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The Effects of Transfusion on Blood Composition and Characteristics after Coronary Artery Bypass Surgery

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The Effects of Transfusion on Blood Composition and Characteristics after Coronary Artery Bypass Surgery

by

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ABSTRACT

Transfusion has been associated with increased morbidity and short- and long-term mortality after cardiac surgery. However, the physiological effects of transfusion in this setting are poorly described. This study aimed to examine the effects of transfusion on blood composition and characteristics after cardiac surgery.

1,134 patients underwent an isolated coronary artery bypass graft surgery with no post-operative complications. Of these, 407 (35.8%) patients received a transfusion. Propensity-matching was used to generate a balanced cohort of 636 patients. 26 variables from standard blood tests were retrospectively collected. A repeated measures analysis of variance test was used to examine how these variables changed over time and if the changes were affected by transfusion.

11 of the 26 variables were shown to be significantly affected by transfusion. Transfusion caused a relative increase in blood urea nitrogen, creatinine, red blood cells, hematocrit, mean corpuscular hemoglobin concentration, and platelets. Conversely, it was associated with a decrease in calcium, carbon dioxide, pH, pO_2, white blood cell count, and mean corpuscular hemoglobin.

When examining associated clinical relevance of the significant (and non-significant) results, several trends begin to emerge. There was little evidence that transfusion cured anemia, at least by the traditional measure of hemoglobin, although the data suggests that it does increase the oxygen-carrying capacity of the blood. However, hepatic and renal function may be impaired by the administration of donor blood products.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning	Abbreviation	Meaning
ALB	Albumin	MI	Myocardial Infarction
ALP	Alkaline Phosphatase	MPV	Mean Platelet Volume
ALT	Alanine Aminotransferase	PLT	Platelet
aPTT	Activated Partial Thromboplastin Time	PT	Prothrombin Time
AST	Aspartate Aminotransferase	RBC	Red Blood Cell
BUN	Blood Urea Nitrogen	RDW	Red Blood Cell Distribution Width
CABG	Coronary Artery Bypass Grafting	SCA	Society Of Cardiovascular Anesthesiologists
CR	Creatinine	STS	Society Of Thoracic Surgeons
HCT	Hematocrit	TACO	Transfusion-Associated Circulatory Overload
HGB	Hemoglobin	TA-GVHD	Transfusion-Associated Graft-Versus-Host Disease
INR	International Normalized Ratio	TBIL	Total Bilirubin
MCH	Mean Corpuscular Hemoglobin	TP	Total Protein
MCHC	Mean Corpuscular Hemoglobin Concentration	TRALI	Transfusion-Related Acute Lung Injury
MCV	Mean Corpuscular Volume	TTI	Transfusion-Transmitted Infection
metHGB	Methemoglobin	WBC	White Blood Cell

CHAPTER 1

INTRODUCTION AND REVIEW OF THE LITERATURE

One-fifth of all blood transfusions in the United States go to patients undergoing cardiac surgery (Stover, Siegel et al. 1998; Shander, Moskowitz et al. 2005). 13% of these transfusions go to patients who received a combination of coronary artery bypass grafting (CABG) and valvular surgery (Stover, Siegel et al. 1998; Shander, Moskowitz et al. 2005). Additionally, patients are more likely to be transfused if the procedure utilizes cardio-pulmonary bypass (on-pump) compared to an off-pump operation (Surgenor, Kramer et al. 2009).

Recent studies further confirmed the negative effects associated with the administration of blood products in both the short- and long-term (Bhaskar, Dulhunty et al. 2012; Shaw, Johnson et al. 2013; Shaw, Johnson et al. 2013). Two separate analyses of 30-day outcomes of CABG showed transfusions were associated with increased short-term mortality, post-operative MI, new onset arrhythmias, stroke, and organ failure (Bhaskar, Dulhunty et al. 2012; Shaw, Johnson et al. 2013). Other studies have linked administration of blood products to increased complication rates, increased risk for low-output heart failure, cardiac events, wound infection, and mortality in all cardiac procedures even in those patients deemed low-risk preoperatively (Surgenor, DeFoe et al. 2006; Bernard, Davenport et al. 2009; Surgenor, Kramer et al. 2009; Mohnle, Snyder-Ramos et al. 2011; Bhaskar, Dulhunty et al. 2012). In addition, the use of blood products was associated with increased 30-day complications and operative mortality regardless of HCT, especially at higher (>42%) HCT levels where transfusion was

linked to a 2.5-fold increased risk for mortality (Shaw, Johnson et al. 2013). Furthermore, transfusions in cardiac surgery have been shown to be associated with as high as a 70% increase in late-mortality (Engoren, Habib et al. 2002; Koch, Li et al. 2006; Surgenor, Kramer et al. 2009; Shander, Javidroozi et al. 2011; Bhaskar, Dulhunty et al. 2012). In the long-term, the amount of blood used and type of blood affects 5-year mortality. Previous studies have demonstrated up to an 18% 5-year mortality rate in patients who received a blood transfusion, with significant differences in survival materializing after just two years (Bhaskar, Dulhunty et al. 2012; Shaw, Johnson et al. 2013). Out of all blood products, cryoprecipitate transfusion was linked to a 2-fold increased risk of mortality. These short- and long-term effects are apparent even in patients that receive 1 or 2 units of blood, regardless of type of cardiac procedure (Surgenor, Kramer et al. 2009). The effect of transfusion in elderly patients (>80 years old) is disputed, with evidence for and against the administration of blood (Surgenor, DeFoe et al. 2006; Surgenor, Kramer et al. 2009; Veenith 2010; Yun 2012).

Risks of Transfusions

There are additional hazards of transfusions beyond an overall decrease in survival. It is estimated that 51,000 patients suffered a transfusion-related reaction in the United States leading to a rate of 2.4 reactions per 1,000 units (Whitaker 2011). The risks associated with transfusion fall into two categories: transfusion-transmitted infections (TTI) (such as HIV or hepatitis) or noninfectious complications. With improved screening and awareness protocols, the risk for TTI has fallen dramatically in the past 20 years; however the discovery of new infectious agents such as prions, the

causative agent of Creutzfeld-Jacob disease, and the dengue virus reveals new risks for TTI (Bihl, Castelli et al. 2007; Stramer, Hollinger et al. 2009; Squires 2011).

Noninfectious complications include acute transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-associated dyspnea and delayed transfusion reactions (such as delayed hemolytic reaction, post-transfusion purpura, and transfusion-associated graft-versus-host disease (TA-GVHD))(Wintrobe and Greer 2004; Toy, Popovsky et al. 2005; Bux and Sachs 2008; Squires 2011). It is believed that the incidence of noninfectious complications are under-diagnosed and under-reported (Shander, Javidroozi et al. 2011).

Acute transfusion reactions include allergic, hemolytic, hypotensive, and febrile reactions. Allergic and hemolytic reactions are similar and are the result of the recipient's immune system attacking a substance in the blood (allergic) or the blood cells themselves (hemolytic). The symptoms of an allergic reaction to blood transfusion are similar to any allergic reaction and tend to be mild (hives and itching), but more serious reactions (such as anaphylaxis and tachycardia) have been documented (Lin, Ho et al. 1990; Shanthi, Bhavanadhar et al. 2013). Hemolytic reactions are most commonly caused by mismatched blood types such as administering Type A blood to someone that is Type B. Blood type is determined by which form(s) of glycophorin is found (or not found, in the case of Type O) on the extracellular cell wall of the red blood cell (RBC). The immune system of the recipient will attack the donor blood cells, which will result in the destruction of the donor erythrocytes in addition to the aforementioned allergic response (Wintrobe and Greer 2004). Acute hypotensive transfusion reactions (AHTR) are the result of a buildup of bradykinin in the blood (Kalra, Palaniswamy et al. 2012).

Bradykinin production is increased when Factor XIIa is exposed to the negatively charged surface of the blood filter. Typically, bradykinin is normally broken down by angiotensin converting enzyme (ACE), which is responsible for 75% of bradykinin inactivation. Febrile reactions are defined as an unexplained fever or chills in a patient who is receiving or has received a transfusion within six hours (Baldwin 2002). The reaction is caused by an accumulation of cytokines produced during blood product storage; therefore febrile reactions can be avoided by filtering out cytokines in the donor blood or prevention of cytokine formation (Heddle 1999).

TRALI, TACO, and transfusion-associated dyspnea are very similar conditions. TRALI, characterized by hypoxemia, decreased blood pressure, and pulmonary edema, is a potentially fatal reaction to blood transfusion (Toy, Popovsky et al. 2005; Squires 2011). It is estimated that 1 out of every 5,000 patients receiving a RBC transfusion will develop TRALI within 2 hours (Wintrobe and Greer 2004; Toy, Popovsky et al. 2005). The development of TRALI is associated with neutrophil activation either by the presence of leukocyte antibodies, cytokines, or other biologically active substances in the donor blood (Toy, Popovsky et al. 2005; Squires 2011). Improved donor blood filtering techniques have reduced the appearance of TRALI (Yazer, Podlosky et al. 2004). TACO also presents with pulmonary edema, but in this condition, blood pressure and heart rate are increased (Squires 2011). Another distinguishing factor between TRALI and TACO is the response to diuretic therapy: it is ineffective in TRALI but rapidly reduces TACO (Squires 2011). If TRALI and TACO are ruled out in the setting of pulmonary edema after transfusion, the patient is diagnosed with transfusion-associated dyspnea (Bux and Sachs 2008).

As the name suggests, delayed transfusion reactions present themselves 5 days to 3 weeks after transfusion. Some are similar to acute reactions, such as delayed hemolytic reaction (although the delayed version is much milder) (Wintrobe and Greer 2004). Post-transfusion purpura is rare condition where a patient develops thrombocytopenia (low platelet (PLT) count) 5-14 days after receiving blood products, resulting in uncontrolled bleeding (McCrae and Herman 1996; Wintrobe and Greer 2004). This sometimes fatal condition is caused by either the patient's immune response to the donor blood or an anti-PLT antigen in the donor blood (McCrae and Herman 1996). Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD) occurs when donor T cells go unrecognized by the recipient, such as in a blood donation between family members or transfusion in immunocompromised patients (Wintrobe and Greer 2004). The graft T cells are then allowed to proliferate unhindered, where they then mount an immune response against the host within 2-3 weeks (Schroeder 2002). There is no truly effective treatment for TA-GVHD, therefore the disease is associated with a 90% rate of mortality (Schroeder 2002; Wintrobe and Greer 2004).

Current Clinical Guidelines

Despite these known risks, there is still no standard protocol guiding blood transfusions in cardiac patients. This most likely stems from the lack of contemporary randomized prospective trials that address the role of blood products in general. In fact, the current Society of Thoracic Surgeons (STS) and The Society of Cardiovascular Anesthesiologists (SCA) clinical practice guidelines are largely based upon a trail that was performed in critical care patients in 1999 (Hebert, Wells et al. 1999; Ferraris,

Ferraris et al. 2007). In this study, Hébert et al. found that transfusing a patient with hemoglobin (HGB) level of <7 g/dL was associated with increased survival. On the other hand, an increase in mortality was noted when patients with HGB <10g/dL were given blood products. The STS/SCA also recommends the administration of red blood cells (RBC) in patients who have experienced uncontrolled blood loss or when they have lost more than 1,500mL or ≥30% of their total blood volume, regardless of HGB levels. Collectively, this is referred to as the "10/30 Rule", despite the fact that there has yet to be a study that demonstrated a clear benefit or consequence to transfusing those patients with HGB levels between 7 and 10 g/dL (Hebert, Wells et al. 1999; Ferraris, Ferraris et al. 2007; Ferraris, Brown et al. 2011). Other indications for administration of blood products include if the patient has chronic cardiovascular/pulmonary disease or HGB ≤6.0g/dL if on cardiopulmonary bypass (Ferraris, Ferraris et al. 2007). The STS/SCA concedes that these transfusion triggers are based upon very limited (mostly observational) studies and therefore require more empirical evidence (Ferraris, Ferraris et al. 2007; Ferraris, Brown et al. 2011). There is a recent randomized study from Brazil that focused on a small group of cardiac surgery patients (Hajjar, Vincent et al. 2010). In this single-center study, Hajjar *et al.* (2010) found no difference in mortality between a liberal transfusion trigger (<30% hematocrit, HCT) and a restrictive strategy (<24% HCT).

Perhaps due to the lack of solid evidence, cardiac surgery transfusion rates vary wildly between institutions (Maddux, Dickinson et al. 2009; Bennett-Guerrero, Zhao et al. 2010). In CABG patients, transfusion rates range from 7.8% to 92.8% for packed RBCs, 0% to 97.5% for fresh-frozen plasma, and 0.4% to 90.4% for PLTs in the United

States (Bennett-Guerrero, Zhao et al. 2010). Furthermore, there has been only minimal change in transfusion rates for cardiovascular procedures since the transfusion guidelines were published in 2007 (Bennett-Guerrero, Song et al. 2010). A recent survey of several American and Canadian anesthesia and perfusion societies revealed that only 22% of anesthesiologists and 33% of perfusionists had even read the guidelines (Varghese and Myers 2010). In addition, the new guidelines were recognized by only 20% of institutions (Varghese and Myers 2010).

