What Factors Guide Physicians' Transfusion Decisions during Coronary Artery Bypass Surgery? A National Survey.

by

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Abstract

Background: The objectives of this study were to determine the hemoglobin transfusion thresholds, and the factors that influence physicians' decisions when transfusing coronary artery bypass surgery patients.

Methods: We conducted a cross-sectional study using pilot tested, self-administered, mailed questionnaires sent to all anesthesiologists and cardiac surgeons in Canada participating in coronary bypass surgery.

Results: The response rates for the intraoperative and postoperative questionnaires were 70.5% (345/489) and 60.7% (297/489), respectively. Responses were received from anesthesiologists from all cardiac centers and from cardiac surgeons from 30/32 cardiac centers. The mean hemoglobin concentrations for transfusion were 69 g/L and 72 g/L for the intraoperative and postoperative base case scenarios, respectively. Regression analysis identified the presence of myocardial ischemia, cardiac index and age as factors affecting the transfusion threshold intraoperatively and postoperatively ($p<0.0001$).

Conclusion: Future studies are required to elucidate whether transfusions based on these variables affect patient morbidity and mortality.

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Chapter I
1.0 Introduction

The purpose of red blood cell transfusions is to improve oxygen delivery (Hebert PC *et al*, 1997). The question of when to transfuse red blood cells to optimize oxygenation is not well defined in patients having coronary artery bypass surgery. Additionally, there are insufficient data available to explain other factors that impact on physicians' decisions to transfuse red blood cells to patients having coronary artery bypass surgery.

Several factors have consistently been shown to affect the transfusion rate in cohort studies of patients having coronary artery bypass surgery. Age, sex, the preoperative hemoglobin concentration, and comorbid illnesses, have been shown to affect transfusion rates (Covin R *et al*, 2003, Karkouti K *et al*, 2001, Surgenor DM *et al*, 1998, Stover EP *et al*, 1998, Bilfinger TV *et al*, 1989). Transfusion rates may also be affected by the hospital where the surgery is conducted (Stover EP *et al*, 1998, Surgenor DM *et al*, 1998). However, the proportion of patients having coronary artery bypass surgery who receive red blood cells can range anywhere from 9% to 100%. (Covin R *et al*, 2003, Karkouti K *et al*, 2001, Thurer RL *et al*, 2001, Dupuis J-Y *et al*, 1999, Stover EP *et al*, 1998, Surgenor DM *et al*, 1998, Kytola L *et al*, 1998, Surgenor DM *et al*, 1996, Magovern JA *et al*, 1996, Chiavetta JA *et al*, 2003, Hasley PB *et al*, 1995, Bracey AW *et al*, 1995, The Sanguis Study Group, 1994, Goodnough LT *et al*, 1993a, Goodnough LT *et al*, 1991, Surgenor LT *et al*, 1992). This wide range of variability suggests that more information is needed to determine how physicians integrate clinical information to determine whether they should transfuse red blood cells.

The most important factor to consider that influences the decision to transfuse is the hemoglobin concentration, as it is often the only trigger used to guide transfusions. A number of studies have attempted to define the optimal hemoglobin threshold at which to transfuse patients having coronary artery disease, but results have been conflicting. Patients with a recent myocardial infarction have been shown to benefit from transfusions if their hemoglobin concentration is 100 g/L or less (Wu W-C *et al*, 2001), and the same population of patients have been shown to have a higher mortality if transfused at a hemoglobin concentration greater than 80 g/L (Rao SV *et al*, 2004).

Defining the hemoglobin threshold and identifying factors that affect the decision to transfuse red blood cells are important for several reasons. Decisions not to transfuse patients may lead to unnecessary harm due to impaired oxygen delivery and impaired hemostasis (Valeri CR *et al*, 1998). Conversely, decisions to transfuse patients can also result in harm (e.g. transfusion transmitted infections, haemolytic transfusion reactions and transfusion related acute lung injury) (Kleinman S *et al*, 2003, Silliman CC *et al*, 2005). Existing evidence and expert opinion suggest that unnecessary transfusions are administered to as many as 15% to 60% of patients (Hasley PB *et al*, 1994, Goodnough LT *et al*, 1993b, Salem-Schatz SR *et al*, 1990, Consensus Conference 1988).

This study attempts to identify the factors that influence physicians' decisions to transfuse red blood cells to patients having coronary artery bypass surgery, focussing primarily on the hemoglobin threshold. A valid and reliable questionnaire was administered to all cardiac surgeons and anesthesiologists in Canada to investigate the factors that affect the decision to transfuse patients having coronary artery bypass surgery. The factors that are identified in this study that modify transfusion decisions can be used to prioritize areas of research in this patient population.

1.1 Research Question:

What factors affect physicians' decisions to transfuse red blood cells to patients undergoing coronary artery bypass surgery?

1.2 The Objectives:

Primary objective: To determine the hemoglobin concentrations in the perioperative period (intraoperative and postoperative) at which anesthesiologists and cardiac surgeons transfuse patients undergoing coronary artery bypass surgery. The hemoglobin concentration at which the physician decides to transfuse the patient will be called the hemoglobin threshold.

Secondary objectives:

1. To determine, based on responses to case vignettes, whether patient age, sex, the presence of myocardial ischemia, cardiac index and physician demographics affect physicians' decisions to transfuse red blood cells to coronary artery bypass surgery patients in the perioperative period.

2. To elicit the perceptions of anesthesiologists and cardiac surgeons about the factors that are most significant in influencing their decisions to transfuse coronary artery bypass patients with red blood cells in the perioperative period.

Chapter 2

2.1 Background

The question of when to transfuse red blood cells to coronary artery bypass patients remains unanswered. Red blood cell transfusions are generally administered to improve oxygen carrying capacity. Few studies, however, have addressed whether oxygenation is improved when patients are transfused. Consequently, transfusion decisions are influenced by clinical trials reporting the risks associated with transfusion and not on the efficacy of transfusions (Spiess BD, 2004). A considerable proportion of patients having coronary artery bypass surgery do receive red blood cells, and the mean number of red blood cells transfused can be high (Tables 2.1 and 2.2). As there are limited data defining the need for transfusion, and transfusion rates are high, it is important to understand the hemoglobin concentration at which physicians consider it necessary to transfuse patients, and the perioperative factors that physicians use to guide their transfusion decisions. This information can then lead to further research to determine the appropriateness of these transfusion triggers.

Table 2.1. Percentage of patients transfused red blood cells having cardiac surgery.

Author, Year	Patients (n)	Surgical Procedure	Patients Transfused Red Cells
Moskowitz DM *et al*, 2004	307	Cardiac Surgery	11%
Lithmathe J *et al*, 2003	400	CABG	33%
Chiavetta JA *et al*, 2003	NA	Bypass	45%
Covin R *et al*, 2003	3.034	CABG	34%
Thurer RL *et al*, 2001	540	Cardiac surgery	55%
Dupuis J-Y *et al*, 1999	176	Cardiac surgery	36%
Kytoloa L *et al*, 1998	804	CABG	87%
Stover EP *et al*, 1998	2,417	CABG	50%
Surgenor DM *et al*, 1998	3,217	CABG	9%-29%
Surgenor DM *et al*, 1996	2,476	CABG	76%
Magovern JA *et al*, 1996	2,033	CABG	61%
Hasley PB *et al*, 1995	6,812	CABG	81%
Bracey AW *et al*, 1995	196	CABG	65%
The Sanguis Study Group, 1994	1,166	CAGB	88%
Goodnough LT *et al*, 1993a	498	CABG	75%
Surgenor DM *et al*, 1992	3,126	CABG	74%
Goodnough LT *et al*, 1991	540	CABG	68%

CABG=coronary artery bypass graft

NA=not available

Table 2.2 The mean or median units of red blood cells transfused to patients having cardiac surgery.

