead to decreased microvascular oxygen tension (PO2) and increased expression of hypoxic molecules (iNOS, nNOS, HIF) in the absence of lactate level increase or of hemodynamic instability. However more studies are necessary to determine whether these are sensitive and effective markers for early detection of hypoxia (Tsui et al., 2010).

For traumatic brain injury (TBI), higher hematocrit levels have been proposed. In the normal subject, ANH induces a redistribution of blood flow that favors brain oxygenation (Ragoonanan et al, 2009; van Bommel et al, 2002). However, such changes in the setting of TBI may bear deleterious effects. A reduction in hematocrit below 30% may promote an increase in intracranial pressure and a consequent decrease in cerebral perfusion. In a dog model of cryogenic brain injury, decrease in hematocrit to 27% by hemodilution with lactated Ringer´s or hydroxyethyl starch was associated with additional increase in intracranial pressure and decrease in cerebral perfusion. In contrast, animals submitted to ANH with target hematocrit 35% had a response similar to the non-hemodiluted animals (Tango et al., 2009).

In an experimental study with rats, Hare et al (2007) demonstrated that hemodilution following TBI could accentuate cerebral injury. Although regional cerebral blood flow had increased similarly in healthy and TBI rats after ANH, the TBI-hemodilution group presented with decrease in brain tissue oxygenation and increase in jugular vein oxygen saturation, indicating impairment in oxygen extraction. This group also showed an increase in cerebral contusion area and greater cell death (TUNEL-positive cells) (Hare et al, 2007).

4. The impact of fluid replacement on tissues

As with other clinical situations that require fluid replacement (e.g. hemorrhagic shock, sepsis), the choice of fluids to maintain normovolemia during ANH is a subject of great controversy. Critical hemoglobin levels are expected to vary according to the type of fluid employed. In an experimental study with dogs submitted to ANH, volume replacement with 6% hydroxyethyl starch 200/0.5 maintained heart contractility at hematocrit levels as low as 10%, while replacement with lactated Ringer's to the same target yielded significant decrease in contractility, with reduction in systolic function, as defined by ejection and shortening fractions. Furthermore, analysis of the myocardial ultrastructure revealed loss in its cellular integrity in the group treated with lactated Ringer´s solution (Fraga et al, 2005).

The infusion of large amounts of acellular fluids promotes important circulatory changes, such as reduction in blood viscosity and alteration in osmolality and oncotic pressure. Such properties determine the period for which the fluid remains within the intravascular space, which impacts maintenance of stroke volume and of cardiac output directly. Likewise, fluid extravasation from the intravascular space may lead to edema. Great variations in osmolality may have deleterious effects on cell homeostasis. Cardiomyocyte swelling after

hypotonic stress has been demonstrated *in vitro* (Butler et al., 2009; Mizutani et al., 2005). Butler and cols. have demonstrated that ischemia may also induce cardiac myocyte swelling (Butler et al, 2009). Cardiac myocyte edema may affect ventricular compliance, thereby compromising cardiac function (Rubboli et al., 1994).

In an ANH protocol using lactated Ringer´s to a target hematocrit of 15%, cardiac function was preserved and no microscopic evidence of myocardial cell injury or edema was found, but ultrastructure analysis revealed disorganization of myofibrils and myofilaments (Otsuki et al., 2007). The observation of such structural alteration only in the crystalloid group points to the possibility that osmolarity and coloidosmotic pressure must be involved in the process. In a similar study by our group, with the same ANH protocol, a significant decrease in serum osmolarity (from 298 ± 4.0 to 279.5 ±2.1 mOsm/kgH2O) was observed with lactated Ringer's (Margarido et al., 2007).

The lung is one of the main organs affected by the administration of large quantities of fluids. Since crystalloids bear smaller permanence within the intravascular space, these solutions leaks out of the circulation into the tissues or interstitial space and may lead to lung impairment with decrease in lung compliance, atelectasis and even the development of alveolar edema. Data regarding the effects of ANH on lungs are mostly based on cardiopulmonary bypass studies. In such scenario, hemodilution and inflammatory response are associated with capillary leak and edema in different organs, including the lungs (Hirleman & Larson, 2008).

In pigs submitted to ANH with lactated Ringer´s to hematocrit 15%, lung microscopy showed areas of alveolar collapse while ventilatory mechanics and oxygenation parameters presented diminished lung compliance with decrease in PaO2/FIO2 ratio and increases in Qs/Qt and dead space. Ultra-structurally, there was enlargement of the alveolar basement membrane, which may explain the observed decrease in arterial oxygenation. Conversely, ANH with hydroxyethyl starch preserved pulmonary mechanics and oxygenation (Margarido et al, 2007).