A blood transfusion can be life-saving in some situations such as extreme blood loss, but most cardiac surgery patients are not in hemorrhagic shock. Furthermore, most experts agree that a blood transfusion is either uncertain or unlikely to improve outcomes in most common clinical scenarios (Shander A. 2011). In addition, several studies investigating Jehovah's Witness patients (who cannot accept blood transfusions) and strict blood conservation programs have demonstrated that patients can safely undergo cardiac surgery with minimal to no blood use and without increased risk for complications and/or mortality (Shander, Moskowitz et al. 2005; Stamou, White et al. 2006; Moskowitz, McCullough et al. 2010; Varghese and Myers 2010; Weltert, Nardella et al. 2012).

Cost of Transfusion

In addition to the clinical risks in blood transfusion, there is a significant cost to be considered when deciding to give blood products to a patient. In 2011, the American Red Cross spent nearly $2.2 billion on biomedical services, a figure that includes all the costs associated with collection, processing, testing, and distribution of blood products

nationwide (Cross 2011). Shander et al (2010) showed the mean total cost per RBC unit was $760.82 ± $293.74, with hospitals in the northeast United States having the highest costs(Shander, Hofmann et al. 2010). While the first priority of a medical institution is to provide the best care possible to patients, it is also a business and therefore, the cost of a procedure must be taken into account.

Anemia

While RBC administration is the fastest method to raise HGB levels, the effects of transfusions on muscle oxygenation and microvascular activity are inconsistent and unpredictable (Creteur, Neves et al. 2009; Shander, Javidroozi et al. 2011). Rather, most post-surgical patients are given blood products with the thought that it will treat post-surgical anemia, ultimately leading to improved patient recovery (Bhaskar, Dulhunty et al. 2012). However, these transfusions may not be necessary as the body can compensate for anemia remarkably well. An individual's response to anemia depends on many factors and, as a consequence, can vary amongst patients (Shander, Javidroozi et al. 2011). In a healthy patient, normal tissue oxygenation can be achieved with a HGB level of 6g/dL and a HCT of at least 15% (Doak and Hall 1995). Increased mortality was only seen once HGB levels fell below 5g/dL and/or HCTs below ≤14% (this raises to 17% in high-risk patients) (Fang, Helm et al. 1997). The lowest reported HGB level in a surviving non-transfused patient is 0.7 g/dL(Dai, Tu et al. 2010). Low HCT level during surgery have been associated with increased risk for in-hospital mortality, peri-operative placement of an intraaortic balloon pump, and failure to separate from cardio-pulmonary bypass (DeFoe, Ross et al. 2001). At a physiological level, minimum levels for proper

tissue oxygenation are HGB levels 4 g/dL, an oxygen extraction ratio of 0.44, a mixed venous oxygen of 34 mm Hg, and a mixed venous oxygen saturation of 56%; tissues become insufficiently oxygenated below these values (Weisel, Charlesworth et al. 1984). While it is likely higher for the cardiovascular surgery patients, the mean HGB level for anemia-induced mortality is 2.5 g/dL (Weiskopf 2010).

This is likely because there are many compensatory mechanisms to manage anemia in the body (Shander, Javidroozi et al. 2011). For instance, in situations where oxygen is unavailable, erythropoiesis, angiogenesis, and anaerobic metabolism are increased in the cells. Furthermore, the lungs raise the partial pressure of blood oxygen by releasing more nitric oxide and increasing respiration rate, thus increasing HGB-O_2 saturation. The body will also increase cardiac output, blood viscosity, systemic vasodilation, and venous return to maintain tissue oxygenation levels. Furthermore, oxygen extraction increases in select organs, with the highest priority given to the brain and the heart. Interestingly, the long-term consequences of anemia are similar to that of transfusion, with higher mortality rates and increased risk of fractures, renal disease, heart failure, cardiovascular events, readmissions, poorer graft outcome, worse functional status, and lower quality of life (Shander, Javidroozi et al. 2011).

In a non-urgent case, anemia can be successfully and quickly treated with hematinic medications (Szlyk, King et al. 1984). In addition, recent studies have shown treatment of anemic patients with pre-operative erythropoietin plus iron has decreased the need for peri-operative transfusions by almost 30% in valve replacement surgeries (Cladellas, Farre et al. 2012). A combined pre-operative treatment of erythropoietin and iron was found to be associated with 30-day survival and shorter post-operative hospital

stay, although it the use of iron did not reduce the need for transfusion (Garrido-Martin, Nassar-Mansur et al. 2012). Post-operative low-dose aprotinin has also been shown to reduce the need for transfusion after cardiac surgery (Mansouri, Attary et al. 2012).

Blood Biochemistry

Blood, in the most basic sense, is made up of two major parts: the liquid plasma and the cells that are suspended in it. If the clotting factors are removed from the plasma, it is referred to as serum (Powar, Chatwal et al. 2008). There are three cell types commonly found in blood: the oxygen- and nutrient carrying erythrocyte (or RBC), the infection-fighting leukocytes (or white blood cells, WBC), and the vascular wall repairing PLT. Collectively, they make up 40-45% of the blood; this percentage is also referred to as the HCT (Powar, Chatwal et al. 2008). All blood cells are formed from hematopoietic stem cells found in the bone marrow(Janeway 2001; Turgeon 2005).

The anucleated RBC are 6-9 μm wide, biconcave discs that are formed in the bone marrow (Powar, Chatwal et al. 2008; Hall, Guyton et al. 2011). Their characteristic red color comes from oxygen binding to their ferrous [Fe2+] iron-containing HGB; in the absence of oxygen, the cells appear blue-violet. HGB is an important component of blood and will be discussed in more detail elsewhere. The RBC cell membrane, like most cells, is semi-permeable and allows water, CO_2, urea, glucose and other small non-ionic molecules through (Powar, Chatwal et al. 2008). In addition, certain ions such as bicarbonate (HCO_3^-), chloride (Cl^-), hydroxide (OH^-), and potassium (K^+) can freely pass through the membrane. The RBC is not permeable to magnesium (Mg^{2+}), but the cation is found inside the cell (Powar, Chatwal et al. 2008). While they contain no

mitochondria, the RBCs will breakdown glucose (albeit very slowly) in order maintain its cell membrane and prevent the accumulation of methemoglobin (metHGB) (a condition known as methemoglobinemia) (Ash-Bernal, Wise et al. 2004; Powar, Chatwal et al. 2008). metHGB contains ferric [Fe^{3+}] iron, which does not bind oxygen as readily as ferrus iron; this results in decreased oxygen-carrying capacity (Ash-Bernal, Wise et al. 2004). RBC also contain large quantities of carbonic anhydrase in order to catalyze the reaction between water and CO_2 to form HCO_3^-, which allows the plasma to transport CO_2 away from the tissues to the lungs to be exhaled (Hall, Guyton et al. 2011). Males have 5.2 million RBCs per mm^3 of blood while females have slightly less at 4.7million/mm^3 (Hall, Guyton et al. 2011). The average RBC breaks down after four months and is filtered out of the blood by the spleen or liver (Powar, Chatwal et al. 2008). RBCs have been shown to become fragmented in patients with valvular disorders and surgeries, especially those receiving a prosthetic valve, likely due to turbulent flow (Wintrobe and Greer 2004).

There are many differences between RBC and WBC. WBC are more active type of cell that contains a nucleus and are able to move on their own (Powar, Chatwal et al. 2008). In fact, WBC can leave the blood vessels in order to move to the site of an infection or injury. Most WBC are phagocytic and will engulf bacteria or dead cells that are then broken down by proteins in the WBC cytoplasm (Powar, Chatwal et al. 2008). There are five types of WBC: bacteria- and fungi-fighting neutrophils, histamine-releasing basophils, parasitic-fighting and allergy modulating eosinophils, the acquired immune system-mediating lymphocytes (not commonly found in the blood), and the large macrophage monocytes (Alberts 2002).

PLTs are formed by fragmentation of the megakaryocytes as they are released from the bone marrow (Hall, Guyton et al. 2011). PLT aggregation is the first step in repairing cuts or lesions in the vascular endothelium (Hall, Guyton et al. 2011). PLTs are not fully functional cells, yet their purpose is integral to vascular repair. Their extracellular membranes are coated in glycoproteins that allow the PLTs to bind to the collagen that exposed when a vessel is injured, allowing the PLTs to identify sites of vascular injury (Hall, Guyton et al. 2011).

Plasma is essentially a water solution containing certain salts (ex. NaCl and $NaHCO_3$), proteins (such as albumin (ALB), fibrinogen, etc.) and antibodies, hormones, glucose and amino acids from digested food, and waste products such as CO_2 and urea (Powar, Chatwal et al. 2008). Proteins make up a bulk of the solids in the plasma (accounting for ~7-9g per 100 mL of blood) and can be separated via electrophoresis, ultracentrifugation, and ethanol fractionation (Powar, Chatwal et al. 2008).

Components of Clinical Hematological Analyses and Their Roles

Blood plays two basic roles in the body: transportation of materials and maintaining homeostasis. Blood is responsible for transporting oxygen from the lungs to the tissues, carbon dioxide from the tissues to the lungs, nitrogenous waste from the liver to the kidneys, hormones throughout the body, the products of digestion from the ileum to the tissues, WBCs to protect the body from infection. Through this transportation, blood provides the tissues with the materials necessary to maintain an optimal environment (Powar, Chatwal et al. 2008). In addition, blood also plays a role in the distribution of heat throughout the body. Many of these functions are analyzed in the

clinical setting via blood tests. This study examines the results of four common blood analyses (Chemistry, Coagulation, Cardiac/Critical Care and Hematology) representing 33 variables overall. These tests are performed multiple times throughout the patient's hospital course. The normal range for each measure can be found in Table 1.

Table 1: The blood components and characteristics analyzed by standard blood tests.

Variable	Normal Clinical Range	Basic Function	Clinical Relevance
Chemistry			
Calcium	8.4-10.2 mg/dL	Secondary messenger, enzyme cofactor, various other roles	Kidney, cardiovascular, and neurologic function
Glucose	70-110 mg/dL	Metabolism	Diabetes, liver function
Blood Urea Nitrogen	6-20mg/dL	Transport of urea to kidneys	Kidney function
Creatinine	0.5-1.2 mg/dL	Muscle metabolism	Kidney function
Sodium	135-145 mmol/L	Osmoregulation, muscle contraction, and neuronal firing	Osmoregulation
Potassium	3.3-51. mmol/L	Muscle contraction and neuronal firing	Kidney function
Chlorine	95-108 mmol/L	Counter-ion	Kidney function
CO_2	22-29 mmol/L	Oxygen/carbon dioxide transport	Oxygen/ CO_2 transport
Coagulation			
Prothrombin Time	11-14.5 sec	Time to activate clotting	Measure of coagulability & liver function
International Normalized Ratio	0.9-1.3	Deviation in clotting time from normal	Measure of coagulability & liver function
Activated Partial Thrombo-plastin Time	21-37.5 sec	Time to activate clotting	Measure of coagulability & liver function
Cardiac/Critical Care			

pH	7.35-7.45	Maintenance of extracellular environment, influences oxygen/carbon dioxide transport	O_2/CO_2 transport
pCO_2	35-45 mmHg	Influences oxygen/carbon dioxide transport	O_2/CO_2 transport
pO_2	80-105 mmHg	influences oxygen/carbon dioxide transport	O_2/CO_2 transport
Bicarbonate (HCO_3^-)	18-23 mmol/L	Oxygen/carbon dioxide transport, counter-ion	O_2/CO_2 transport
O_2 Saturation	95-100%	Amount of O_2 carried by blood	O_2/CO_2 transport
Hematology			
White Blood Cell Count (WBC)	4.50-10.5 k/mm^3	Immune response	Measure of infection
Red Blood Cell Count (RBC)	4-5.4 m/mm^3	Oxygen transport	O_2/CO_2 transport, identifies anemia
Hemoglobin(HGB)	12-16 g/dL	Oxygen transport	O_2/CO_2 transport
Hematocrit (HCT)	36-48%	Cell to Plasma Ratio	O_2/CO_2 transport, identifies anemia
Mean Corpuscular Volume (MCV)	80-95 fL	Size of RBC	Identifies anemia
Mean Corpuscular Hemoglobin (MCH)	27-31 pg	Average mass of HGB in RBC	O_2/CO_2 transport, identifies anemia
Mean Corpuscular Hemoglobin Concentration (MCHC)	32-36 g/dL	HGB Concentration in RBC	O_2/CO_2 transport, Identifies anemia
Red Blood Cell Distribution Width (RDW)	11.5-14.5%	Measures variance of RBC size	Identifies anemia
Platelet Count (PLT)	150-450 k/mm^3	Initiates coagulation	Measure of coagulability
Mean Platelet	7.4-10.4 FL	Size of PLT	Measure of platelet

Volume (MPV)	health

Chemistry

The Chemistry test reveals the ion and protein content of the blood. The studied metabolites are: calcium (Ca^{2+}), blood glucose (GLU), blood urea nitrogen (BUN), creatinine (CR), sodium (Na^{+}), potassium (K^{+}), chlorine (Cl^{-}), and carbon dioxide (CO_2, discussed in *Cardiac/Critical Care*).