Author, Year	Patients (n)	Surgical Procedure	Mean (SD) or Median Units Transfused
Kytoloa L *et al*, 1998	804	CABG	3.9(3.2)
Chiavetta JA *et al*, 1996	NA	CABG	3.3(4.0)
Magovern JA *et al*, 1996	2,033	CABG	2.9(0.3)
Hasley PB *et al*, 1995	6,812	CABG	4.7(3.0)
Bracey AW *et al*, 1995	196	CABG	2.2
The Sanguis Study Group, 1994	1,166	CABG	3
Surgenor DM *et al*, 1992	3,126	CABG	3.4
Goodnough LT *et al*, 1991	540	CABG	2.9
Hardy J-F *et al*, 1991	1,480	CABG	2.8(3.7)

CABG=coronary artery bypass surgery

NA=not available

2.2 Physiologic Effects of Anemia and the Need for Red Cell Transfusions

2.2.1 Oxygen Transport

Oxygen delivery (DO_2) to the whole body or to specific organs is the product of blood flow (or cardiac output (CO)) and arterial oxygen content (CaO_2) (Madjdpour C and Spahn DR, 2004, Hebert PC *et al*, 1997).

$DO_2 = CO \times CaO_2$ (Hebert PC *et al*, 1997)

The arterial oxygen content is the amount of oxygen that is carried in the blood, which includes both oxygen bound to hemoglobin and oxygen dissolved in plasma (Klein SL, 1993).

CaO_2 = percent saturation x 1.39 x the hemoglobin concentration (Hebert PC *et al*, 1997)

Under normal physiological conditions, more than 98% of oxygen is bound to hemoglobin and the remainder is dissolved in plasma (Madjdpour C and Spahn DR, 2004). The human body can adapt to significant increases in oxygen requirements or decreases in one of the determinants of oxygen delivery due to various diseases because each of the determinants of oxygen delivery have considerable physiological reserve (Hebert PC *et al*, 1997). The major determinant of oxygen delivery, however is the cardiac output (Hebert PC *et al*, 1997).

The heart requires a continuous supply of oxygen (Hebert PC *et al*, 1997). This supply is primarily regulated through blood flow instead of increased oxygen extraction (Hebert PC *et al*, 1997). In the heart, if oxygen delivery is permitted to decrease to a level at which tissues do not have enough oxygen to meet metabolic demands, tissue hypoxia will occur (Hebert PC *et al*, 1997). Hypoxia can be caused by a decreased oxygen delivery due to decreases in the hemoglobin concentration, cardiac output or hemoglobin saturation (Hebert PC *et al*, 1997).

Generally, the amount of oxygen delivered to the whole body exceeds the amount of oxygen utilized by the body at rest (oxygen consumption) by a factor of two to four (Madjdpour C and Spahn DR, 2004, Hebert PC *et al*, 1997). This results in an oxygen extraction ratio (the ratio of oxygen consumption to oxygen delivery) of 20 to 30% (Madjdpour C and Spahn DR, 2004). Because of the excess of oxygen delivered, oxygen delivery can still be maintained even at a drop in hemoglobin concentration to 100 g/L from 150 g/L if cardiac output and arterial oxygen content are unaltered (Madjdpour C and Spahn DR, 2004, Hebert PC *et al*, 1997). Below a critical level of oxygen delivery, oxygen consumption decreases with further decreases in the hemoglobin concentration and results in tissue hypoxia (Madjdpour C and Spahn DR, 2004, Hebert PC *et al*, 1997).

There is a biphasic relationship between oxygen delivery and oxygen consumption; an oxygen delivery independent portion where oxygen consumption is independent of oxygen delivery above a threshold and a supply-dependent portion where oxygen delivery is linearly related to oxygen consumption (Figure 2.1) (Hebert PC *et al*, 1997). The supply-dependent relationship between oxygen delivery and oxygen consumption is indicative of tissue hypoxia (Hebert PC *et al*, 1997). The critical oxygen delivery threshold may differ due to several factors (Hebert PC *et al*, 1997). It differs according to metabolic rate, disease states, and age, and it differs for different organs (Hebert PC *et al*, 1997).

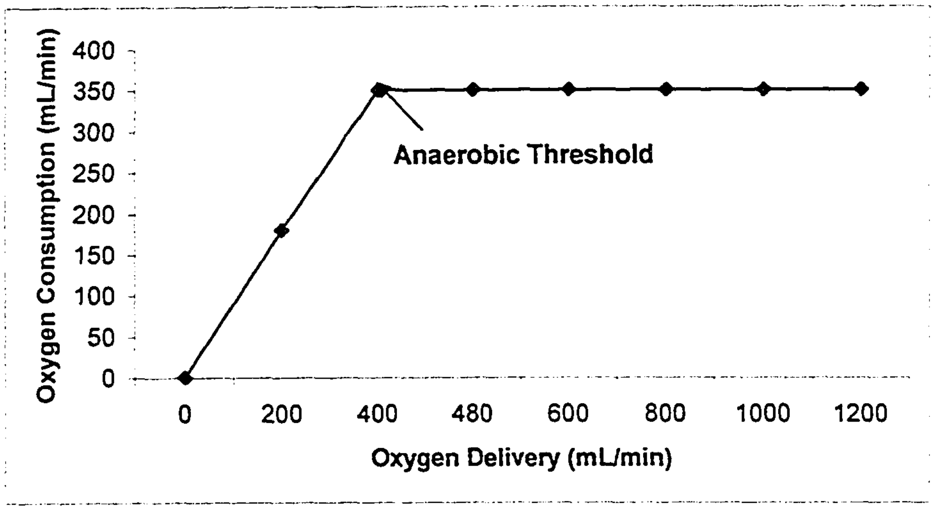


Figure 2.1 The biphasic relation between oxygen consumption and oxygen delivery (Adapted from Hebert PC *et al*, 1997). The anaerobic threshold indicates the point at which the supply-dependant relationship between oxygen delivery and consumption occurs. Below this threshold, tissue hypoxia occurs.

The hemoglobin concentration at which oxygen consumption becomes supply dependent has not been definitively determined but there are suggestions that it may be 70 g/L for neurological impairment in healthy individuals. Isovolemic removal of blood to reduce the hemoglobin concentration to 50 g/L in healthy subjects did not produce evidence of inadequate systemic oxygen delivery other than in two female subjects (n=34) who developed transient ST segment changes that were asymptomatic (at hemoglobin concentrations of 62 g/L and 46 g/L to 53 g/L) (Weiskopf RB *et al*, 1998b). However, when cognition was assessed, isovolemic removal of blood to reduce the hemoglobin concentration to 50 g/L to 60 g/L in nine other healthy subjects resulted in concentration that would lead to inadequate oxygen delivery in individuals with different disease states has not been determined.

2.2.2 Physiological Effects of Anemia

There are several adaptive mechanisms to normovolemic anemia. The main responses are a change in blood flow, an increase in the oxygen extraction ratio and a shift in the oxyhemoglobin dissociation curve (Madjdpour C and Spahn DR, 2004, Expert Working Group, 1997). The change in blood flow results from an increase in cardiac output because of a reduced blood viscosity, an increased sympathetic stimulation of the heart, a redistribution of blood flow from non-vital to vital organs mediated by the adrenergic system (Bak Z *et al*, 2000, Madjdpour C and Spahn DR, 2004), and an increase in oxygen consumption and oxygen extraction (Ickx BE *et al*, 2000, Mathru M *et al*, 1992). Additionally, there is an increased synthesis of 2,3-diphosphoglycerate in red cells leading to more hemoglobin bound oxygen to be released at given partial pressures of oxygen (Madjdpour C and Spahn DR, 2004).

2.2.3 When are Red Cells Needed?

The rationale for red cell transfusion is to increase oxygen delivery to prevent insufficient oxygen delivery to tissues (Weiskopf RB, 1998a), however, the difficulty is to determine when inadequate oxygen delivery to tissues occurs to warrant a transfusion i.e. when do the risks of anemia outweigh the risks of transfusion. Controversy exists as to whether the hemoglobin concentration should be used to guide transfusions (Weiskopf RB, 1998a). Ideally, the intracellular partial pressure of oxygen should be directly measured to determine tissue oxygenation (Weiskopf RB, 1998a), but this cannot be directly measured in clinical settings. Alternatively, surrogate markers can be used to determine tissue oxygenation (Weiskopf RB, 1998a).

