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# A novel approach to modeling acute normovolemic hemodilution

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## ABSTRACT

Acute normovolemic hemodilution (ANH) was introduced as a blood conservation technique to reduce patient exposure to allogenic blood transfusion during surgery. Despite years of research and experience, the best practice procedure, efficacy and safety of ANH remain in question. In this work, a numerical model is developed for the ANH procedure based upon a multi-compartmental, fluid model of the body. The model also analyzes the most commonly used acellular fluids for ANH or for fluid therapy following hemorrhage. The model allows user input of critical ANH parameters, providing the ability to simulate the patient's response in real time to many clinical scenarios, using various types of resuscitation fluids. First, the patient's response to a representative, clinical ANH protocol and surgery was simulated. Then, the effect of several variables was investigated including: type/amount of resuscitation fluid, number of blood units collected during ANH, and amount of surgical blood loss. Our simulations highlighted the importance of osmotic molecules within the blood in preventing excessive fluid retention and initiating fluid clearance after surgery. The developed model can be utilized as a tool to simulate and optimize a variety of proposed protocol related to the ANH procedure and surgery. It can also be utilized as an educational or training tool to become familiar with the ANH procedure.

## 1. Introduction

Certain risks and disadvantages associated with allogenic blood transfusion have spurred efforts to find alternative strategies to manage patients with surgical blood loss. In the 1970's, acute normovolemic hemodilution (ANH) emerged as a potential strategy to reduce allogenic blood transfusions during the perioperative period. Given its potential for blood conservation, ANH continues to be an active area of research [1–18]. The ANH procedure involves removal of a patient's blood prior to surgery and simultaneous replacement with crystalloids, colloids, or both to keep the patient normovolemic. During this process, the patient's blood becomes diluted until a 'target hematocrit' is reached or the desired blood volume is removed. As a result of the induced anemia, blood lost during surgery contains fewer blood cells per unit volume, and the total loss of red blood cells is reduced. Also, fresh, autologous blood is available to provide a supply of red blood cells and clotting factors. The 'transfusion trigger hematocrit' refers to the lowest red blood cell concentration that is safely tolerated during surgery. If the hematocrit reaches this threshold, collected blood is transfused back to the patient to maintain the blood's oxygen carrying capacity. Blood is generally transfused in the opposite order of collection, leaving the highest quality blood for last. If the transfusion trigger threshold is not reached during surgery, collected blood is saved until the end of major surgical blood loss, at which point it is transfused.

ANH provides several theoretical advantages over other blood saving techniques, such as preoperative autologous donation (PAD). ANH is a "point-of-care" (POC) strategy that can be performed on the day of surgery in the operating room. It also utilizes the patient's own blood and nearly eliminates the risk of mis-transfusion (transfusing blood to the wrong patient), since blood is kept at the patient's bedside. There have been many successful implementations of ANH in the clinical setting. Monk et al. [19] concluded that ANH could replace PAD as a standard of care for autologous blood procurement in radical prostatectomy because it is less costly and equally effective. Similarly, a randomized trial comparing ANH and PAD in total hip arthroplasty concluded that ANH is safe, while providing an equally effective, less costly method for reducing exposure to allogenic RBC's [20]. ANH also

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reduced the number of patients that required allogenic blood transfusion in major liver resection surgery [21]. Although risks associated with ANH have not been fully quantified, they appear to be minimal when performed correctly by a skilled, experienced clinician [22]. Despite these advantages, ANH remains underutilized compared to PAD, due to unanswered questions regarding efficacy and safety [23,24]. Additionally, several important ANH protocol have still not been standardized, including the target hematocrit, transfusion trigger hematocrit, the amount of blood to be withdrawn, the type and amount of acellular resuscitation fluid. A large variety of surgical procedures, dissimilar patient populations, varying surgical blood loss levels, and blinding/randomization difficulties have all contributed to difficulties in protocol standardization.

Given the large number of relevant variables, mathematical models are more practical to provide better insight into the ANH procedure. Previous mathematical descriptions of ANH have utilized the isovolemic, dilution equation developed by Bourke and Smith [25]. This equation models the decreasing concentration of a constituent (red blood cells) within an isovolemic fluid, by incrementally replacing this constituent with fluid. The solution to this differential equation results in an exponential relationship between blood volume removed/lost and the change in hematocrit. Brecher and Rosenfel developed an iterative program based upon this equation to determine the red blood cell volume savings provided by ANH [26]. More recently, Weiskopf utilized the same equation to describe the efficacy of ANH as a function of the fraction of blood volume lost [27]. These mathematical studies have shown that, in terms of red blood cell savings, the benefits of ANH are modest. However, these models only relate red blood cell savings to the hematocrit. An improved mathematical model of ANH would simulate the patient response to the procedure over time. Ideally, the model would accept input of ANH parameters and simulate the patient's response, as determined by several vital signs.