The electrolytes Ca^{2+}, Na^{+}, K^{+}, and Cl^{-} have a well-defined role in neuronal conduction and muscle contraction as well as maintaining electrical, osmotic, and concentration gradients. Calcium is a known second messenger in many chemical pathways, such as those involved in PLT activation and T-cell activation (Heemskerk, Bevers et al. 2002; Wintrobe and Greer 2004). Calcium also acts a co-factor of many enzymes, including those involved in blood clotting, such as Factor X and Prothrombin (Hall, Guyton et al. 2011). Hypocalcemia is rare under normal conditions, but in situations of extreme blood loss or ion-quenching with citrate or oxalate, active calcium levels can fall enough to affect enzyme kinetics (Hall, Guyton et al. 2011). Hypocalcemia can be found secondary to myocardial infarction (MI), sepsis, renal insufficiency, and/or hemorrhagic shock (Marino 1998; Whitted, Stanifer et al. 2010). Hypocalcemia can cause neurologic (hyperreflexia, seizures, and tetany) and cardiovascular (hypotension, lowered cardiac output, and ventricular arrhythmias) issues (Marino 1998). Hypercalcemia is rare and only develops in 1% of patients (Marino 1998). However, patients can develop hypercalcemia after surgery with cardiopulmonary bypass (Westhorpe, Varghese et al. 1978). Increased serum calcium can lead to kidney stones, neurologic dysfunction, polyuria, renal failure, and coma

(Reagan, Pani et al. 2013). Interestingly, hypercalcemia can also disrupt electrocardiograms, making it appear as if a patient has had a MI (Wesson, Suresh et al. 2009; Reagan, Pani et al. 2013).

Sodium in the blood plasma drives osmolality of the extracellular fluid (Marino 1998). Due to this, sodium can be thought to maintain the relative extra- and intracellular volumes. The most common cause of hypernatremia (high blood sodium) is loss of low sodium fluids such as urine, sweat, and diarrhea (Marino 1998). Higher concentrations of sodium in the plasma draws water out of the RBCs, causing hypovolemia and decrease oxygen transport. Hypernatremia can indicate water intoxication, syndrome of inappropriate anti-diuretic hormone (a marker of tumors and/or infections), and heart, renal, and hepatic failure (Marino 1998). If untreated, hypernatremia can result in irreversible and potentially fatal brain damage due to cerebral edema (Marino 1998).

Only 2% of potassium in the body is found in the plasma (Marino 1998; Wintrobe and Greer 2004). Intracellular potassium is of particular importance to the heart; being a muscle, heart contraction is dependent on potassium to maintain the resting membrane potential. In hypokalemia, the already low levels of serum potassium fall even further, causing hyperpolarization, elongated heart contraction, and delayed myocardial repolarization(Whitted, Stanifer et al. 2010). Due to this, hypokalemia is associated with the development of cardiac arrhythmias (in patients with digitalis and/or magnesium depletion), muscle weakness, and mental status changes (Marino 1998; Whitted, Stanifer et al. 2010). Hypokalemia can also indicate alkalosis (basic blood, plasma pH >7.4), diarrhea, and/or hypothermia (Marino 1998). While hypokalemia can

be easily tolerated, hyperkalemia is very serious and potentially fatal. Increasing extracellular potassium causes an increasingly slower heart rate and at high enough concentrations can cause the heart to stop completely; this is why potassium chloride is used for lethal injection in the United States (Marino 1998; Khanna and White 2009). Hyperkalemia in heart failure patients is commonly caused by renal insufficiency, massive blood transfusions (replacing more fluid than what was lost), and use of the anti-hypertensive medications angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (Marino 1998; Khanna and White 2009).

Chloride is generally thought of as a counter-ion (along with HCO_3^-) to neutralize the charges of the serum cations. Increased diuresis and/or alkalosis can cause a loss of Cl^- (hypochloremia), leading to an increase in serum HCO_3^- levels to compensate (Marino 1998). Patients with hypochloremia have been shown to spend more time in the intensive care unit. Hyperchloremia can be caused by administration of saline during surgery, renal failure, or diarrhea(McCluskey, Karkouti et al. 2013). Both hypo- and hyperchloremia have been associated with increased in-hospital mortality, however both conditions are relatively well-tolerated (Boniatti, Cardoso et al. 2011; Tani, Morimatsu et al. 2012; McCluskey, Karkouti et al. 2013).

Glucose is strictly monitored throughout a patient's hospital stay. Aside from its aforementioned role in maintaining the RBC membrane, glucose is used throughout the body as a source of chemical energy. However, too much (hyperglycemia, >180mg/dL) or too little (hypoglycemia <60mg/dL) glucose post-cardiac surgery has been associated with poor outcomes (Hermanides, Bosman et al. 2010; Haga, McClymont et al. 2011; Stamou, Nussbaum et al. 2011). Furthermore, the stress of the surgery itself causes

patients to become hyperglycemic (McCowen, Malhotra et al. 2001). Glucose levels are also elevated in patients with liver failure and diabetes (Wintrobe and Greer 2004). Diabetes is a major risk factor in cardiac surgery and is associated with increased short- and long-term mortality, stroke, and infection (Furnary, Zerr et al. 1999; Thourani, Weintraub et al. 1999; Lazar, Chipkin et al. 2004). Through tight or moderate glycemic control, it is possible to reduce the risk of hyper- and hypo-glycemia (Leibowitz, Raizman et al. 2010; Bhamidipati, LaPar et al. 2011; Haga, McClymont et al. 2011; Stamou, Nussbaum et al. 2011). By giving insulin to keep their blood glucose within 127-179 mg/dL (moderate control), patients suffered less infection, lower length of stay, and fewer incidences of recurrent ischemic attack, especially in those with diabetes (Furnary, Zerr et al. 1999; Lazar, Chipkin et al. 2004; Leibowitz, Raizman et al. 2010; Bhamidipati, LaPar et al. 2011; Haga, McClymont et al. 2011; Stamou, Nussbaum et al. 2011). Uncontrolled hyperglycemia can result in hypovolemia, hypertonic encephalopathy, and ketoacidosis (Marino 1998).

BUN and CR are markers of renal function. Concomitant renal and heart failure is known as cardiorenal syndrome and is associated with reduced cardiac output, increased systemic blood pressure, and fluid overload (Aronson 2012). As the kidneys decompensate, less urine is produced and more urea is found in the blood (Kazory 2010). Of particular relevance to the current study, a BUN >43mg/dL is significantly associated with in-hospital mortality in heart failure patients (Kazory 2010). Elevated BUN is also a marker for gastrointestinal bleeding (Sleisenger, Feldman et al. 2010). Creatine is found in muscles and is a source of adenosine triphosphate (ATP) during intense energy demand (Wyss and Kaddurah-Daouk 2000). When creatine is broken

down, it is converted to CR. CR circulates through the blood to the kidneys, where it is filtered out and excreted in the urine; however, if there is an issue in the kidney, CR will go back into the bloodstream (Wyss and Kaddurah-Daouk 2000). Thus, serum CR is inversely related to renal function. An increase in CR in the blood of greater than 10% is predictive of acute kidney injury; an increase of 25% is associated with a two-fold risk of mortality (Ho, Reslerova et al. 2012). On the other hand, a decrease in CR after surgery is associated with improved survival (Lassnigg, Schmidlin et al. 2004). Interestingly, the predictive performance of CR for renal function is strongest in patients with severe heart failure (Smilde, van Veldhuisen et al. 2006). CR >1.5mg/dL is also associated with hepatorenal syndrome (Sleisenger, Feldman et al. 2010). In this disease, failure of the liver and kidneys compromises the other and can even result in lower cardiac output (Sleisenger, Feldman et al. 2010). Elevated CR is also a marker for gastrointestinal bleeding (Sleisenger, Feldman et al. 2010). It is important to note that BUN has been shown to be the more reliable predictor of renal function and cardiac-related complications than CR(Kazory 2010; Beier, Eppanapally et al. 2011; Aronson 2012).

Coagulation

The Coagulation characteristics -prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) are used to evaluate the clotting characteristics of the blood. If the blood does not clot, there is a high risk for bleeding; however, if clots form too readily, the patient has a high risk for thrombosis and stroke. PT is generated by measuring the time it takes blood to clot via

the extrinsic pathway, representing the conversion of prothrombin to thrombin in the presence of calcium and tissue factor (Turgeon 2005; Hall, Guyton et al. 2011). However, PT time is difficult to standardize due to variation from test to test and system to system. In order to address this, the INR was developed. The INR develops a ratio from the results of the current PT test to a control sample; this ratio is then raised to the power of the international sensitivity index, which is a manufacturer-generated assessment of the tissue factor used in the analysis (Hall, Guyton et al. 2011).

$$INR = \left(\frac{PT_{test}}{PT_{control}}\right)^{ISI}$$

aPTT is yet a third way to measure coagulation factors, although this assay reflects the intrinsic coagulation pathway via the activity of prekallikrein, high-molecular weight kininogen, and Factors I, II, V, VIII, IX, X, XI, and XII (Turgeon 2005). A short or long aPTT is indicative of too little or too many, respectively, of these factors or the presence of an anticoagulant (Turgeon 2005). As the liver is responsible for the synthesis of coagulation factors, the PT, INR, and aPTT will all be elongated in patients with liver disease (Turgeon 2005).

Hematology

The Hematology variables look at the physical makeup of the blood and its component parts. These include: WBC count, RBC count, HGB, HCT, mean corpuscular volume (MCV), mean corpuscular HGB (MCH), MCH concentration (MCHC), RBC distribution width (RDW), PLT count, and mean PLT volume (MPV).

The role of HGB is to transport oxygen to the tissues throughout the body. HGB is a heme-containing protein that binds oxygen to form oxyhemoglobin, an unstable

molecule that readily breaks down in environments of low partial pressure oxygen (Powar, Chatwal et al. 2008). Interestingly, the four subunits that make up HGB demonstrate cooperative (or allosteric) binding (Wintrobe and Greer 2004). This forms a sigmoidal oxygen dissociation curve, which is displayed in Figure 1. It is this relationship that allows HGB to carrying oxygen from the O_2-rich lungs to the O_2-deficient tissues. HGB's role as oxygen transporter is what makes it so important. When a patient is given donor RBC, HGB level quickly rise; a study found HGB levels to rise by 1.3 g/dl and in oxygen delivery to increase 50ml/minute/m^2 after a transfusion (Creteur, Neves et al. 2009). However, there was no corresponding significant increase in oxygen saturation or consumption (Creteur, Neves et al. 2009).

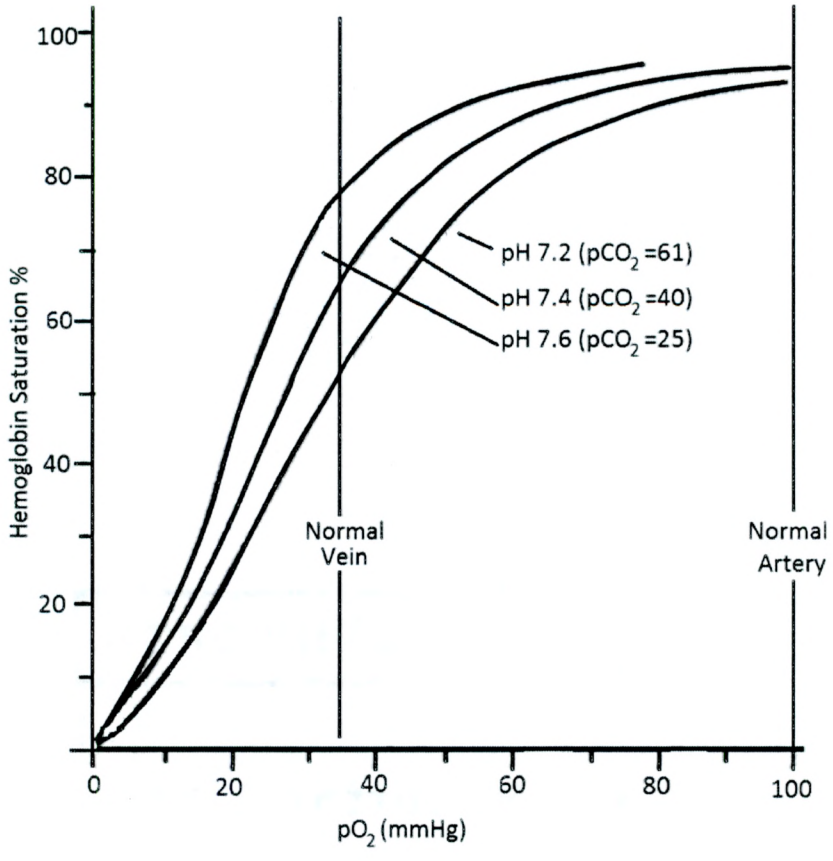

Figure 1: The Oxygen Dissociation Curve. The partial pressure of oxygen (pO_2) drives oxygen binding and dissociation from hemoglobin. The sigmoidal shape is due to the cooperative binding effect of the four subunits in hemoglobin. (Adapted from (Wintrobe and Greer 2004))

As previously stated, the HCT is the % volume of cells in whole blood. It has been shown that the lower a patient's HCT goes during surgery, the higher risk for post-operative complications (DeFoe, Ross et al. 2001). Patients with anemia will have a low HCT; likewise, erythrocytosis (overproduction of RBCs) results in raised HCT. Blood viscosity increases exponentially with HCT which leads to reduced blood flow and, consequently, decreased oxygen delivery (Wintrobe and Greer 2004). Previous work at the study location revealed that the most patients were discharged with HCT between 28.5-31.3%, regardless of baseline HCT (Shaw, Johnson et al. 2013). This was thought to be indicative of a target discharge HCT and that the patient would be transfused to reach this target, despite lack of evidence or support for this practice (Shaw, Johnson et al. 2013).