Surrogate markers to determine adequate tissue oxygenation have included the oxygen extraction ratio (Sehgal LR *et al*, 2001), the calculated oxygen consumption, the mixed venous oxygen saturation, and measurements of intracellular hypoxia such as intracellular pH and lactate or a surrogate of tissue hypoxia, blood lactate levels (Doak GJ, Hall RI, 1995, Mathru M *et al*, 1992, Weiskopf RB, 1998a). The use of any of these surrogate markers in a clinical setting is problematic. An oxygen extraction ratio of 50% has been considered as a transfusion trigger in coronary artery bypass patients (Sehgal LR *et al*, 2001), but the ratio has never been tested in large controlled trials. The use of oxygen consumption is also problematic, as oxygen consumption is influenced by many factors such as exercise, body temperature, heart rate, and drugs (Weiskopf RB, 1998a). Additionally, few studies have documented an increase in oxygen consumption with transfusions. In a systematic review of studies that evaluated the impact of red blood cell transfusions on oxygen delivery and consumption, 13 studies were identified (Hebert PC *et al*, 1997). Oxygen delivery increased in all studies but oxygen consumption changed only in five of the studies (Hebert PC *et al*, 1997). The mixed venous oxygen saturation, calculated based on arterial oxygen content, the hemoglobin concentration, cardiac output and oxygen consumption is also used to detect inadequate tissue oxygenation, but several factors, such as sepsis and inappropriate placement of a pulmonary catheter, may falsely elevate the measurement (Moon RE, Camporesi EM, 2005). Measurement of intracellular pH and lactate is feasible experimentally but not clinically, and blood lactate levels may not adequately reflect tissue oxygenation (Weiskopf RB, 1998a). Thus, which patients will benefit from red blood cell transfusions cannot yet be determined using biochemical markers.

Accordingly, clinicians typically use the hemoglobin concentration as the factor to trigger the need to transfuse red blood cells because it is easy to measure, it is the most important determinant of blood oxygen content and there are no other better physiological indicators for transfusion at this time.

2.3 Adverse Events Associated with Transfusion

Decisions regarding when to transfuse are important because transfusions may result in increased morbidity and mortality. Although the risk of acquiring the human immune deficiency virus and hepatitis C virus is low (Table 2.3), (Kleinman S *et al*, 2003) new emerging pathogens such as West Nile Virus constantly threaten the blood supply (Iwamoto M *et al*, 2003). Additionally, non-infectious risks from transfusions (e.g. haemolytic transfusion reactions and transfusion related acute lung injury) (Kleinman S *et al*, 2003, Silliman CC *et al*, 2005) can be life threatening. In addition, pulmonary edema, due to the volume of red cells transfused, has been shown to occur more frequently in patients with critical illness and cardiovascular disease who were transfused at a hemoglobin concentration of 100 g/L compared to a hemoglobin concentration of 70 g/L (Hebert PC *et al*, 1999, Hebert PC *et al*, 2001). Furthermore, mortality in patients transfused has been demonstrated to be higher than non-transfused critically ill patients (Michalopoulos A *et al*, 1999, Vincent JL *et al*, 2002, Corwin HL *et al*, 2004, Engoren MC *et al*, 2002).

Table 2.3. Risk of Transfusion Transmissible Diseases (Kleinman S, 2003)

Transfusion Transmissible Disease	Risk/Red Cell Unit
Human Immunodeficiency Virus	1/4 million
Hepatitis C Virus	1/3 million
Hepatitis B Virus	1/31,000-1/82,000
Human T-Lymphotrophic Virus	1/1.9 million
Bacterial Contamination	0.7-3.6/100,000

The increase in morbidity and mortality may be attributed to various red blood cell changes that occur with the storage of red blood cells. Duration of storage of red blood cells affects red cell deformability which may affect tissue oxygen availability by impairing microcirculatory blood flow (Kirkpatrick UJ *et al*, 1998, Marik, PE *et al*, 1993, van Bommel J *et al*, 2001, Sollberger T *et al*, 2002). Extended red cell storage also depletes the red cell of adenosine triphosphate (Nakao M *et al*, 1960, Haradin AR, Weed RI, Reed CF, 1969) and 2,3-diphosphoglycerate (Bartlett GR, Barnet HN 1960, Valeri CR, *et al*, 1969), and shifts the hemoglobin oxygen dissociation curve to the left (Valtis

DJ, Kennedy AC, 1954), resulting in an increased oxygen affinity and impairing oxygen release to tissues. Red cells that have been stored also show an increase in red blood cell aggregation and increased adhesion, and stored red cells have an increase in bioactive substances that may lead to inflammation and infection (Haradin AR, Weed RI, Reed CF, 1969, Vamvakas S, Carven JH, 1999, Pereira A, 2001, Leal-Noval, SR *et al*, 2003, Ho J *et al*, 2003).

Unnecessary transfusions also have a negative impact economically. Optimum utilization of blood components is essential at times when periodic shortages of blood occur. Periodic shortages of blood may result in surgeries that are delayed. Furthermore, as the cost of blood is increasing (Amin M *et al*, 2004), unnecessary transfusions in coronary artery bypass patients result in increased resource utilization (Goodnough LT *et al*, 1993b).

Consequently, as there are risks and benefits to red blood cell transfusion, it is important to determine at which hemoglobin concentration anesthesiologists and cardiac surgeons are using to transfuse patients having coronary artery bypass surgery to optimize outcomes. Additionally, the factors that influence the hemoglobin concentrations at which patients are transfused need to be ascertained to establish whether these variables should modify the transfusion threshold.

2.4 What Is the Optimal Hemoglobin Threshold for Transfusion?

Several studies have attempted to define the optimal hemoglobin threshold at which to transfuse patients with cardiovascular disease, but results have been conflicting. Often it is difficult to distinguish whether an outcome is secondary to a reduced hemoglobin concentration or secondary to the transfusion used to treat the anemia. Only a randomized controlled trial design is able to address this issue. However, there has only been one randomized controlled trial comparing two hemoglobin concentrations for transfusion in critically ill patients with a subgroup analysis in patients with cardiovascular disease (Hebert PC *et al*, 1999) and two small trials in patients with coronary artery bypass surgery (Johnson RG *et al*, 1992, Bracey AW *et al*, 1999). Thus, there are limited data in patients with cardiovascular disease (Carson JL *et al*, 2002a).

2.4.1 The Impact of Anemia and Transfusions on Morbidity and Mortality

Reports of cohort studies on patients who refuse blood for religious reasons have attempted to correlate low hemoglobin levels with morbidity and mortality particularly in patients with cardiovascular disease. The largest report was a retrospective cohort of 1,958 patients having surgical procedures excluding open-heart procedures (Carson JL *et al*, 1996). Mortality increased with decreasing preoperative hemoglobin concentrations. At hemoglobin concentration between 110 g/L and 120 g/L, 30-day mortality was 2.4 %. Mortality increased to 12.8% at hemoglobin concentrations between 80 g/L and 90 g/L. In patients with cardiovascular disease, the odds of death was double that for those without cardiovascular disease. The same investigators subsequently published a similar series of 300 surgical patients to determine the association between lowest postoperative hemoglobin concentration and 30-day mortality in patients with a hemoglobin concentration of 80 g/L or less (Carson JL *et al*, 2002). Contrary to their first report, there were no deaths in 99 patients with hemoglobin levels between 71 g/L and 80 g/L. Mortality increased to 8.9% at a hemoglobin level of 61 to 70 g/L. Patients with cardiovascular disease exhibited a trend towards increased mortality, but this did not achieve statistical significance ($p=0.09$) (Carson JL *et al*, 2002).