Recently, more advanced mathematical models regarding the body's response to hemorrhage and fluid resuscitation have been developed. These models generally describe the body as several, well-mixed fluid compartments. Exchange of fluid and constituents between compartments is governed by time-dependent ordinary differential equations and various auxiliary equations. One of the first fluid compartment models of hemorrhage was developed by Pirkle et al. [28]. An extensive, multi-compartment fluid model was developed by Gyenge et al. [29] and subsequently validated for several fluid resuscitation scenarios [30]. Other researchers have used similar models to validate and investigate various hemorrhage and fluid resuscitation scenarios [31,32]. This type of model provides the ability to simulate various scenarios and predict the dynamic changes of fluid, protein, and solute concentrations in each of the compartments. This means that predictions of important, clinical parameters such as plasma volume, red blood cell volume, blood pressure, etc. can be made as a function of time. Although these models have been applied many times to hemorrhage and resuscitation, they have not yet been used to model the body's response to the ANH procedure. We investigated this aspect and our effort represents the first such application of the multi-compartment fluid model to the procedure of ANH. The developed computer model accepts input of critical ANH parameters and allows for simulation of the patient's response over time. Furthermore, the model incorporates resuscitation with various fluids including 0.9% saline, 6% hydroxyethyl starch (HES), 6% Dextran (DEX), and 5% human serum albumin (ALB).

## 2. Methods

This fluid-exchange model was developed based upon previous models of microvascular exchange, specifically those introduced by Gyenge et al. [29] and Carlson et al. [31]. The fluid within the body is divided into two compartments: the intravascular space and the interstitial space. The intravascular space was further divided into the plasma volume and red blood cell volume. Mathematical equations describe fluid/protein exchange between the vascular and interstitial compartments. The ANH procedure and surgery can be modeled as changes to the vascular compartment, via infusion or hemorrhage. Lymphatic function [29] and urinary dynamics [33] were also incorporated into the model. Intracellular components of the interstitial space were not taken into account, as they do not play a central role in fluid exchange during the perioperative period [32,35]. It was assumed that the properties of all plasma proteins could be represented using those of albumin. A schematic of the fluid compartment system and relevant transport is shown in Fig. 1. Average values for important fluid model parameters are shown in Table 1.

The differential equations governing fluid exchanges can be obtained using a volumetric or mass flow balance between fluid compartments. The balances for plasma volume, $V_P$, red blood cell volume, $V_{RBC}$, and interstitial volume, $V_{INST}$, are given as:

$$\frac{dV_P}{dt} = J_{INF,AF} + J_{INF,BL}\left(1-\frac{\text{Hct}}{100}\right) + J_L - J_{TRANS} - J_U - J_{HEM}\left(1-\frac{\text{Hct}}{100}\right) \quad (1)$$

$$\frac{dV_{RBC}}{dt} = J_{INF,BL}\left(\frac{\text{Hct}}{100}\right) - J_{HEM}\left(\frac{\text{Hct}}{100}\right) \quad (2)$$

$$\frac{dV_{INST}}{dt} = J_{TRANS} - J_L - J_{EVAP} \quad (3)$$

In these equations, $dV/dt$ represents the volume change per unit time or the rate of change of volume. $J_{INF,AF}$ and $J_{INF,BL}$ are the infusion rate of acellular fluid and the infusion rate of blood, respectively. $J_{HEM}$ is the rate of hemorrhage, including either surgical blood loss or removal of blood during the ANH procedure. $J_L$, $J_{TRANS}$, $J_U$ and $J_{EVAP}$ are the rate of lymphatic flow, rate of fluid transfer from plasma to interstitium, rate of urine production, and rate of evaporative fluid loss, respectively. Hct is the hematocrit expressed as a percentage.

The balances for plasma protein content, $A_P$, and interstitial protein content, $A_{INST}$, are given as:

$$\frac{dA_P}{dt} = \dot{A}_{INF,BL} + \dot{A}_L - \dot{A}_{HEM} - \dot{A}_{TRANS} \quad (4)$$

$$\frac{dA_{INST}}{dt} = \dot{A}_{TRANS} - \dot{A}_L \quad (5)$$

In these equations, $dA/dt$ represents the protein quantity (mass) change per unit time or the rate of change of plasma protein content. $A_{INF,BL}$ is the infusion rate of protein contained within transfused blood. $A_{HEM}$ is the rate of protein loss due to hemorrhage. $A_{TRANS}$ and $A_L$ are the rate of protein transfer from plasma to interstitium and the rate of protein transfer back to the plasma via the lymphatics.

Additional equations used in the model to govern transcapillary exchange, lymph transport, and urinary dynamics can be found in Appendix A [29,31,33]. Further explanation will focus on the methods specific to this model and unique to the ANH procedure and surgical period. In this work, a Simulink-based algorithm was created using blocks within the Simulink Library. All ordinary differential equations were solved using an ode-45 solver based upon the Runge–Kutta method. Computations were carried out within the Simulink software on a PC with a 2.2 GHz Intel Core i7