The MCV, MCH, and MCHC are used to measure the size and HGB content of RBCs. Since the 1930's, they have been used to characterize anemias (Brugnara and Mohandas 2013).

$$MCV = \frac{HCT\ (\frac{L}{L})}{RBC\ count\ (\frac{X1012}{L})}$$

$$MCH = \frac{HGB\ (X\frac{10gm}{dL})}{RBC\ count\ (X\frac{1012}{L})}$$

$$MCHC = \frac{HGB}{HCT}$$

MCV tends to increase as a person ages with no apparent relation to anemia (Gamaldo, Ferrucci et al. 2011). Most automated hematology analyzers (like the one used in this study) use MCV to generate HCT (Brugnara and Mohandas 2013). By comparing MCV and MCH, it is possible to distinguish between certain kinds of anemia, such as β-thalassemia (a genetic disorder requiring transfusions) and iron deficiency anemia (a relatively treatable condition). While both conditions result in decreased MCV and MCH, patients with β-thalassemia will have an increased number of small RBCs (microcytic RBCs) than hypochromic (HGB-deficient); however, this relationship is reversed (more hypochromic than microcytic) in iron deficiency anemia (d'Onofrio, Zini et al. 1992). Interestingly, iron deficiency will affect MCHC and MCH first and only influence MCV and RDW later on (Patton, Cave et al. 1991). In addition, low MCV (<80fL) can indicate a chronic gastrointestinal bleed, while a high MCV (>100fL) is suggestive of chronic liver disease (Sleisenger, Feldman et al. 2010).

A more recently developed measure, the RDW, can also be used to characterize anemias (Turgeon 2005; Brugnara and Mohandas 2013). RDW is a coefficient of variation percentage, representing the most commonly found RBC volume by excluding the extreme volumes at the low (likely clumped PLTs) and high end (clumped RBC) (Turgeon 2005).

$$RDW = \frac{Standard\ Deivation}{Mean\ RBC\ Size}\ x\ 100\%$$

While a low RDW has not been linked to any abnormalities, a high RDW is associated with anemia and iron insufficiency, vitamin B_{12}, and/or folic acid (Turgeon 2005). Taken together, RDW and MCV can offer insight into the status of the erythrocytes; for instance, a high RDW and a low MCV indicate iron-deficiency anemia while a high RDW and a high MCV suggest a megoblastic anemia (Turgeon 2005). However, the efficacy of this method has been contested in literature (Flynn, Reppun et al. 1986; Brugnara and Mohandas 2013). Of particular note to the current study, RDW is associated with mortality in patients with heart failure, MI, and/or in the intensive care unit (as in after surgery) (Forhecz, Gombos et al. 2009; Borne, Smith et al. 2011; Wang, Pan et al. 2011; Wang, Hua et al. 2011). In elderly patients, a 1% increase in RDW is correlated with as much as a 14% increased risk of mortality (Semba, Patel et al. 2010). It is hypothesized that increased RDW is a result of inflammation, oxidative stress, and/or vascular injury (Semba, Patel et al. 2010; Brugnara and Mohandas 2013).

The role of PLTs in healthy physiology has been previously discussed. However, deviations from normal PLT values can have disastrous consequences. For instance, if there are too few PLTs (thrombocytopenia), vascular injury can go untreated resulting in uncontrolled bleeding. Of particular relevance to the current subject, thrombocytopenia can occur as a result from using cardiopulmonary bypass in surgery (Schmidt, Peden et al. 1961; Turgeon 2005). On the other hand, if there are too many PLTs in the blood (thrombocytosis), they could form a clot (a thrombus) where it could block the vessel and lead to ischemia (a lack of oxygen to a given tissue). If the clot breaks off and travels through the blood stream, it is referred to as an embolus. Interestingly, 1-3% of patients can develop heparin-induced thrombocytopenia (HIT), an auto-immune disorder

which can also lead to thrombus formation (Warkentin and Greinacher 2003; Turgeon 2005). Heparin, an anti-anticoagulant commonly prescribed to cardiac surgeon patients, acts by binding to PLT factor 4; HIT occurs in those patients that form antibodies to this heparin-PLT factor 4 complex (Warkentin 2003; Turgeon 2005). While it will cause PLT levels to fall, the antibody-heparin-PLT binding will also increase the clotting abilities of the PLTs, leading to thrombosis formation in 30% of HIT patients; 25% of HIT thrombi are fatal (Turgeon 2005). In the absence of any other explanation, HIT should be suspected whenever there is a >50% decrease in PLT after exposure to heparin.

In a healthy patient, the volume of the average PLT shares an inverse relationship to the total amount of PLTs; that is, the more PLTs there are, the smaller each individual PLT is. Larger PLTs are more active enzymatically and more likely to generate a thrombus (Karpatkin 1969; Giles, Smith et al. 1994; Kamath, Blann et al. 2001). Anti-coagulation with EDTA, which decreases PLT count, also causes PLTs to swell by almost 20% their normal volume for about 12 hours (Turgeon 2005). The formula for calculating MPV is similar to that for MCV (like HCT, plateletocrit is the percent volume of PLTs in the blood):

$$MPV = \frac{Plateletocrit}{PLT\ count}$$

Due to this variability of PLT volume, the range of an acceptable MPV depends on the patients' PLT count; a MPV nomogram is generally used to determine the healthy range (Figure 2) (Turgeon 2005). A low MPV can indicate anemia and hypersplenism, while an elevated MPV after surgery is associated with an overproduction of blood cells, graft

failure and MI, and septic thrombocytopenia, in which a bacterial infection leads to the destruction of PLT (Giles, Smith et al. 1994; Turgeon 2005; Chu, Becker et al. 2010).

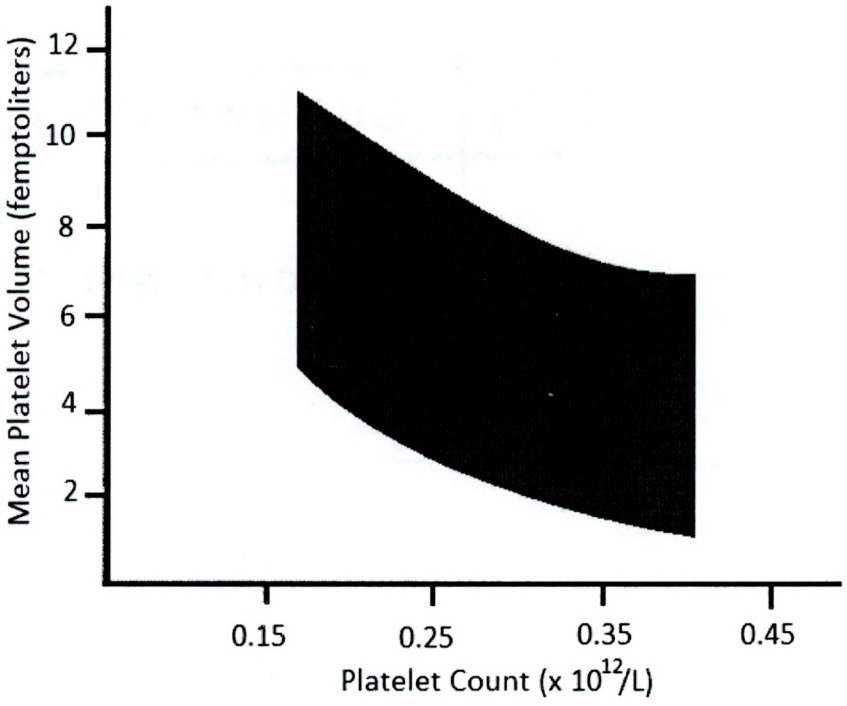

Figure 2: Mean Platelet Volume Nomogram. Normal mean platelet volume varies with platelet count. (Adapted from (Pierre 1985)).

Cardiac/Critical Care

The variables covered under the Cardiac/Critical Care blood tests are: pH, pCO_2, pO_2, HCO_3^-, and O_2 saturation. In addition, these blood gas tests can be used to estimate serum Na^+, K^+, Cl^-, Ca^{2+}, and glucose levels.

The pH, pCO_2, and pO_2 of the blood affect oxygen and transport (Figure 3). As demonstrated in Figure 1, HGB's oxygen affinity (the pO_2 at which 50% of HGB is bound to oxygen, P_{50}) can be shifted to the right (decreased affinity) or the left

(increased affinity); this change in affinity is known as the Bohr Effect. The tissues have high levels of CO_2 and low pH, w-hich causes decreased oxygen affinity and HGB's subsequent release of O_2 into the tissues. The opposite is seen at the lungs, where pCO_2 is lower and pH is higher, resulting in increased oxygen binding. In addition, oxygen transport is also affected by pH and CO_2 via CO_2 binding to the *N*-terminus of HGB, forming carbaminohemoglobin. This causes a conformation shift which decreases the heme group's O_2 affinity (Wintrobe and Greer 2004). At a normal blood pH of 7.4, about 10% of HGB is normally found as carbaminohemoglobin; however this percentage increases in response to increasing acidity (Marino 1998; Wintrobe and Greer 2004).

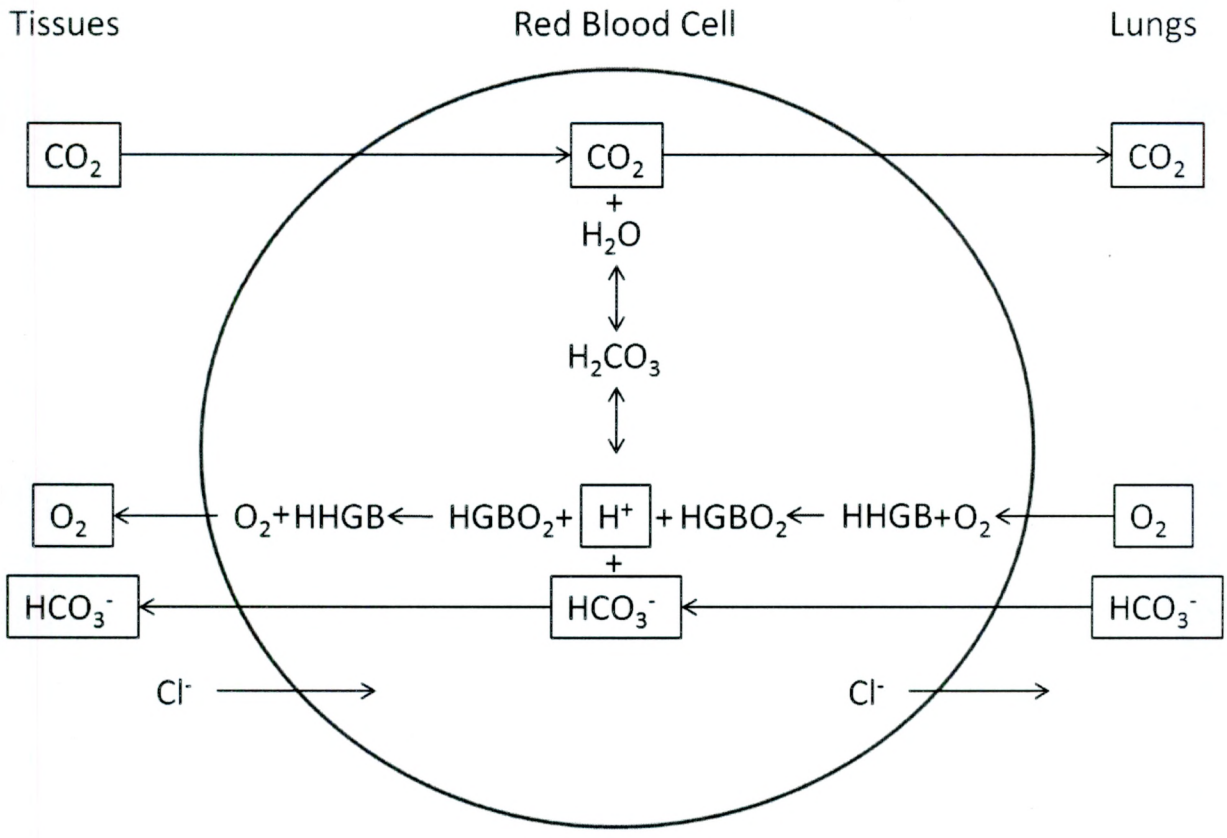

Figure 3: Mechanism of Oxygen and Carbon Dioxide Transport in Red Blood Cells. HGB = hemoglobin, HCO_3^- = bicarbonate, $HGBO_2$ = oxyhemoglobin, HHGB = protonated hemoglobin. (Adapted from (Wintrobe and Greer 2004)).

CO_2 is not transported in the blood via carbaminohemoglobin, but rather as HCO_3^-. CO_2 is converted to HCO_3^- via the following reversible reaction:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

The reaction equilibrium is dependent on the concentration of CO_2, HCO_3^-, and H^+ (Wintrobe and Greer 2004). CO_2 passively diffuses into RBCs, where the formation of H_2CO_3 is catalyzed by carbonic anhydrase in the cells. Interestingly, the proton released by the breakdown into HCO_3^- is taken up by HGB which reduces its affinity for oxygen (as demonstrated by the Bohr Effect) (Wintrobe and Greer 2004). The HCO_3^- diffuses out of the cell passively or by facilitated transport via ion exchange for Cl^-. The HCO_3^- travels in the blood to the lungs, where the low pCO_2 drives the conversion back to CO_2. CO_2 dissociation is inversely affected by oxygen-bound HGB; this is known as the Haldane Effect (Figure 4). Higher concentrations of protons in the blood (acidosis) will cause hyperventilation to rid the body of CO_2 and increased HCO_3^- reabsorption in the kidneys; the reverse is true for alkalosis(Marino 1998). Due to increased fatty acid catabolism in diabetes, patients with this condition can develop ketoacidosis (Marino 1998).