A review of 54 reports from 1970 to 1993 of patients with various medical illnesses and surgeries who refused blood for religious reasons and who had a hemoglobin concentration of 80 g/L or less or a hematocrit of 24% or less reported that patients who died primarily or exclusively from anemia died with a hemoglobin concentration of less than 50 g/L (Viele MK, Weiskopf RB, 1994). The authors suggested that hemoglobin concentrations lower than those usually used as transfusion triggers may be used without increasing morbidity and mortality.

However, moderately low hemoglobin concentrations may be detrimental in patients with vascular disease and critically ill patients because of limitations in blood flow and increased metabolic demands (Vincent JL *et al*, 2002). In critically ill patients, the lowest hematocrit measured during hospitalization has been associated with increased length of stay in hospitals ($p<0.0001$) (Corwin HL *et al*, 2004). Of 27 patients undergoing infra-inguinal arterial bypass surgery (Nelson AN *et al*, 1993), six patients who had symptomatic cardiac events had a hematocrit level below 28% (a hemoglobin concentration of approximately 93 g/L). Additionally, patients with anemia who undergo percutaneous coronary angioplasty electively or following episodes of angina or myocardial infarction also have higher one-year mortality rates than those without anemia (Table 2.4).

Table 2.4. Anemia and Mortality in Patients Having Percutaneous Coronary Angioplasty

First Author, Year	Patients	Anemia as Defined by the Hemoglobin Concentration (g/L)	Hazard Ratio for Mortality at 1 year (95% CI)
Nikolsky, 2004a	Acute myocardial infarction patients who undergo angioplasty	<130 for men <120 for women	2.4(1.2-4.8)
Nikolsky, 2004b	Elective angioplasty, excluding patients with acute myocardial infarction	<130 for men <120 for women	2.9(1.8-5.0) 3.2(1.8-6.4)
Lee, 2004	All patients having angioplasty	<100 100-120	1.8(1.3-3.2) 1.5(1.3-1.8)
Reinecke, 2004	Elective angioplasty, excluding patients with myocardial infarction	<130	4.1(1.5-11.1)

CI=confidence interval

Whether transfusion of red blood cells improves the outcomes in patients with anemia has not been determined. There was no difference in mortality rates in critically ill patients randomized to transfusions at a hemoglobin concentration of less than 70 g/L (the restrictive group) or less than 100 g/L (the liberal group) (Hebert PC *et al*, 1999). A subgroup analysis of patients with cardiovascular disease (Hebert PC *et al*, 2001) showed similar results. Thirty-day mortality was similar in both groups; 18% in the restrictive group compared to 23% in the liberal group (95% confidence interval, 8.4% to 9.1%; p=1.00).

Additionally, there is evidence to suggest that transfusions may be detrimental. Data collected on 3,534 patients from 146 intensive care units in Europe showed that the odds of dying increased by a factor of 1.7 in those who underwent blood transfusions. An analysis that adjusted for differences in patient factors, demonstrated that mortality for patients transfused was 22.7% compared to 17.1% for patients who were not transfused (p=0.02) (Vincent JL *et al*, 2002). Consistent with these results, investigators from the United States also showed that transfusion was associated with increased risk for death in critically ill patients (adjusted mortality ratio 1.7, 95% confidence interval, 1.4 to 2.0, p<0.001) (Corwin HL *et al*, 2004).

Patients with acute coronary syndromes however, may differ from patients with stable cardiovascular disease and critically ill patients in that they may not tolerate low hemoglobin levels. In a subgroup analysis (Hebert PC *et al*, 2001) of the randomized controlled trial of transfusion triggers in critically ill patients (Hebert PC *et al*, 1999), mortality rates in patients with acute myocardial infarction and unstable angina differed between the two intervention groups, but were not statistically significant. Thirty-day mortality was 26% in the group receiving transfusions at a hemoglobin concentration less than 70 g/L and was 21% in patients receiving transfusions at a hemoglobin concentration less than 100 g/L (Hebert PC *et al*, 2001). The five percent difference was deemed to be clinically important. Similar findings were found in a retrospective database study of 78,974 Medicare beneficiaries 65 years of age or older who had experienced a myocardial infarction (Wu W-C *et al*, 2001). Transfusion was found to be associated with a reduction in mortality among patients transfused at a hemoglobin concentration less than 100 g/L than those transfused at higher hemoglobin concentrations.

Somewhat different results were shown in an analysis of 24,112 participants from three large international randomized controlled trials of patients with acute coronary syndromes. Transfusions above a hematocrit of 25% (a hemoglobin concentration of 100 g/L) were associated with an increased mortality (Rao SV *et al*, 2004). The adjusted predicted probability of 30-day mortality demonstrated that below a hematocrit of 25%, 30-day mortality was not increased compared to higher hematocrit levels (adjusted odds ratio, 1.13(95% confidence interval, 0.70 to 1.82)) but above this hematocrit, mortality increased (at a hematocrit of 30%, adjusted odds ratio, 168.64 (95% confidence interval, 7.49 to 3797.69)). Thus, it has not been determined whether patients with cardiovascular disease should be transfused at a hemoglobin concentration less than 80 g/L or a hemoglobin concentration less than 100 g/L.

2.4.2 The Impact of Anemia and Transfusions on Morbidity and Mortality in Patients Having Coronary Artery Bypass Surgery

Reports of the association of anemia, transfusion and morbidity and mortality in patients having coronary artery bypass surgery are often conflicting. In addition, several reports associate a single hemoglobin concentration or hematocrit level with an outcome without considering the various hemoglobin concentrations that are assessed during the preoperative, intraoperative and postoperative period. An assessment of the impact of anemia should account for the various hemoglobin concentrations that are assessed in the perioperative period.

2.4.2.1 Preoperative Hemoglobin Concentration/Hematocrit and Mortality

There has been only one study addressing the association between the preoperative hemoglobin concentration and mortality. In an observational study of 2,059 patients having coronary artery bypass surgery, hospital mortality in patients with a preoperative hemoglobin concentration less than 100 g/L was higher than in those with a hemoglobin concentration of greater than 100 g/L (odds ratio, 3.17, 95% confidence interval 1.2 to 8) (Zindrou D *et al*, 2002).

2.4.2.2 Intraoperative Hemoglobin Concentration/Hematocrit and Morbidity and Mortality

The lowest hemoglobin concentration intraoperatively has been associated with increased morbidity and mortality, but the level of hemoglobin concentration correlated with increased adverse events differs between studies (Habib RH *et al*, 2003, DeFoe GR *et al*, 2001, Fang WC *et al*, 1997). Three studies found that a hematocrit below 23% (a hemoglobin concentration of 77 g/L) was associated with increased morbidity and mortality (Habib RH *et al*, 2003, DeFoe GR *et al*, 2001 Swaminathan M *et al*, 2003). Contrary to these findings, a different study found that patients could tolerate a hematocrit level of 15% (a hemoglobin concentration of 50 g/L). Mortality increased only with a hematocrit level of 14% or less; odds ratio of 1 for a hematocrit level of 15% or more compared to 2.7 for a hematocrit level of 14% or less (a hemoglobin concentration of 47 g/L) (Fang WC *et al*, 1997). Additionally, the latter study identified that mortality based on hematocrit was dependent on risk factors. In patients without any risk factors, the hematocrit level was not an independent risk factor for mortality, but with even one risk factor, patients with a hematocrit of 17% (a hemoglobin concentration of 57 g/L) or lower during cardiopulmonary bypass had an increased mortality rate (odds ratio, 2.2 (confidence intervals not provided), p=0.017).

2.4.2.3 Postoperative Hemoglobin Concentration/Hematocrit and Morbidity and Mortality

The results of reports addressing postoperative hemoglobin concentrations and morbidity and mortality are consistent. In cardiovascular surgery patients, low versus high hematocrit levels postoperatively have been associated with a decreased risk of myocardial infarction (Spiess BD *et al*, 1998). Patients with a hematocrit level of 24% or less (a hemoglobin concentration of 80 g/L) in the immediate postoperative period had the lowest incidence of myocardial infarction (Spiess BD *et al*, 1998). Patients with hematocrit values of 34% (a hemoglobin concentration of 110 g/L) or higher appeared to have an increase in morbidity (Spiess BD *et al*, 1998). The odds ratio for myocardial infarction for the group with a hematocrit of 34% or higher was 2.2 (95% confidence interval 1.04 to 4.76) compared to the group with a hematocrit of 24% or less (Spiess BD *et al*, 1998).