Another ANH study with dogs using Lactated Ringer´s to hematocrit 10% showed an increase in lung water content as evaluated by presence of fluid in the peribronchial space and by gravimetric analysis. The restoration of oncotic pressure by albumin administration reversed these alterations (Cooper et al., 1975).

Different fluids may also affect microcirculation differently. Recent studies have demonstrated that even with maintenance of systemic perfusion variables (cardiac index, arterial blood pressure), decrease in blood viscosity may result in impairment of microcirculatory function (Cabrales & Tsai, 2006; Cabrales et al., 2004; Tsai et al., 1998).

This effect of blood viscosity on the microcirculation was demonstrated by Cabrales et al, who used a hamster window chamber model. Extreme ANH to a final hematocrit of 11% was performed with high- (dextran 500) or low-viscosity (dextran 70) plasma expanders. The maintenance of blood viscosity promoted by dextran 500 was associated with maintenance of microvascular capillary diameter, flow and functional capillary density whereas with dextran 70 it was observed an impairment of microvascular hemodynamics (Cabrales & Tsai, 2006).

An additional important aspect regarding ANH pertain the effect of fluid choice on the immune system. The effects of different fluids on immune system response have been demonstrated *in vitro* and *in vivo* studies during sepsis, hemorrhagic shock and hemodilution. The activation of the inflammatory system following massive fluid resuscitation is intimately related to negative outcomes (Cotton et al., 2006; Lee et al., 2005; Rhee et al., 1998; Welters et al., 2000). Several studies have shown divergent results because different colloids may bear pro-inflammatory (Alam et al., 2004; Lee, 2005; Rhee et al., 2000) and anti-inflammatory effects (Alam et al., 2000; Jaeger et al., 2001; Lang et al., 2003). When compared with 6% hydroxyethyl starch 200/0.5 or lactated Ringer´s, resuscitation with gelatin following hemorrhagic shock seems to exacerbate levels of interleukin-6 and TNF-α and decrease IL-10 production. Furthermore, neutrophil and mononuclear cell aggregation and important histological changes were observed in animals lungs treated with gelatin (Lee et al, 2005).

Systemic and pulmonary inflammatory effects of ANH with 6% hydroxyethyl starch 130/0.4, saline solution 0.9%, and gelatin 4% were evaluated in pigs submitted to ANH to hematocrit 15%. Gelatin was associated with increases in serum cytokines (TNF-α, Il-1, Il-6 and Il-10) and pulmonary COX-2 and E-selectin expression was higher in gelatin and hydroxyethyl starch-treated animals (Kahvegian et al., 2009; Kahvegian et al., 2010).

Endothelial activation after ANH was demonstrated by Morariu et al using real-time PCR of E- and P-selectin gene expression in different organs. Hemodilution in pigs with hydroxyethyl starch 3% (200/0.5) triggered pro-inflammatory endothelial activation as evidenced by E- and P-selectins mRNA up-regulation in the lung and other tissues (Morariu et al., 2006).

5. Conclusion

In particular settings, ANH has been proposed as an alternative to blood transfusion. However, safe limits for this procedure have not been properly established, and hypoxia remains a major concern, particularly for its effect on the heart and brain. Proper markers must be identified to monitor the effects of critical levels of hemoglobin in the various clinical settings and further studies must be conducted before ANH may be implemented in daily medical practice.

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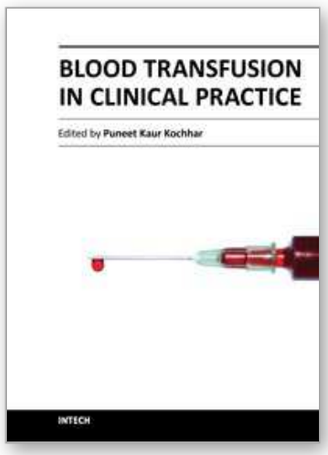

Blood Transfusion in Clinical Practice

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Blood Transfusion in Clinical Practice focuses on the application of blood transfusion in different clinical settings. The text has been divided into five sections. The first section includes a chapter describing the basic principles of ABO blood group system in blood transfusion. The second section discusses the use of transfusion in various clinical settings including orthopedics, obstetrics, cardiac surgery, etc. The third section covers transfusion transmitted infections, while section four describes alternative strategies to allogenic blood transfusion. The last section speculates over immunomodulatory effects of blood transfusion.

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