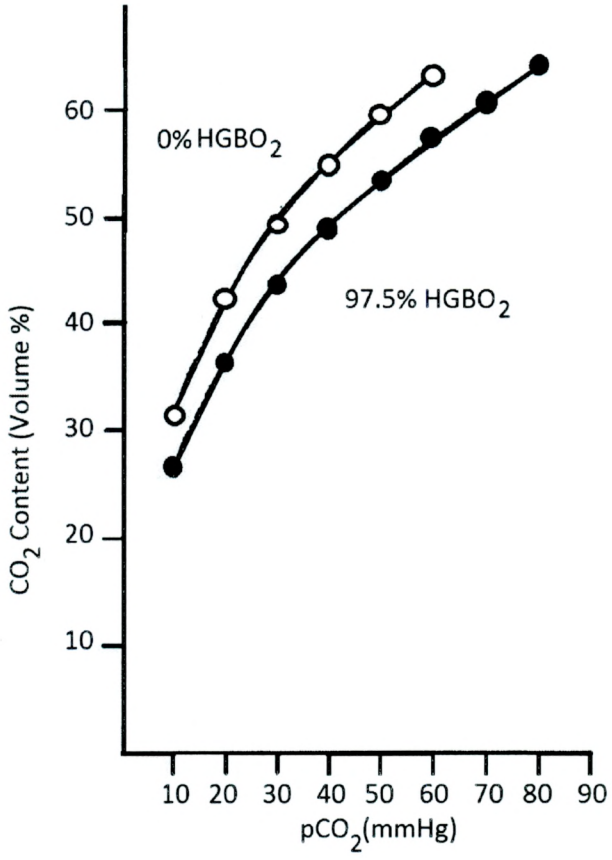

Figure 4: Carbon Dioxide Dissociation Curve. CO_2 content is dependent on pCO_2. The right shift due to $HGBO_2$ concentration is called the Haldane Effect. $HGBO_2$ = oxyhemoglobin (Adapted from (Wintrobe and Greer 2004)).

Goals

This study aims to track the physiological effects of blood transfusion after cardiac surgery. This will be accomplished by retrospectively analyzing the trends in blood chemistry and blood characteristics over time in a series of propensity-matched transfused and non-transfused patients undergoing isolated CABG.

CHAPTER 2

METHODS

Database Characteristics

Demographic data was collected from in a database certified by the STS. All variables were defined and coded using STS standards (Shahian, O'Brien et al. 2009; Overman, Jacobs et al. 2013; Shahian, Jacobs et al. 2013). Between July 2004 and June 2011, 3,516 consecutive patients underwent cardiac surgery at The Valley Columbia Heart Center. In order to limit the confounding effects of additional treatments related to post-operative care, any patients with 30-day complications and/or mortality (defined using the STS standard definition of operative mortality as death within 30 days of surgery) were removed from this study (Overman, Jacobs et al. 2013; Shahian, Jacobs et al. 2013). This left a cohort of 1,134 patients that underwent an isolated CABG with no complications (Table 2). Of these, 407 (35.8%) patients received a blood transfusion.

Table 2: Overall Patient Characteristics

Demographic	Non-Transfused		Transfused	
n=	727		407	
Age	63.6	±10.58	67.8	±10.27
Male	607	83.49%	280	68.80%
Body Surface Area	2.1	±0.24	1.9	±0.23
Emergency Surgery	362	49.79%	116	28.50%
Previous Myocardial Infarction	288	39.61%	208	51.11%
Left Main Disease >50%	280	38.51%	195	47.91%
Smoker	431	59.28%	243	59.71%
Angina	383	52.68%	201	49.39%
Diabetes	237	32.60%	157	38.57%

Ejection Fraction	53.3	±13.78	52.2	±10.57
New York Heart Association Class III-IV	32	4.40%	129	31.70%
Renal Failure	20	2.75%	35	8.60%
Dialysis	2	0.28%	8	1.97%
Cardiogenic Shock	9	1.24%	6	1.47%
Intraoperative Blood	0	0.00%	142	34.89%
Postoperative Blood	0	0.00%	355	87.22%
Readmission Within 30 Days	23	3.16%	15	3.69%

Propensity-matching was used to provide a more balanced patient population (Rosenbaum 1983; Rosenbaum 1985; Rubin 1997). Using a logistic regression model, the probability of a patient receiving a blood transfusion was developed based upon 22 baseline covariates that included gender, age, BMI, diabetes, smoking, hypertension, dyslipidemia, number of diseased coronary vessels, peripheral vascular disease, presence of heart failure, New York Heart Association (NYHA) class, history of stroke, chronic lung disease, MI history, renal failure, left main disease, left ventricular ejection fraction, CR, cardiogenic shock presentation, and urgent status. The resulting propensity scores were then employed to identify as many 1:1 matches between the transfusion and non-transfusion group using the nearest neighbor-matching algorithm with Greedy 5-1 Digit Matching (Cormen 2001; Soriano 2012). The model produced a balanced cohort of 636 patients: 318 transfused (TG) and 318 (NTG). The Society of Thoracic Surgeons (STS) uses many of these categories to calculate a patient's risk for post-surgical complications and mortality (Shahian, O'Brien et al. 2009; Jin, Furnary et al. 2010; Overman, Jacobs et al. 2013). STS Risk Adjusted Scores were calculated for each patient using eCardio (Velos, Fremont, CA), a STS-approved software. These scores

were then used to generated predicted rates of overall morbidity and mortality, mortality, renal failure, need for re-operation, stroke, prolonged ventilation, deep sternal wound infection, and lengths of stay of greater than 6 and 14 days.

Data Collection

For each patient, 26 variables derived from traditional blood analyses (Chemistry, Coagulation, Cardiac/Critical Care, and Hematology) were collected (Table 1, see page 13). These tests are performed multiple times throughout the patient's hospital course except Cardiac/Critical Care, which is only performed in the intensive care unit. Each available measurement was recorded for each patient. The Chemistry metabolites were: Ca^{2+}, GLU, BUN, CR, Na^{+}, K^{+}, Cl^{-}, and CO_2. The Coagulation characteristics were PT, INR, and aPTT. The Hematology variables were: WBC, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLT, and MPV. The variables covered under the Cardiac/Critical Care blood tests are: pH, pCO_2, pO_2, HCO_3^{-}, and O_2 saturation.

Data was taken at five time points for the TG and NTG. The TG data was taken at the last measure before surgery, the first measure after surgery, the last measure before transfusion, the first measure after transfusion, and the last measure before discharge. The NTG used the last measure before surgery, the first measure after surgery, two points during the recovery period, and the last measure before discharge. The two values from the NTG recovery period were generated by averaging the results from the first and second halves of the patient's post-surgical stay. Patients without data at all five time points were removed from the analysis.

Statistical Analysis

A repeated measures analysis of variance (rANOVA) was used to look at changes in metabolites/blood characteristics over time. The rANOVA reports on the significance of trends within and between subjects. The within subject analysis was utilized to determine if the values changed significantly over time. More importantly, the within subject analysis were used to identify if transfusion had a significant effect on the values over time. The Mauchly's Test of Sphericity was implemented to determine sphericity, a statistical test to see if there is equal variance in the differences between the data points within a group (Lund 2013). The Greenhouse-Geisser correction, considered to be a conservative correction, was applied to situations where sphericity could not be assumed (Lund 2013). The between subjects portion of the rANOVA made it possible to examine if there was a significant difference in the values of NTG and TG overall and at a given time point.

Analyses were performed using the SPSS statistical software package version 19.0 (IBM/SPSS Inc., Chicago, IL). All statistical tests were performed by an experienced statistician (Dr. Richard Shaw, PhD, The Valley Columbia Heart Center). A value of $p < 0.05$ was used to determine the statistical significance of all tests used.

CHAPTER 3

RESULTS

Descriptive Statistics

Patients receiving blood products were found to be older, more likely to be female, with higher rates of diabetes, MI history, renal failure, NYHA Class III-IV heart failure, more severe coronary disease and more urgent presentation. A comprehensive breakdown of the overall patient population can be found in Table 2 (page 31). The baseline characteristics of the two groups did not differ significantly as demonstrated by a univariate analyses (Table 3). Using the Society of Thoracic Surgeons (STS) Risk Adjusted Scores (Shahian, O'Brien et al. 2009; Jin, Furnary et al. 2010), the two groups were predicted to have similar outcomes; this further supports the homogeneity of the two groups (Table 4).

Table 3: Propensity-Matched Patient Characteristics and Predicted Outcomes

Group	Non-Transfused		Transfused	
n=	318		318	
Male	228	71.7%	240	75.5%
Age	68.45	±11.0	66.69	±6.3
Body Surface Area	1.98	±0.2	1.96	±0.2
Body Mass Index	28.25	±4.1	28.68	±5.8
Urgent Surgery	209	65.7%	202	63.5%
Smoker	176	55.3%	191	60.1%
Myocardial Infarction	158	49.7%	167	52.5%
Angina	147	46.2%	171	53.8%
New York Heart Association Class III-IV	68	21.4%	77	24.2%

Diabetes	117	36.8%	113	35.5%
Ejection Fraction	52.06	±11.1	52.88	±13.8
Renal Failure	20	6.3%	16	5.0%
Dialysis	2	0.6%	4	1.3%
Cardiogenic Shock	4	1.3%	1	0.3%

Table 4: Calculated Society of Thoracic Surgeons Predicted Outcomes

Group	Non-Transfused		Transfused	
Predicted Morbidity and Mortality	13.0%	±12.5%	12.0%	±9.5%
Predicted Mortality	1.8%	±8.4%	1.6%	±3.4%
Predicted Renal Failure	3.5%	±9.0%	3.1%	±3.9%
Predicted Re-Operation	4.9%	±3.7%	4.8%	±3.1%
Predicted Stroke	1.4%	±3.3%	1.5%	±1.2%
Predicted Prolonged Ventilation	7.3%	±12.1%	5.8%	±9.1%
Predicted Deep Sternal Wound Infection	0.4%	±0.5%	0.5%	±0.6%
Predicted Length of Stay > 6 Days	50.3%	±10.0%	53.1%	±10.1%
Predicted Length of Stay >14 Days	4.9%	±9.6%	4.3%	±4.9%

During data collection, it was discovered that 13 patients in the TG had transfusions before their CABG and were subsequently removed from the study. The descriptive statistics for each measure will be discussed below.

Within Subjects

All of the measures were found to have p=0.000 for Mauchly's Test of Sphericity, indicating none of the data could be considered to meet the condition of assumed sphericity for the within subjects categories of Time and Time*Group. Therefore, the Greenhouse-Geisser correction is reported for these categories (Table 5, next page).

Table 5: Within Subject Effects of Time and Transfusion on Blood Characteristics.

	Df	df_{error}	F_{Time}	Time p-value	$F_{Time * Transfusion}$	Time * Transfusion p-value
Ca^{2+}	2.86	1431.88	687.50	**0.000**	26.49	**0.000**
GLU	2.26	1147.39	15.11	**0.000**	0.50	0.629
BUN	2.61	1325.24	55.42	**0.000**	3.28	**0.026**
CR	2.98	1514.47	49.11	**0.000**	3.28	**0.020**
Na^{+}	1.01	513.49	2.02	0.156	0.72	0.399
K^{+}	1.01	512.86	3.03	0.082	1.49	0.223
Cl^{-}	2.32	1175.85	93.30	**0.000**	2.56	0.069
CO_2	3.31	1680.11	335.78	**0.000**	22.76	**0.000**
PT	1.18	497.43	26.54	**0.000**	0.18	0.714
INR	1.81	760.02	42.85	**0.000**	2.31	0.105
aPTT	1.96	735.11	1.23	0.294	1.11	0.330
pH	1.62	684.96	6.93	**0.002**	3.67	**0.035**
pCO_2	1.67	708.34	10.85	**0.000**	3.17	0.052
pO_2	1.87	791.39	292.68	**0.000**	37.73	**0.000**
HCO_3^{-}	1.10	467.16	3.11	0.075	3.04	0.078
O_2 Sat	1.25	529.32	1.69	0.194	0.18	0.732
WBC	2.34	1224.26	270.34	**0.000**	8.85	**0.000**
RBC	2.15	1123.87	192.99	**0.000**	8.75	**0.000**
HGB	1.01	562.66	8.05	**0.005**	2.02	0.155
HCT	1.39	780.46	150.76	**0.000**	11.52	**0.000**
MCV	1.05	546.61	1.23	0.271	0.90	0.348
MCH	2.71	1414.84	16.80	**0.000**	3.15	**0.029**
MCHC	3.43	1791.54	12.11	**0.000**	5.87	**0.000**
RDW	1.04	541.40	11.59	**0.001**	0.89	0.356
PLT	2.24	1164.69	226.97	**0.000**	23.48	**0.000**
MPV	1.85	963.83	4.03	**0.021**	1.32	0.267

Time refers to the test to determine if the measure changes over time. The Time * Group test determines if transfusion significantly affects this change over time. The results in Table 5 indicate that 21 blood characteristics (Ca^{2+}, GLU, BUN, Cr, Cl^{-}, CO_2, PT, INR, pH, pCO_2, pO_2, O_2 saturation, WBC, RBC, HGB, HCT, MCH, MCHC, RDW, PLT, and MPV,) change significantly over time. However, when the effect of

transfusion on these changes over time was tested, there were fewer significant changes with only 12 factors being significant: Ca^{2+}, BUN, Cr, CO_2, pH, pO_2, WBC, RBC, MCH, MCHC, PLT, and HCT. There were no significant differences seen in Na^+, K^+. aPTT, HCO_3^-, and MCV in either within subject test.