Consistent with the above report, patients randomized to transfusions in the postoperative period at a hematocrit level of 25% (hemoglobin concentration of 83 g/L) versus 32% (hemoglobin concentration of 107 g/L) did not exhibit different exercise stress test results (Johnson RG *et al*, 1992), and patients randomized to transfusions at a postoperative hemoglobin concentration of 80 g/L or 90 g/L did not have different rates of mortality (1.4% vs. 2.7 %,) arrhythmias (20% vs. 23%), myocardial infarction (0.5% vs. 0%) or pulmonary complications (27% vs. 30%) (Bracey AW *et al*, 1999). A caveat that needs to be mentioned is that the outcomes reported in all the above studies related to postoperative transfusions and do not take into account the impact of anemia or transfusions that occurred in the preoperative or postoperative periods.

Thus, the optimal hemoglobin concentration for transfusion in the intraoperative and postoperative periods in patients having coronary artery bypass surgery has not been established. As outcomes may be dependent on the severity of anemia and timing of transfusion, it is particularly important to understand at what hemoglobin threshold physicians consider it crucial to transfuse patients.

2.5 Factors Associated with Increased Transfusion Rates

In addition to the hemoglobin concentration, it is not known what other factors physicians select to guide their transfusion decisions. There are several factors that have been found to be associated with increased transfusion rates in cohort studies (Table 2.5). Consistently age, sex, and comorbid illnesses, have been shown to be associated with increased transfusion rates (Lithmathe J *et al*, 2003, Scott BH *et al*, 2003, Covin R *et al*, 2003, Engstrom KG *et al*, 2003, Isomatsu Y *et al*, 2001, Karkouti K, *et al* 2001, Surgeoner DM *et al*, 1998 Magovern JA *et al*, 1996 Bilfinger TV *et al*, 1989). Red cell transfusions are more frequently administered to patients who are older in age, who are female, who are lower in weight, and who have more comorbid illnesses (Lithmathe J *et* *al*, 2003, Scott BH *et al*, 2003, Covin R *et al*, 2003, Isomatsu Y *et al*, 2001, Karkouti K, *et al*, 2001 Surgeoner DM *et al*, 1998 Magovern JA *et al*, 1996 Bilfinger TV *et al*, 1989). Transfusion rates may also be associated with the hospital where the surgery was conducted (Surgeoner DM *et al*, 1998, Stover EP *et al*, 1998).

There have also been several transfusion surveys published in the literature that describe factors associated with increased transfusion rates. Most of these surveys used vignettes to assess transfusions (Stehling LC *et al*, 1987, Salem-Schatz SR *et al*, 1990, Brown RL *et al*, 1992, Hebert PC *et al*, 1998, Boralessa H *et al*, 2002, Nuttal GA *et al*, 2003, Matot I *et al*, 2003, Hebert PC *et al*, 2005). Three surveys also used a question-based approach in addition to vignettes (Stehling LC *et al*, 1987, Salem-Schatz SR *et al*, 1990, Nuttal GA *et al*, 2003), and one survey exclusively used a question-based approach to assess transfusion knowledge (Rock G *et al*, 2002). The surveys focused on surgical patients (Nuttal GA *et al*, 2003, Stehling LC *et al*, 1987), obstetrical patients (Matot I *et al*, 2003), general medicine patients (Brown RL *et al*, 1992), surgical and general medicine patients (Salem-Schatz SR *et al*, 1990) and critically ill patients (Hebert PC *et al*, 2005, Hebert PC *et al*, 1998, Boralessa H *et al*, 2002). Six of the above studies also assessed the effect of physician characteristics on transfusions rates (Salem-Schatz SR *et al*, 1990, Brown RL *et al*, 1992, Hebert PC *et al*, 1998, Boralessa H *et al*, 2002, Matot I *et al*, 2003, Hebert PC *et al*, 2005).

Several factors have been identified in these surveys that affect transfusion thresholds based on vignettes. The hemoglobin concentration has commonly been found to be associated with transfusion thresholds (Salem-Schatz SR *et al*, 1990, Brown RL *et al*, 1992). Age, history of heart disease, coronary ischemia, chronic anemia, blood loss, and comorbid illness have also been associated with increased hemoglobin thresholds (Hebert PC *et al*, 2005, Nuttal GA *et al*, 2003, Salem-Schatz SR *et al*, 1990, Stehling LC *et al*, 1987, Brown RL *et al*, 1992, Hebert PC *et al*, 1998, Boralessa H *et al*, 2002). The physician characteristics shown to affect hemoglobin thresholds include physician specialty (Matot I *et al*, 2003, Brown RL *et al*, 1992), academic affiliation (Hebert PC *et al*, 1998) and personal experience (Salem-Schatz SR *et al*, 1990). None of these transfusion surveys have focused specifically on patients having cardiac bypass surgery nor did they specifically ask physicians to select the factors that they considered significantly affected their decision to transfuse red blood cells.

2.6 Variability of Transfusions in Coronary Artery Bypass Surgery

The importance of determining the hemoglobin thresholds and factors that affect transfusion rates is that a considerable number of patients having coronary bypass surgery receive red cell transfusions. In Ontario, 45% of patients having bypass surgery receive red cell transfusions (Chiavetta J *et al*, 2003). The proportion of patients having coronary artery bypass surgery who have receive red blood cells can range anywhere from 9% to 100% (Table 2.1). Only speculations exist to explain this variability. Some explanations for the variability in transfusion rates include: increasingly more surgeries are being performed on sicker, older patients with more complications; more patients are being treated with antiplatelet agents and anticoagulants; and there is an increased perception that blood transfusions carry less risks than they used to (Covin R *et al*, 2003, Thurer RL, *et al*, 2001). Rates of transfusions may be lower at some institutions because of the greater use of pharmacological interventions that reduce bleeding and a heightened awareness of transfusion transmissible diseases (Thurer RL, *et al* 2001). Regardless of the possible explanations for the variability in transfusion rates, the existence of this wide variability suggests that more information is needed to help us understand the patient characteristics and perioperative variables that physicians consider when selecting hemoglobin thresholds for transfusion.

Table 2.5. Variables predicting or influencing transfusion in patients having coronary artery bypass surgery.

Author, Year	Study Design	Variables predicting transfusion
Moskowitz DM *et al*, 2004	Prospective Assessing perioperative risks	Preoperative RBC mass, PT, type of operation, urgency, number of vessels diseased
Lithmathe JL *et al*, 2003	Retrospective Assessing perioperative risks	Age, sex, anemia, renal insufficiency, urgency and type of surgery, low cardiac output, sepsis, respiratory failure
Scott BH *et al*, 2003	Prospective Assessing preoperative risks	Anemia, sex, low body weight, age
Covin R *et al*, 2003	Retrospective, Assessing preoperative risks	Age, hemoglobin concentration, non-smoker status, left ventricular dysfunction, renal impairment, PVD, low BMI
Engstrom KG *et al*, 2002	Retrospective Assessing perioperative risks	Sex, weight, age, during on bypass pump
Isomers Y *et al*, 2001	Retrospective Risks not clearly specified	Low hematocrit, age, PVD, emergent surgery
Karkouti K *et al*, 2001	Prospective Assessing preoperative and intra-operative risks	Preoperative hemoglobin concentration, weight, age, sex
Surgenor DM *et al*, 1998	Retrospective, Assessing preoperative risks	Preoperative hematocrit, age, sex, previous CABG, active tobacco use, catheterization during admission, coagulation defects, IDDM with renal or circulatory impairment, first treatment of an MI, complications (cardiogenic shock), hospital
McGovern JA *et al*, 1996	Retrospective, Assessing preoperative, intra-operative and post-operative risks	Low red cell volume (anemia, age, sex, low weight), comorbidities (PVD, LV dysfunction, renal insufficiency, IDDM) unstable patients, (cardiogenic shock, post infarction angina, emergent/urgent surgery), repeat operation
Stover EP *et al*, 1998	Prospective, Assessing preoperative and intra-operative risks	Volume loss and institution
Bilfinger TV *et al*, 1989	Retrospective, Assessing preoperative risks	Preoperative hematocrit, age, sex, weight

RBC= red blood cell, PT=prothrombin time, PVD=peripheral vascular disease, BMI=body mass index, CPB=cardiopulmonary bypass, CABG=coronary artery bypass surgery, IDDM=insulin dependant diabetes, MI=myocardial infarction, LV=left ventricular.

2.7 Significance

Patients with coronary artery disease may experience considerable morbidity if transfused unnecessarily. Existing evidence and expert opinion suggest that as many as 15% to 60% of patients receive unnecessary transfusions (Speiss BD *et al*, 1998, Hasley PB, *et al*, 1994, Goodnough LT *et al*, 1993b, Salem-Schatz SR *et al*, 1990, Consensus Conference, 1988). Conversely, decisions not to transfuse patients may lead to unnecessary harm as a result of impaired oxygen delivery and impaired hemostasis (Valeri CR *et al*, 1998).

From previous studies, it is unclear at what hemoglobin concentration patients having coronary artery bypass surgery should be transfused and what patient factors physicians consider as modifying factors of these hemoglobin thresholds. A starting point to clarifying these issues is to determine at what hemoglobin concentration physicians are transfusing a specific patient population that is frequently transfused. None of the surveys published in transfusion medicine have focused on a single population of patients (Stehling LC *et al*, 1987, Salem-Schatz SR *et al*, 1990, Brown RL *et al*, 1992, Hebert P *et al*, 1998, Rock G *et al*, 2002, Boralessa H *et al*, 2002). This study will focus on a single population of patients that has a high transfusion rate and will assess the impact of various factors on the hemoglobin concentrations at which physicians think that patients should be transfused. It is the first study that surveys a specific group of physicians that transfuse a specific population (i.e. coronary artery bypass patients). A high proportion of these patients are at high risk of receiving red cell transfusions (Table 2.1). It is also the first questionnaire of transfusion decisions in the intraoperative period and in the postoperative period for coronary artery bypass patients. In addition, there has not been a questionnaire that specifically asked physicians about factors that they considered important in influencing their transfusion decisions.

Chapter 3

3. Methods

3.1 Development of Survey Instrument

We used a cross-sectional study design using self-administered mailed questionnaires sent to anesthesiologists and cardiac surgeons in Canada, as there are several benefits of using a cross sectional study design as opposed to a cohort study. Cross-sectional studies are used to examine associations between demographics and clinical characteristics and outcomes (Newman TB *et al*, 2001). Since all measurements are made at a single point in time, there is no waiting time for outcomes to take place. Thus, completion of a cross-sectional study is generally fast, inexpensive and there is no loss of data because of loss of participants to follow-up (Newman TB *et al*, 2001). A cross-sectional design was used for this study because there are no published data on the associations between physicians' characteristics and clinical characteristics and transfusion decisions in patients undergoing coronary artery bypass surgery. The results from this initial study can then be used to help design future cohort studies. A major limitation of the cross-sectional design is that causal associations cannot be made (Newman TB *et al*, 2001), but the intent of this study is not to determine cause and effect, rather to establish associations that can be investigated further in future studies.

The questionnaire aimed to assess factors that may affect physicians' decisions to transfuse red blood cells to coronary artery bypass surgery patients during the perioperative period. The factors to be included in the questionnaire were identified by an extensive literature search. A systematic search was conducted of the databases MEDLINE (1966 to September 2003), PUBMED (to September 2003) and the Cochrane Library (2003 Issue 3). The search terms included: exp coronary artery bypass graft, coronary artery bypass graft ti., coronary artery bypass graft (MESH), exp CABG, CABG ti., CABG (MESH), exp cardiovascular surgery, cardiovascular surgery ti, and cardiovascular surgery (MESH). These terms were combined with the search terms: exp transfusion, transfusion ti., transfusion (MESH), exp blood transfusion, blood transfusion ti., and blood transfusion (MESH). A study was included if 1) published in English 2) was an original report and 3) and aimed to assess factors that predicted transfusion of packed red blood cells or whole blood in the perioperative period. Reports were excluded if they were 1) editorials, 2) letters, 3) abstracts 4) if the patient population was solely pediatric or 5) if the study only assessed pharmacological interventions.

Only the perioperative period was considered, as 60% to 80% of all red cells are transfused during this time (Consensus Conference, 1988, Goodnough LT *et al,* 1993). We have defined the perioperative period as the intraoperative period and the postoperative period in an intensive care unit.

We elected to use vignettes to assess transfusion decisions for several reasons. Using vignettes enables an investigator to collect information simultaneously from large numbers of subjects and to manipulate a number of variables at once (Gould D, 1996). We used vignettes instead of a question-based survey because vignettes have been shown to have better discriminatory ability than questions where an individual has to choose one correct answer (Carroll RG, 1993). Physicians' responses to vignettes have also been shown to be highly correlated with performance using standardized patients (Kuyvenhoven MM *et al*, 1983, Kirwan JR *et al*, 1983, Peabody JW *et al*, 2000, Peabody JW *et al*, 2004) and data abstraction (Katz JN *et al*, 1996).

We developed the questionnaire according to previously published techniques (Dillman D, 2000, Streiner DL, Norman GR, 2001, Woodward CA, Chambers LS, 1983). Specifically, we developed a simple and short instrument with mutually exclusive response categories (Appendix I). The structure of the questionnaire was that of eight case scenarios, which simulate patient encounters, with closed-ended questions. Since the presence of comorbidities can affect transfusion decisions, we designed the vignettes to reflect a patient without any additional comorbidities beyond coronary artery disease in order to ensure that transfusion decisions would be based on the factors that we were varying in the questionnaire and not on the presence of one or more comorbidities (Covin R *et al*, 2003, Brown RL *et al*, 1992, Surgenor DM *et al*, 1996). The case scenarios described patients that did not have hemodynamic instability and had a normal mixed venous oxygen saturation, as the former is associated with increased transfusion rates (Lithmathe J *et al,* 2003, Surgeoner DM *et al,* 1996 Magovern JA *et al*, 1996), and some physicians use the latter to guide transfusion decisions. The case scenarios were constructed such that we consecutively introduced each factor that may influence the decision to transfuse red blood cells. This allowed for the analysis of each factor separately, and for the analysis of the interaction of factors. Four case-scenarios dealt with the intraoperative setting and four dealt with the post-operative setting. One additional partially closed-ended question was added to determine what factors physicians considered significant when transfusing coronary artery bypass patients (Appendix I). Physicians were asked to rank the three most significant factors that influenced their transfusion decisions. The list of factors included, the hemoglobin concentration, age, sex, myocardial ischemia, cardiac index, blood loss, mixed venous oxygen saturation, lactic acidosis, and comorbid illnesses. There was also a category "other" that permitted a physician to record a factor that was not included in the list. The question of ranking the three most significant factors was added to determine how physicians ranked factors and to ensure that the factors selected in this question were similar to those identified as changing the hemoglobin concentration in the vignettes. Physician demographics including age, and specialty were ascertained.

3.2 Pretesting

The questionnaire was piloted to assess face and content validity, comprehensibility, time to completion, and ambiguity. We used a semi-structured interview format to assess the pilot study.

Twelve anesthesia and cardiovascular surgery residents completed the questionnaire for the pilot study. The resident physicians indicated that the questionnaire was clear and not ambiguous. The residents described that the questionnaire as being comprehensive and reflective of patient encounters. The time to completion ranged from 10 to 30 minutes. The majority completed the questionnaire in 15 minutes. The residents suggested that additional descriptive information be added to improve the realism of the case scenarios (i.e. the heart rate and blood pressure of the subjects described in the scenarios). Most of the variables included in the scenarios affected transfusion decisions, except for the sex of the patient.