Between Subjects

The between subject test identifies if the values of a given measure for NTG and TG are significantly different. Overall, 11 categories were different between the NTG and TG: Ca^{2+}, BUN, CR, CO_2, ALP, INR, pH, pO_2, HCO_3^-, O_2 saturation, RBC, and HCT (Table 6).

Table 6: Between Subjects Test to Determine if Transfusion Effects Overall Measurement Values

Category	Df	df_{error}	F	p-value	Category	df	df_{error}	F	p-value
Ca^{2+}	1	508	21.877	**0.000**	**pCO_2**	1	424	0.461	0.497
GLU	1	508	0.209	0.648	**pO_2**	1	424	46.313	**0.000**
BUN	1	508	4.775	**0.029**	**HCO_3^-**	1	424	27.397	**0.000**
CR	1	508	3.981	**0.047**	**O_2 Sat**	1	424	8.068	**0.019**
Na^+	1	508	0.743	0.389	**WBC**	1	523	2.078	0.150
K^+	1	508	1.437	0.231	**RBC**	1	523	41.424	**0.000**
Cl^-	1	508	1.084	0.298	**HGB**	1	560	0.001	0.980
CO_2	1	508	19.600	**0.000**	**HCT**	1	560	60.885	**0.000**
PT	1	422	1.408	0.236	**MCV**	1	523	1.061	0.303
INR	1	421	28.631	**0.000**	**MCH**	1	523	0.018	0.894
aPTT	1	375	2.078	0.150	**MCHC**	1	523	2.634	0.105
TBIL	1	159	0.559	0.456	**RDW**	1	523	0.854	0.356
pH	1	424	32.035	**0.000**	**PLT**	1	523	2.962	0.086
ALT	1	159	0.587	0.445	**MPV**	1	523	0.785	0.376

A sub-analysis of the between groups analysis was performed to examine if there is difference between the NTG and TG values at each time point. The results of the Chemistry tests are displayed in Table 7. A graphical representation of these results can be found in Supplemental Figure 1 (page 55). Significant differences were found at certain time points for Ca^{2+} (at time points 3 & 4), BUN (1, 3, & 5), CR (1), Cl^- (4), and CO_2 (4). There were no significant differences in GLU, Na^+, and K^+ concentrations between the two groups.

Table 7: Mean Chemistry Values over Time

	Group	N	T=1	T=2	T=3	T=4	T=5
Calcium	NTG	317	9.24	8.01	8.22	8.60	8.66
	TG	185	9.18	8.00	8.01	8.13	8.63
	p-value		0.243	0.810	**0.000**	**0.000**	0.423
Glucose	NTG	317	126.57	142.50	130.89	126.25	123.44
	TG	193	127.04	139.98	132.48	126.25	118.03
	p-value		0.933	0.374	0.495	0.999	0.402
BUN	NTG	317	19.35	17.68	19.45	22.10	21.39
	TG	193	21.19	18.21	22.07	22.87	23.65
	p-value		**0.041**	0.421	**0.002**	0.410	**0.018**
Creatinine	NTG	317	1.00	0.91	0.97	1.04	1.02
	TG	193	1.13	0.99	1.13	1.14	1.13
	p-value		**0.022**	0.088	0.100	0.125	0.105
Sodium	NTG	317	138.96	143.15	140.30	136.99	137.78
	TG	193	138.75	139.21	137.93	137.51	137.47
	p-value		0.422	0.417	0.330	0.087	0.218
Potassium	NTG	317	4.05	4.22	4.30	4.19	4.10
	TG	193	4.09	4.98	4.93	4.15	4.09
	p-value		0.277	0.191	0.268	0.206	0.860
Chlorine	NTG	317	103.47	108.45	106.59	102.84	102.85
	TG	193	103.77	108.94	106.45	104.61	102.49
	p-value		0.527	0.562	0.831	**0.006**	0.249
CO2	NTG	317	26.49	23.07	23.93	26.51	26.91
	TG	193	26.04	22.65	23.91	24.35	26.44

	p-value	0.062	0.280	0.923	**0.000**	0.057

Table 8 represents the results of the Coagulation tests between measures analysis. All three measures had significant differences: PT (time point 1), INR (2-5), and aPTT (5). Supplemental Figure 2 (page 57) displays traces of how these three measurements change over time.

Table 8: Mean Coagulation Times

	Group	N	T=1	T=2	T=3	T=4	T=5
PT	NTG	313	13.76	16.54	16.53	15.79	15.85
	TG	111	14.33	16.78	17.09	15.95	16.25
	p-value		**0.000**	0.743	0.475	0.367	0.106
INR	NTG	313	1.11	1.32	1.31	1.28	1.29
	TG	110	1.17	1.46	1.50	1.36	1.40
	p-value		0.316	**0.000**	**0.000**	**0.000**	**0.000**
aPTT	NTG	283	36.08	32.52	2.89	32.79	32.94
	TG	94	34.94	35.09	35.00	34.12	35.17
	p-value		0.614	0.142	0.224	0.108	**0.036**

The results of the Cardiac/Critical Care group can be found in Table 9 (Supplemental Figure 3, page 58). There were significant differences at each time point for both pH and HCO_3^-. Significant differences were seen in pO_2 at time points 1-3 and O_2 saturation at time point 3. There were no significant differences for pCO_2.

Table 9: Mean Results of the Cardiac/Critical Care Measurements

	Group	N	T=2	T=3	T=4	T=5
pH	NTG	318	7.39	7.39	7.39	7.39
	TG	108	7.42	7.42	7.40	7.43
	p-value		**0.000**	**0.000**	**0.042**	**0.000**

pCO2	NTG	318	37.58	38.04	38.50	38.34
	TG	108	36.82	37.14	39.37	37.87
	p-value		0.234	0.146	0.147	0.406
pO2	NTG	318	211.20	191.07	130.49	125.72
	TG	108	322.81	243.43	175.65	126.18
	p-value		**0.000**	**0.000**	**0.000**	0.960
CSHCO3	NTG	318	22.17	22.15	22.65	22.81
	TG	108	23.27	25.81	24.08	29.44
	p-value		**0.000**	**0.005**	**0.000**	**0.000**
O2 Sat	NTG	318	98.06	97.86	97.70	97.55
	TG	108	99.35	99.14	98.86	98.41
	p-value		0.065	0.075	**0.000**	0.095

The Hematology results are displayed in Table 10 (Supplemental Figure 4, page 59). Values were significantly different for HCT at all points. Significance was also achieved at difference time points for WBC (at time point 3), RBC (1, 3, 4, & 5), HBG (2-5), MCHC (3 & 4), and PLT (2-5). MCV, MCH, and MPV showed no significant differences.

Table 10: Mean Hematology Values Over Time

	Group	N	T=1	T=2	T=3	T=4	T=5
WBC	NTG	317	8.08	14.50	12.93	10.36	9.22
	TG	208	8.03	13.37	11.24	10.13	9.57
	p-value		0.855	0.083	**0.000**	0.557	0.405
RBC	NTG	317	4.39	3.67	3.50	3.35	3.29
	TG	208	4.13	3.46	2.89	3.09	3.19
	p-value		**0.000**	0.085	**0.000**	**0.001**	**0.006**
HGB	NTG	317	13.48	11.70	11.35	10.32	10.12
	TG	245	17.46	11.36	8.96	9.43	9.86
	p-value		0.286	**0.014**	**0.000**	**0.000**	**0.008**
HCT	NTG	317	40.63	34.30	33.11	30.28	29.68
	TG	245	36.85	33.23	26.69	27.58	28.95
	p-value		**0.006**	**0.010**	**0.000**	**0.000**	**0.012**

MCV	NTG	317	90.11	90.13	91.31	90.84	90.49
	TG	208	89.95	89.94	90.07	89.79	90.24
	p-value		0.729	0.685	0.303	0.092	0.563
MCH	NTG	317	30.77	30.85	30.88	30.93	30.88
	TG	208	30.71	30.86	30.94	30.88	30.80
	p-value		0.747	0.953	0.733	0.775	0.639
MCHC	NTG	317	34.12	34.21	34.17	34.14	34.11
	TG	208	3.13	34.29	34.33	34.38	34.11
	p-value		0.964	0.215	**0.050**	**0.000**	0.996
RDW	NTG	317	13.91	13.83	14.07	14.26	14.38
	TG	208	13.62	13.57	13.77	14.32	14.34
	p-value		**0.039**	0.068	**0.031**	0.793	0.927
PLT	NTG	317	224.74	184.31	176.03	204.98	238.59
	TG	208	220.52	172.25	162.32	166.75	261.25
	p-value		0.553	**0.028**	**0.008**	**0.000**	**0.010**
MPV	NTG	317	8.24	8.14	8.27	8.66	8.36
	TG	208	8.18	8.10	8.27	8.29	8.39
	p-value		0.524	0.588	0.950	0.087	0.909

CHAPTER 4

DISCUSSION AND CONCLUSIONS

Effect of Transfusion on Anemia and Oxygen Transport

The primary goal of a blood transfusion is to provide the patient's tissues with more oxygen through replacement of lost or impaired RBC. For the most part, transfusion does have an effect on how measures of anemia and oxygen transport trend over time. In total, ten of the sixteen measures used to monitor anemia and oxygen transport were found to be significantly affected by the administration of blood products.

Patients developed anemia after surgery. As demonstrated by Figures 5-9, RBC, HGB, and HCT for of the average NTG and TG patient fell below normal values. It is interesting to find that the TG has lower RBC, HGB, and HCT than NTG throughout their post-operative stay, which could be the driving factor for why those patients received transfusions. However, even with after their transfusion, these patients fail to reach non-significant differences with their NTG counterparts. Furthermore, the changes in HGB were significant over time, but were not found to be affected by transfusion. This suggests that HGB levels did not respond to transfusion. This is important as most guidelines use low HGB as an indicator for the need of blood transfusion (Ferraris, Ferraris et al. 2007). Regarding these guidelines, it is interesting to note that the average TG patient received a transfusion at a HGB of ~9g/dL, suggesting that most of these patients could did not meet the basic requirement for a transfusion. However, there

could have been other factors that guided the physician's decision to transfuse these patients beyond HGB.

There does not appear to be a standard type of post-surgical anemia, as the average MCV, MCH, and MCHC stay within their normal ranges. The MCV, based upon the ratio of HCT to RBC, demonstrated no significant changes or differences, which was not surprising given how similarly the two measures tracked. On the other hand, MCH and MCHC (ratios dependent on the HGB), were found to be significantly affected by transfusion. This may be an artifact due to the fact the changes in HGB were not influenced by transfusion while RBC and HCT (the denominator of MCH and MCHC, respectively) were. Lastly, the fourth method available to identify the type of anemia, RDW, demonstrated no effects from transfusion. Notably, the NTG RDW is initially much higher (significant at T=1 and T=3), but transfusion brings the RDW of the TG up to the level of the NTG's RDW. This is not necessarily a benefit, as a higher RDW is an indicator of anemia.

It would be a reach to claim that transfusions do not effectively treat anemia. It is possible that that transfusion either helps to jump-start the body's natural response to anemia or simply stabilizes the patient long enough for the recovery process to begin on its own, as RBC, HGB, and HCT values continue to rise after transfusion.

The main concern for patients with anemia is the potential for decreased tissue oxygenation. This study looks at several factors that affect or describe the blood's oxygen-carrying capacity. It is hard to state with any certainty the true effects of transfusion on the Cardiac/Critical Care variables as most TG patients started with

significantly higher values. However, it is possible to compare the trends between the two groups. Looking at oxygen directly, the results show that pO_2 and O_2 saturation were higher in the TG than NTG immediately after transfusion. Transfusion was shown to be associated with the TG's pO_2 decline to that of the NTG's; however, this was not the case with O_2 saturation.

As stated previously, pH and CO_2 also affect pO_2 carrying-capacity. The blood pH of the TG was significantly higher than that of the NTG, but not so much that is was outside of the normal range. Paradoxically, CO_2 concentration in TG was lower than the NTG immediately after transfusion, but pCO_2 was higher (albeit not to a significant extent). Likewise, CO_2 levels were significantly affected by transfusion, but not pCO_2. This could be a manifestation of the Haldane effect due to the increase in O_2-saturated HGB after transfusion. Even more striking is the fact that while HCO_3^- was significantly higher in the TG, it was not affected by transfusion itself (or time, for that matter). This may be the result of decreasing concentrations of H^+ and CO_2, which would maintain the equilibrium of the HCO_3^- reaction (found on page 29). It would also explain the increase in O_2 saturation, as a decrease in both of these concentrations would create a left shift in the oxygen dissociation curve.

Effect of Transfusion on Coagulation

Overall, transfusion does not seem to affect coagulation in any significant way. The administration of blood products was only associated with increasing PLT, inducing a steep increase at T=4. Otherwise, the other measures of coaguability (PT, INR, aPTT, and MPV) were shown to change independently of transfusion. This may be explained

by the common practice of administering anti-coagulant medications to patients after cardiac surgery to reduce the risk of clotting. While both groups should have received the same treatment in this regard, it is possible that the drugs masked the effects of transfusion.

Effect of Transfusion on Liver Function

It is difficult to determine if transfusion has an effect on liver function. However, it has already been established that three of the "liver function" measures (PT, INR, aPTT) were likely affected by anti-coagulation medications. The last liver function measurement that was found to be associated with transfusion was glucose. However, this too may be the result of normal hospital practice. As previously stated, patients become hyperglycemic after surgery (McCowen, Malhotra et al. 2001); this is evident in the glucose traces in Figure 6. However, glucose levels rapidly fall in both groups. This is likely due to the fact that glucose levels are tightly controlled in the hospital as a means to prevent infection (Lazar, Chipkin et al. 2004; Leibowitz, Raizman et al. 2010; Bhamidipati, LaPar et al. 2011; Haga, McClymont et al. 2011; Stamou, Nussbaum et al. 2011). Given that all four hepatic function measurements are tightly controlled by physicians in the hospital, it is nearly impossible to draw any definitive conclusions on the possible effects of transfusion on the liver.

Effect of Transfusion on Renal Function and Osmoregulation

As the organ responsible for filtering metabolic waste from the blood, it stands to reason that the introduction of new blood would have an effect on kidney function. The

results shown here may support this idea, as Ca^{2+}, BUN, and CR (three of the five markers of renal function) were shown to be significantly affected by transfusion. The TG patients were shown to be hypocalcaemic and have higher levels of BUN and CR overall, all are indicative of renal insufficiency. However, Ca^{2+} levels are affected by many things, not just the kidneys. In addition, BUN and CR (the measures most reflective of renal function) were not significantly higher after transfusion, so it is possible that additional factors may be at play here other than transfusion. Looking at the secondary function of the kidney, osmoregulation, the results indicate that the other ions measured in this study (Na^+, K^+, and Cl^-) were all unaffected by transfusion.

Limitations

There are several limitations to this study. The most apparent is the fact that this is a retrospective observational study and because of this, the patient population is not randomized and there is no true control. The time and amount of measurements were not standardized among the patient population. In addition, patients were being treated according to their personal needs and not a protocol; therefore, patients likely had different experiences and treatments during their stay.

However, steps were taken to address these issues. The propensity-matching was utilized to create balanced groups with similar background demographics, thus creating a pseudo-randomization. When groups are propensity matched, the researcher can confidently use standard statistical models to estimate casual relationships within the dataset (Rubin 1997). Furthermore, given that data for 26 variables were collected for every blood test that the 636 patients underwent during their hospital stay, thousands of

data points were analyzed in this project. Furthermore, the patient population was selected to be free of post-operative mortality and complications, in order to limit the effects of secondary treatments. These methods lend tremendous power and credibility to the results.

Conclusions

This study aimed to examine the effects of transfusion on blood composition and characteristics using a propensity-matched cohort of 636 patients that underwent CABG with no complications. The investigation did not provide evidence that transfusion cured anemia, the most commonly cited concern linked to the need for blood products. However, it did support the claim that transfusion provides a boost in oxygen-carrying capacity. This boost may come at the cost of renal function.

As a retrospective study, these results do not prove that transfusion causes anything. Causation can only be determined by a prospectively randomized and controlled study. Rather, this study identifies certain aspects that physicians may want to consider when deciding to give a patient blood.

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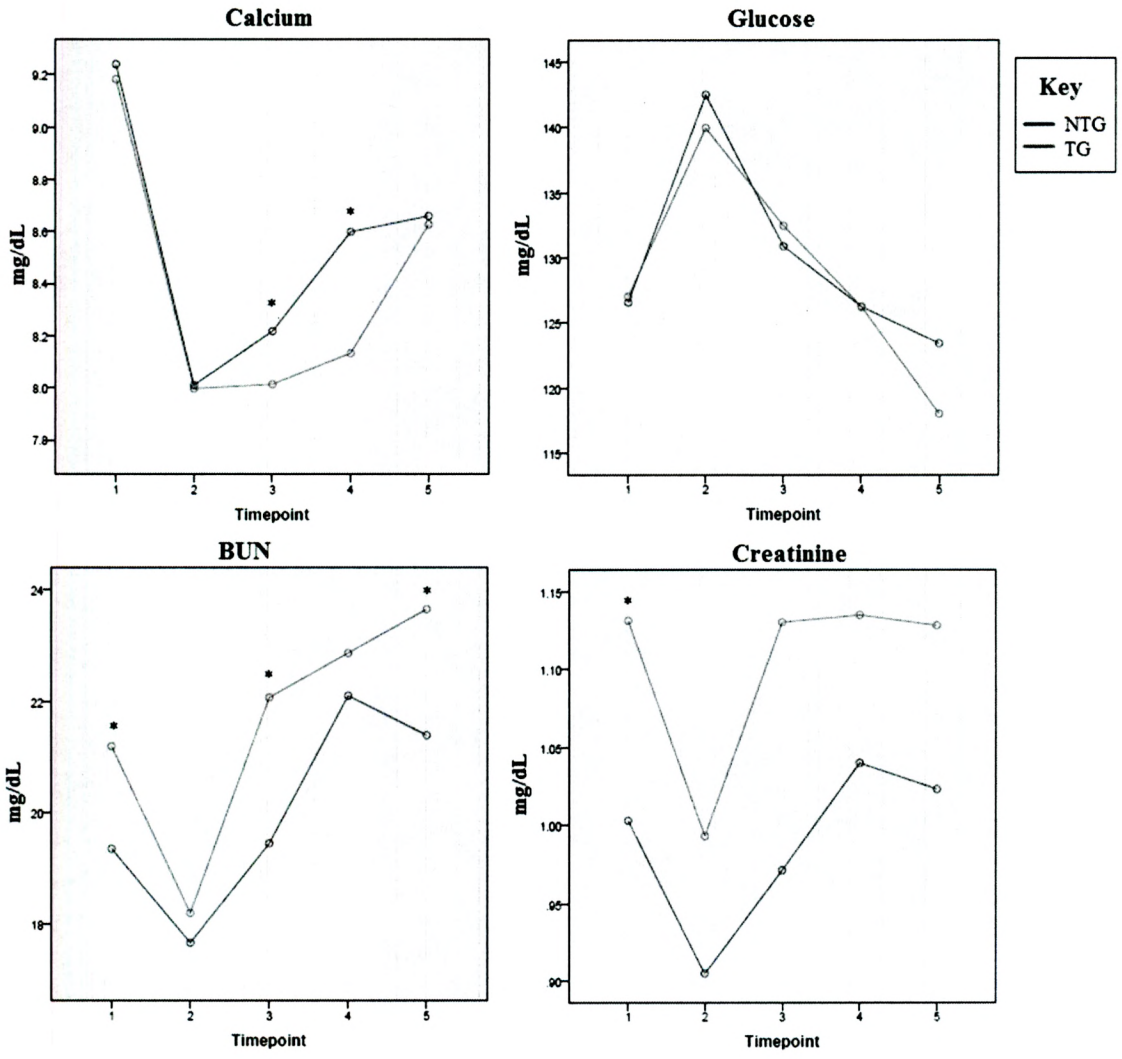
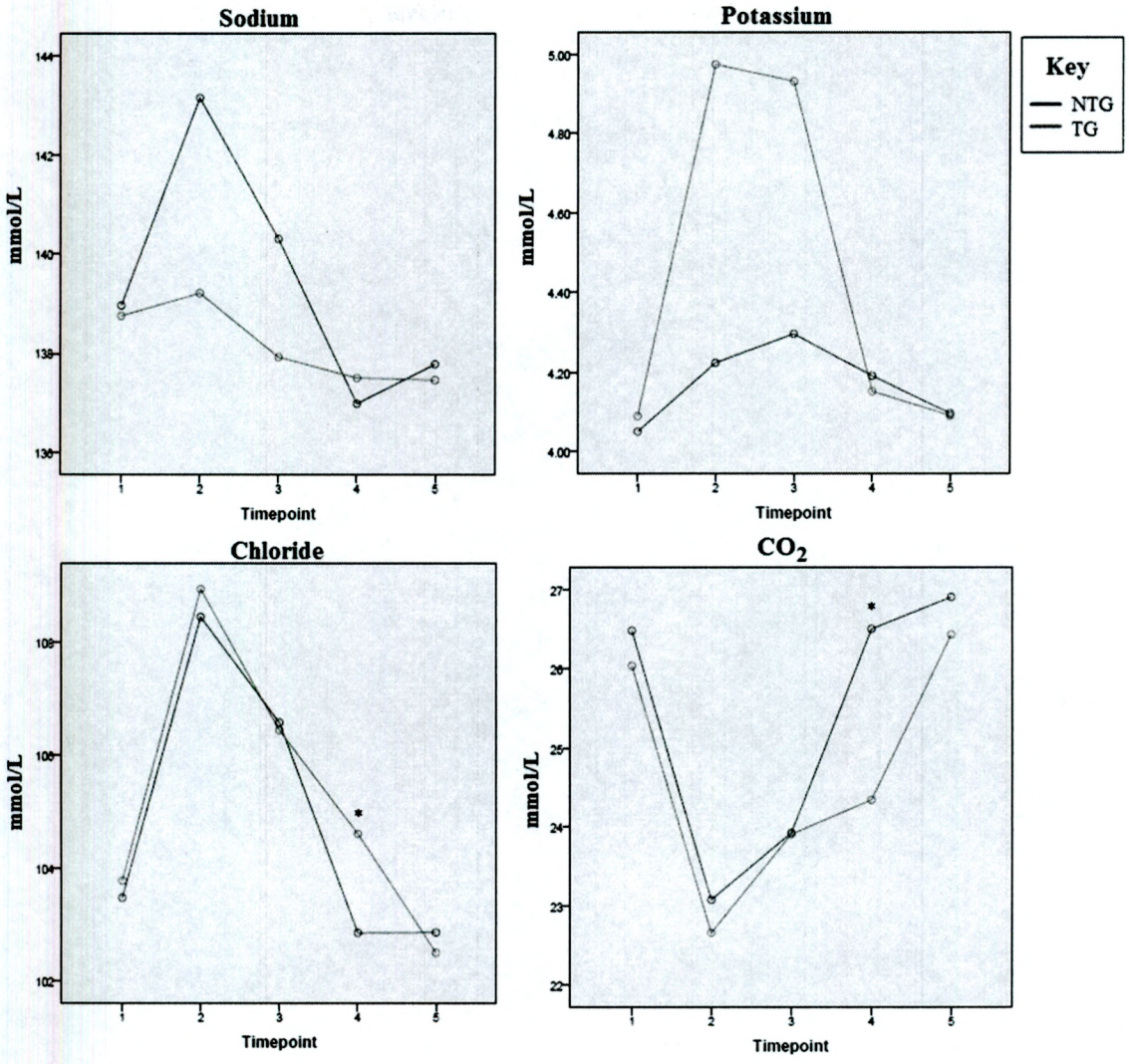
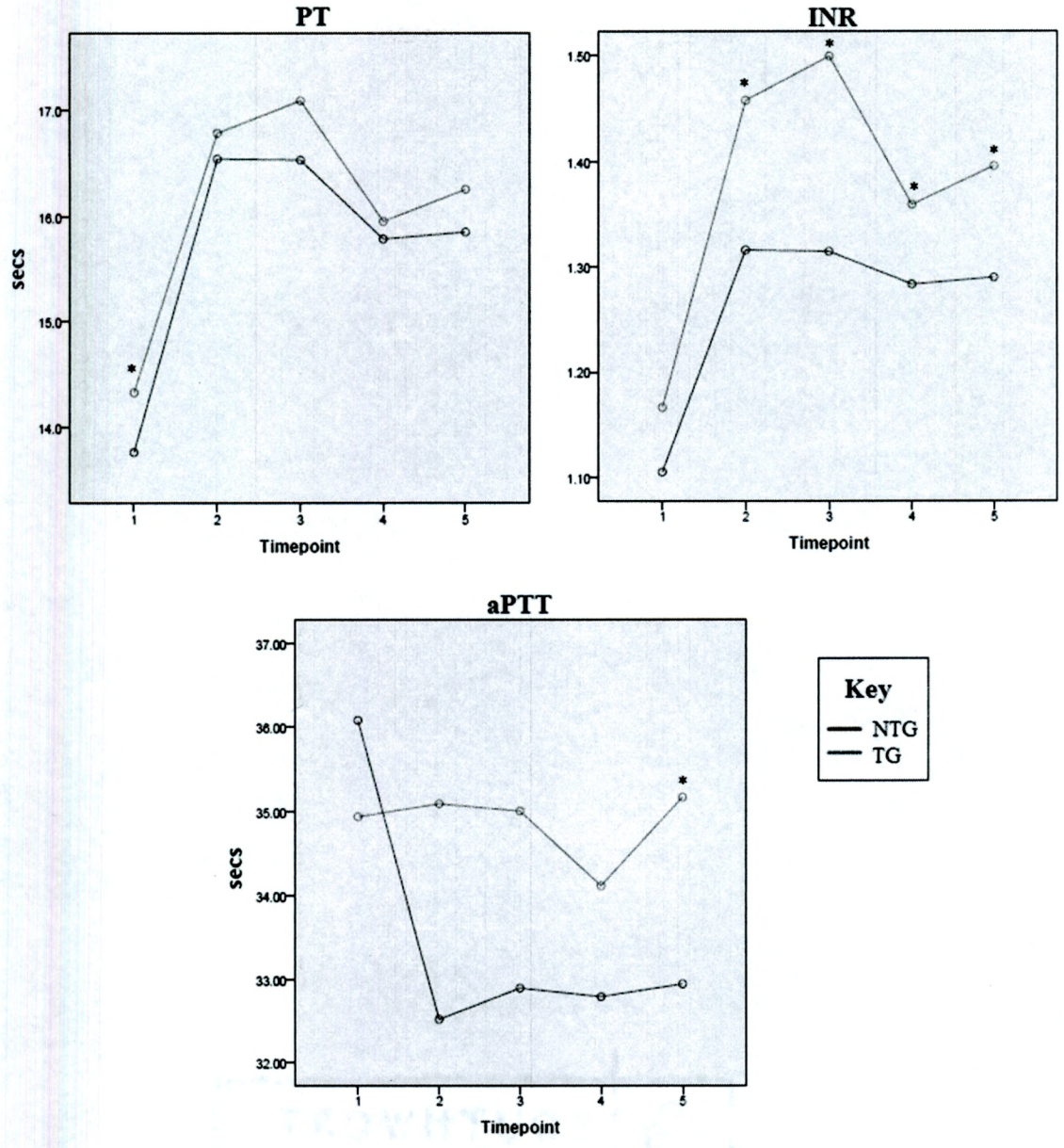
APPENDIX