The partially closed-ended question that asked individuals to rank the three most significant factors that guided their decision to transfuse was answered as follows:

1. For the most significant factor affecting transfusion decisions, 36% chose hemoglobin concentration, 27% chose myocardial ischemia, and 9% chose

each of the following: age, cardiac index, blood loss and other (e.g. hemodynamic instability).

2. For the second most significant factor affecting transfusion decisions, 27% chose hemoglobin concentration; 18% chose each of the following: cardiac index, blood loss, and venous oxygenation; and 9% chose age and myocardial ischemia.
3. For the third most significant factor affecting transfusion decisions, 45% chose the mixed venous oxygenation, 27% chose age, and 9% chose each of the following: lactic acidosis, blood loss and cardiac index.

Overall, 21% chose preoperative hemoglobin, 21% chose the mixed venous oxygenation, 15% chose age, and 12% chose cardiac index, blood loss, and myocardial ischemia, as important factors affecting transfusion decisions. Thus, the most important factors affecting transfusion decisions were the hemoglobin concentration, the mixed venous oxygen saturation, age, cardiac index, blood loss and myocardial ischemia.

Based on the results of the pilot study, several changes were made. It would have been difficult to vary all factors identified in the pilot study in the final questionnaire. It was decided to include myocardial ischemia in the vignettes. The rationale for this decision was that myocardial ischemia was selected by a large proportion of individuals as affecting transfusion decisions, and the literature describes conflicting evidence on when to transfuse patients with myocardial ischemia (Wu W-C *et al*, 2002, Hebert PC *et al*, 2001 Hebert PC *et al*, 1999, Rao SV *et al*, 2004). Although the same proportion of individuals identified myocardial ischemia and blood loss as important factors in influencing transfusion decisions, blood loss was excluded as a variable because of constraints of the length of the questionnaire. Additionally, it is widely accepted that transfusions are required for blood loss whereas the hemoglobin concentration at which to transfuse red blood cells in patients having myocardial ischemia has not been determined. Although sex was not identified as factor that affected transfusion decisions in the pilot study, this factor has been consistently shown in the literature to be associated with increased transfusion of red blood cells (Karkouti K *et al,* 2001, Surgenor DM *et al*, 1998, Magovern JA *et al*, 1996, Bilfinger TV *et al*, 1989). Thus, sex was retained as a variable. The mixed venous oxygen saturation was selected as an important factor in assessing transfusion decisions, however, it was not used as a variable in this study since it has not been well described in the literature as affecting transfusion rates. Instead, it was used as a fixed descriptor in the vignettes to enhance clinical fidelity. Lastly additional fixed descriptors were added to the case scenarios (i.e. the heart rate and blood pressure of the subjects described in the scenarios) to increase clinical fidelity.

The questionnaires were re-piloted on three individuals: a nurse practitioner, and two physicians (a cardiovascular anesthesia fellow and an anesthesia resident). The only consistent comment was that the description of a cardiac index of less than two L/min/m^2 with a mixed venous oxygen saturation of 75%, which appeared in the scenarios, was not clinically plausible. Five anesthesiologists were informally polled by one of the investigators (DM) regarding what value to use in the scenarios for the mixed venous oxygen saturation. As a result of the poll, the mixed venous oxygen saturation was changed to 70% for all case scenarios.

3.3 Administering the Questionnaire

There are several potential methods of administering a questionnaire: interview based (telephone or face to face), postal questionnaires, fax, web based questionnaires or a combination of methods. The questionnaires in this study were self-administered postal questionnaires. Using postal questionnaires has the benefit of being inexpensive (McHorney DA *et al*, 1994, O'Toole BI *et al*, 1986, Rolnick SJ *et al*, 1989), particularly when information is required from large geographically dispersed populations (Edwards P *et al*, 2002) such as in this study, and interviewers do not have to be recruited and trained (Smeeth L *et al*, 2001). Although responses to postal questionnaires may be delayed in comparison to fax or web based surveys, faxed surveys require that an individual have a fax machine and an easily accessible fax number, while web-based questionnaires require computer and internet access and need to be password protected (McMahon SR *et al*, 2003). Additionally, postal questionnaires tend to have comparable response rates to fax questionnaires and higher response rates than web-based questionnaires (McMahon SR *et al*, 2003, Leece P *et al*, 2004). Although postal questionnaires may result in more missing data than interview based questionnaires (Smeeth L *et al*, 2001, Addington-Hall J *et al*, 1998, McHorney CA *et al*, 1994), response rates are comparable (Addington-Hall J *et al*, 1998) or higher (Smeeth L *et al*, 2001, McHorney CA *et al*, 1994)), and the characteristics of respondents for interview or postal questionnaires are not considerably different (Picavet HSJ, 2001). Additionally, postal questionnaires tend to elicit more accurate responses by minimizing social desirability bias (Picavet HSJ, 2001, Addington-Hall J *et al*, 1998, McEwan RT *et al*, 1992).

The validity of a questionnaire can be affected by a poor response rate. Thus, to maximize the response rate for the final questionnaire, multiple techniques to improve response rates were followed (Dillman D, 2000, Edwards P *et al*, 2002). We incorporated Dillman's (Dillman D, 2000) five techniques to enhance response rates: a respondent friendly questionnaire, personalization (i.e. real stationary, real names instead of Dear Sir/Madam, and real signatures), stamped self-addressed envelopes, a token-prepaid financial incentive, and five contacts with each subject. The first of the five contacts was a pre-notice letter sent prior to mailing the questionnaire, informing the physicians about the arrival of the questionnaire (Appendix II). The questionnaire package, which included a personalized detailed cover letter, a stamped self-addressed envelope, using first-class postage rather than a bulk rate stamp, and a token financial incentive (i.e. a $5 bill), was sent shortly after the pre-notice letter. Thank you/reminder cards were sent one week after the questionnaire package. A replacement questionnaire was sent to non-respondents three weeks after the first mailing. A final contact, which included a cover letter detailing the importance of the study and another questionnaire, was sent three weeks after the replacement questionnaire. We also used methods reported in a meta-analysis to increase response rates; namely the token financial incentive was not conditional on response, and we used coloured ink (Edwards P *et al*, 2002).

3.4 Re-mailing of a Corrected Questionnaire

A respondent noted a typographical error in the four vignettes discussing postoperative transfusion decisions. The instructions for the four postoperative vignettes described the vignettes as "postoperative" case scenarios, but within the wording of each of these vignettes, they were described as "intraoperative" cases. The questionnaires were corrected for the second and third mailing.

To determine whether respondents to the initial questionnaire with the typographical error had interpreted the case scenarios as intraoperative or postoperative, a separate mailing was sent to these respondents. The package included a letter explaining the error, their completed questionnaires to remind them of their responses, a form asking them whether they had interpreted the postoperative case scenarios as intraoperative or postoperative, and a new questionnaire with corrected postoperative case scenarios for them to complete if they had interpreted the postoperative case scenarios as intraoperative (Appendix III). A financial incentive was included with this mailing. Two subsequent mailings were also sent. For this document, we only report results for the postoperative vignettes for those individuals who returned a corrected questionnaire.

3.5 Participant Selection

All anesthesiologists and cardiac surgeons involved in coronary artery bypass surgery in Canada were eligible to participate in the survey. We used the following methods to identify the eligible population. A list of anesthesiologists, cardiac surgeons and cardiovascular surgeons practicing in Canada in 2003 was obtained from the Royal College of Physicians and Surgeons of Canada. The list included 1,890 anesthesiologists and 73 cardiac and cardiovascular surgeons. By accessing the Canadian Cardiovascular Society's website (www.ccs.ca) we determined that there are 32 adult centres where coronary artery bypass surgeries are performed in Canada. To ensure that physicians identified through the Royal College were involved in coronary artery bypass surgery and that physicians not registered with the Royal College were included, each centre was contacted to confirm the names of the physicians. The eligible survey population was confirmed at 399 anesthesiologists and 146 surgeons (Table 3.1)

Table 3.1. The number of physicians involved in coronary bypass surgery at each cardiac centre.