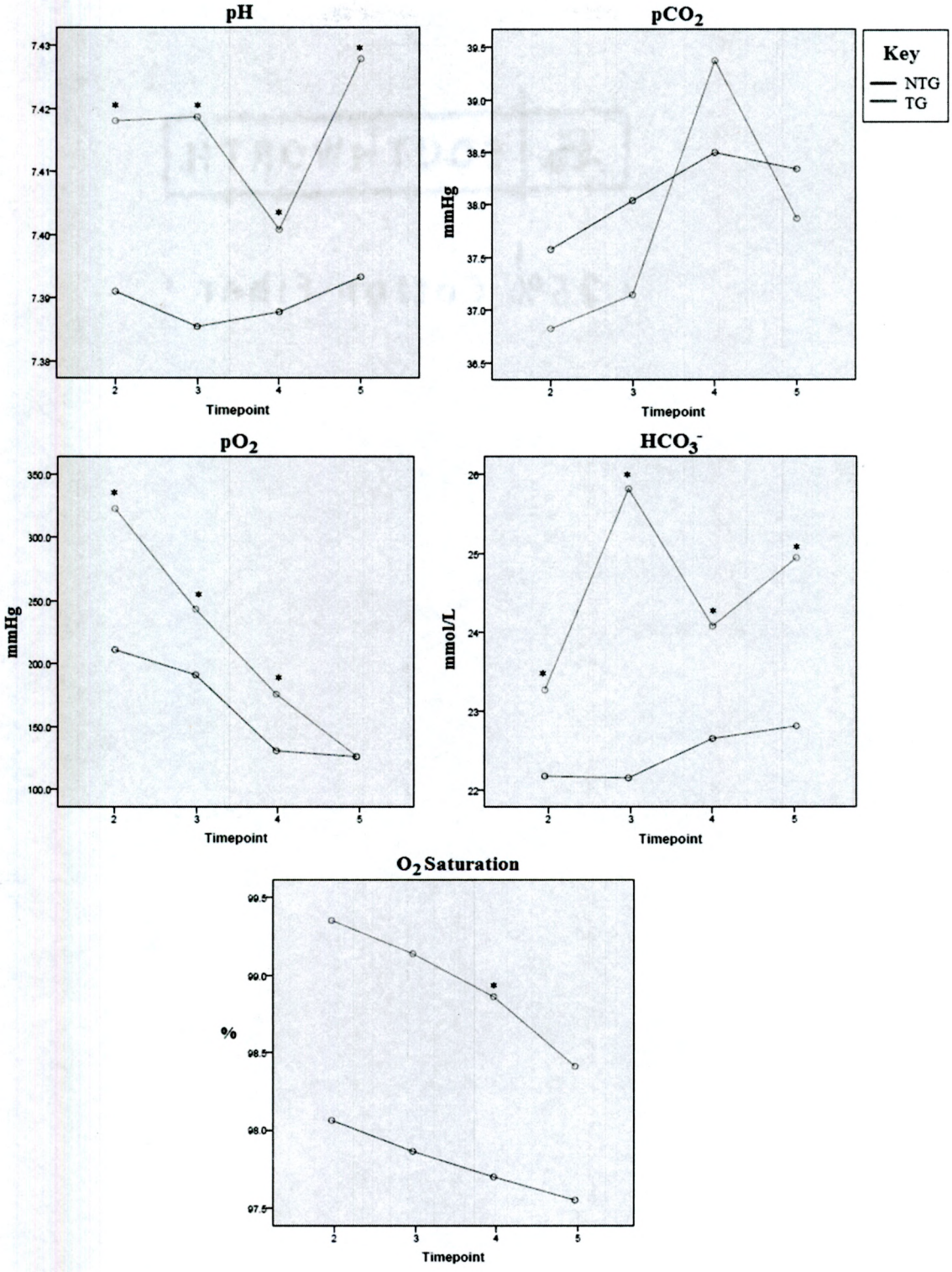




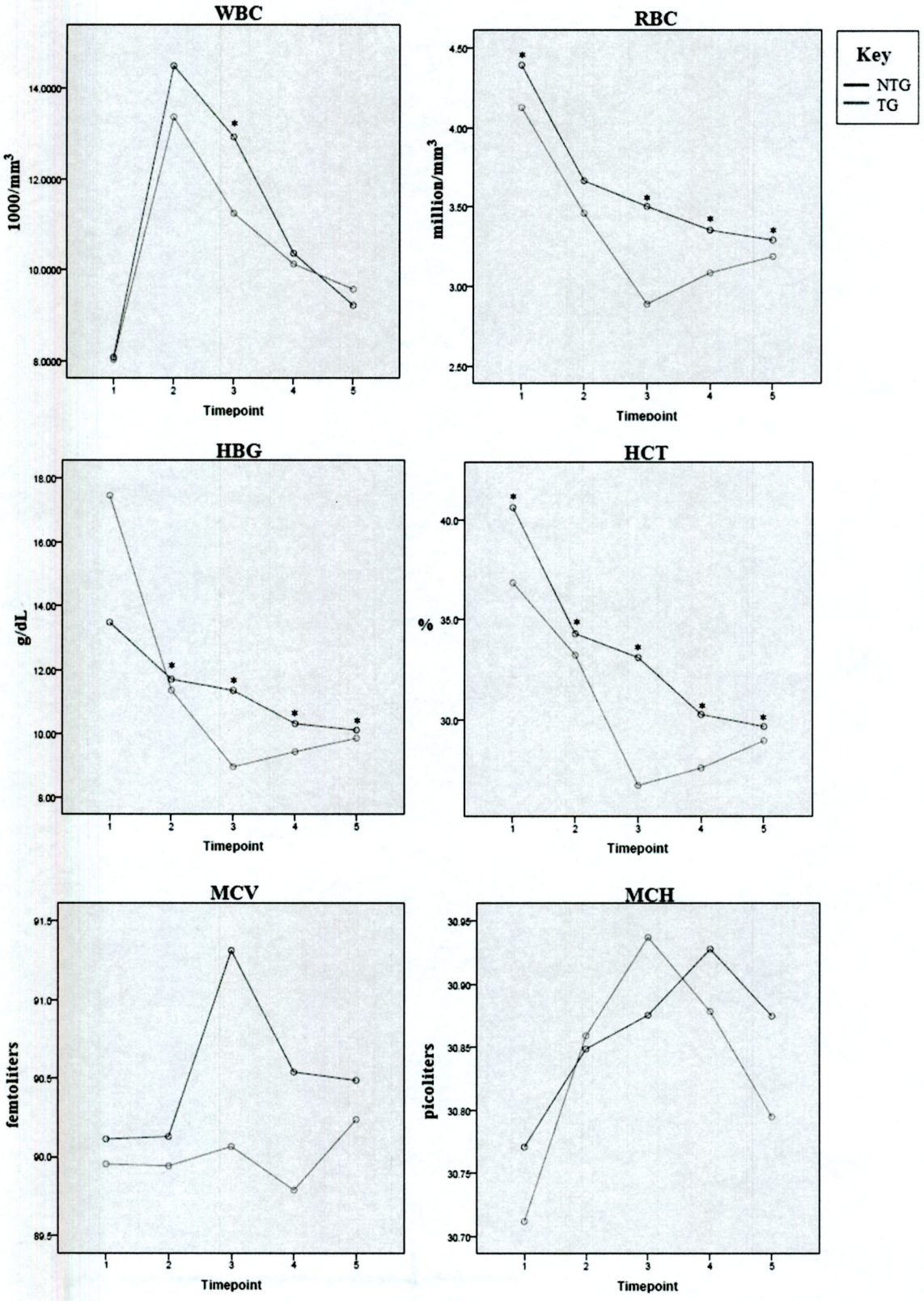
Supplementary Figure 1: The Effects of Transfusion on Chemistry Values over Time



Supplemental Figure 2: The Effects of Transfusion on Coagulation Measures



Supplemental Figure 3: The Effects of Transfusion on Cardiac/Critical Care Measurements.


WBC
1000/mm3
14.0000
12.0000
10.0000
8.0000
1
2
3
4
5
Timepoint
RBC
million/mm3
4.50
4.00
3.50
3.00
2.50
Timepoint
Key
NTG
TG
HBG
g/dL
18.00
16.00
14.00
12.00
10.00
8.00
Timepoint
HCT
%
40.0
35.0
30.0
Timepoint
MCV
femtoliters
91.5
91.0
90.5
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MCH
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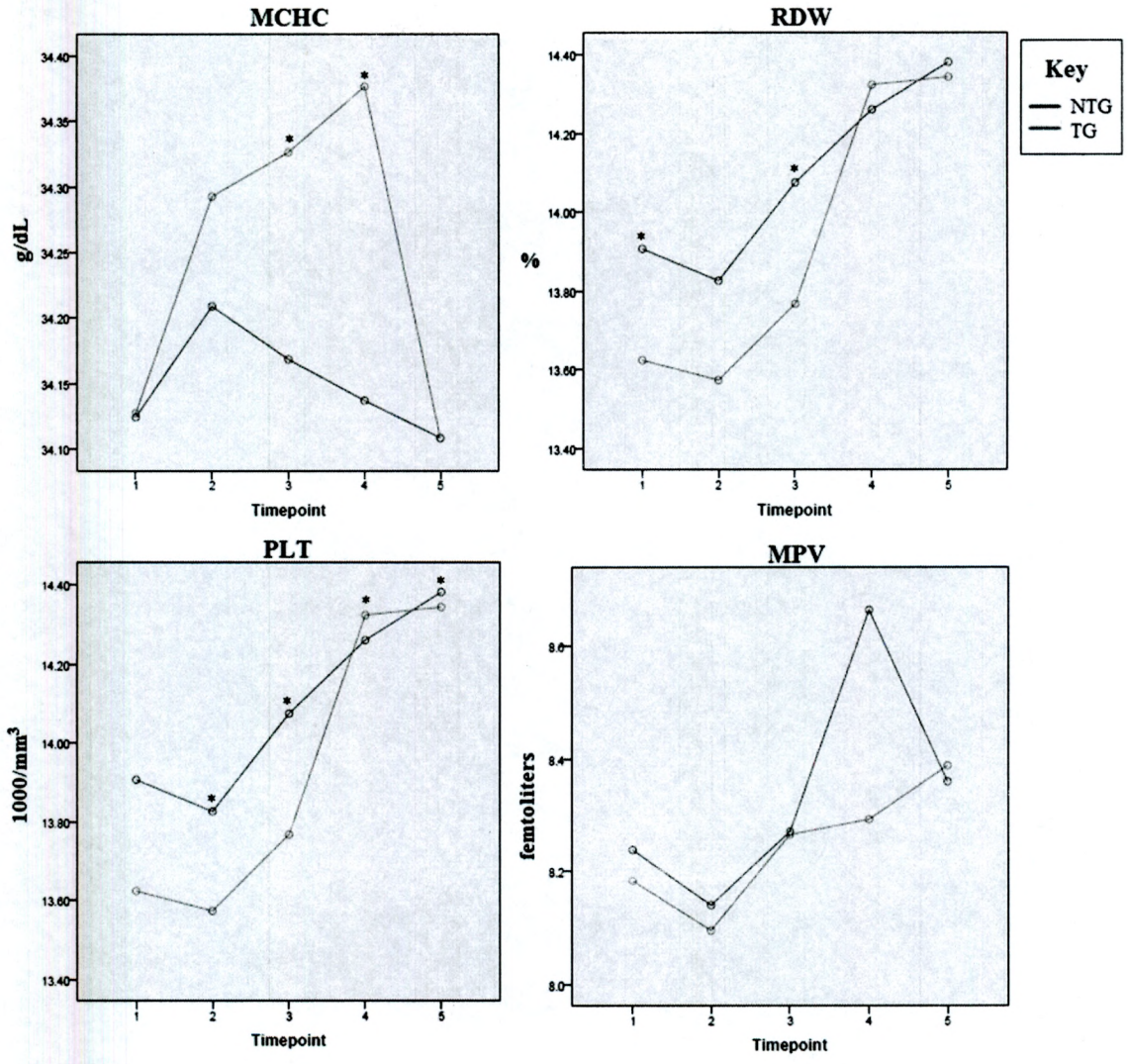
Timepoint



Supplemental Figure 4: The Effects of Transfusion on Hematology Measurements