Cardiac Centre	Number of Anesthesiologists	Number of Surgeons
St. Paul's Hospital, B.C.	6	5
Vancouver General, B.C	20	4
New Westminister, B.C.	22	3
Victoria Hospital, B.C.	8	4
Foothills Hospital, AL	7	6
University of Alberta Hospital, AL	15	6
Regina General Hospital, SK	9	4
Health Sciences Centre, MB	6	2
St. Boniface General Hospital, MB	6	4
Sudbury Memorial Hospital (ON)	10	3
London Health Sciences Centre, ON	9	5
Royal Victoria Hospital (London), ON	11	2
Hamilton General Hospital (ON)	16	6
Toronto Western Hospital*	1	0
Mount Sinai Hospital (ON)*	1	0
Toronto General Hospital (ON)	26	10
St. Michael's Hospital (ON)	20	4
Sunnybrook Health Sciences Centre (ON)	11	5
Kingston General Hospital	11	3
University of Ottawa Heart Institute (ON)	11	8
Hôpital de Chicoutimi, QC	8	3

Table 3.1(continued) The number of physicians involved in coronary bypass surgery at each cardiac centre.

Cardiac Centre	Number of Anesthesiologists	Number of Surgeons
Hôtel-Dieu de Montreal,QC	12	2
Hôpital du Sacré-Coeur de Montréal,QC	14	3
Hôpital Notre-Dame, QC	19	3
Hôpital Saint-Luc, QC	10	1
Institut de cardiologie de Montreal, QC	7	9
Royal Victoria Hospital, QC	13	5
The Montreal General Hospital, QC	5	2
The Sir Mortimer B. Davis, Jewish General Hospital, QC	10	3
L'Hotel-Dieu de Quebec, QC	11	6
Hôpital Laval, QC	13	8
Centre hospitalier universitaire de Sherbrooke, QC	22	2
Saint John Regional Hospital, NB	4	3
QE II Health Sciences Centre, NS	11	9
General Hospital, Health Sciences Centre, NL	14	3
Total	399	146

*The Toronto Western Hospital and Mount Sinai Hospital are not cardiac centres but physicians with primary addresses at these hospitals were involved in cardiac surgery.

3.6 Statistical Analysis

3.6.1 Sample Size

We surveyed all cardiac surgeons and anesthesiologists involved in cardiac surgery in Canada. Although physicians of other specialties are involved in postoperative transfusion decisions in the intensive care unit, we only surveyed cardiac surgeons and anesthesiologists because they would be responsible for transfusions both in the intraoperative and postoperative setting. We determined *a priori* the confidence interval half-length for various response rates to determine the precision of our results (Table 3.2) (Streiner DL, 1994, Dillman DA, 2000)

$$B^2 = \frac{C^{2*}[N_p(p)(1-p) - N(p(1-p))]}{N(N_p - 1)}$$

B=Confidence Interval Half-Length

N_p=size of population

N=sample size

p=proportion expected to choose one of two response categories

C=Z statistic (1.96)

Although p represents the proportion of respondents who choose between one of two response categories and our questionnaire has more than two response categories, we assigned a value of 0.5 to p, which allows for a maximum heterogeneity of responses and can used in circumstances when there are more than two response categories. The size of the population was 550 (N_p) and the sample size (N) used was dependent on the response rates i.e. a response rate of 30% is equivalent to a sample size of 165 respondents.

Table 3.2 depicts the confidence interval half-lengths for three response rates. A response rate of 50% or 70% would allow us to estimate percentages within plus or minus four or three percentage points, respectively reflecting a high precision (Dillman, 2000).

Table 3.2 The confidence interval half-lengths for different response rates.

Response Rate	N (N_p=550)	Confidence Interval Half Length
30%	165	0.06
50%	275	0.04
70%	385	0.03

3.6.2 Data Analysis

3.6.2.1 Primary Analysis

Descriptive statistics (i.e. measures of central tendency and of dispersion) were used to describe the cohort. The mean hemoglobin concentrations were calculated for each case scenario.

3.6.2.2 Secondary Analyses

3.6.2.2.1 Univariate Analyses

Univariate analyses were used to determine the impact of cardiac index, myocardial ischemia, age and sex on the hemoglobin concentrations for each case scenario. We used Student's t-test to assess the effect of binary physician variables (sex, academic affiliation, specialty, involvement in preoperative, intraoperative and postoperative transfusion decisions) on the dependent variable (hemoglobin concentration), and p-values were calculated based on Satterthwaite's method assuming unequal variances. Linear regression was used for continuous physician variables (age, cases per individual, cases per centre). For univariate analysis of patient variables (cardiac index, myocardial ischemia, age, sex), paired Student's t-tests were used. The analysis of variance was used to determine the effect of the hospital variable on the dependent variable (the hemoglobin concentration).

3.6.2.2.2 Multivariable Analyses

A repeated measures mixed effects regression model was developed for multivariable analysis as the format of the case scenarios represented repeated measures. "Repeated measures refers to sets of data with multiple measurements (i.e. the impact of age, sex, cardiac index and myocardial ischemia) of a response variable (i.e. the hemoglobin concentration) on the same experimental unit (i.e. the case scenario)" (Littell RC *et al*, 2002). This study used a repeated measures model as all vignettes were used to develop the model, thus there were serial hemoglobin concentrations for each respondent. The repeated measures mixed effects regression model also allowed for comparison of physician variables and patient variables within the model. All patient variables were included in the regression model. We used a compound symmetric covariance structure for the model (Littell RC *et al*, 2002).

Univariate analysis revealed that the transfusion thresholds differed according to the hospital where a physician practised. When an outcome is dependant on two levels of variables, i.e. physician demographics and patient characteristics, a multilevel or hierarchical model is required to allow for analysis of data at the individual level because of the probability of clustering within units (Rice N, Leyland A, 1996). The final model was a multilevel model as the repeated measures mixed effects regression model allowed us to control for clustering secondary to the hospital variable.

Interaction terms were also included in the multivariable model. Published reports of factors affecting transfusion rates do not include interaction terms, so they were not helpful in selecting possible important interactions between variables. Therefore, the interaction terms were chosen based on the clinical plausibility of interactions between variables. The following interaction terms were considered: sex of the physician and years in practice, cardiac index and sex of the patient, age and sex of the patient, sex and presence of myocardial ischemia in the patient, myocardial ischemia and age of the patient, cardiac index and myocardial ischemia, and cardiac index and age. Chi-square analysis was used to compare the models with and without interaction terms to determine whether the inclusion of interaction terms would add to the model. The p-values were significant ($p<0.001$) for the postoperative case scenarios and the subgroup analyses for the intraoperative and postoperative case scenarios. This indicates that the interaction terms did improve the performance of the model. Thus, the interaction terms were included in all models except for the model of intraoperative case scenarios for all physicians. A p-value less than 0.05 was considered significant for all analysis. The statistical software package SAS™ (SAS Institute, Cary, NC) version 8.2 was used for data analyses.

3.6.2.2.3 Subgroup Analyses

We had planned to analyze data for the whole cohort and for the subgroups for anesthesiologists and cardiac surgeons. The same univariate and multivariable analyses used in the analyses of all physicians was used for the subgroup analyses.

3.6.2.2.4 Factors Affecting Transfusion Decisions

Physicians were asked to rank the three most significant factors that influenced their transfusion decisions. Each factor that was ranked first was given three points. Factors ranked second and third were given two and one point, respectively. The number of points was then summed for each factor.

3.6.2.2.5 Comparison Between Intraoperative and Postoperative Case Scenarios

Univariate analyses (paired Student's T-tests) were used to compare the hemoglobin thresholds selected for base case scenarios in the intraoperative and postoperative setting.

3.6.3 Dependent/Independent Variables

The variables used in the analysis are listed in Table 3.3. Generally, the choice of variables to be included in a questionnaire can be determined by expert opinion, clinical observations, theory, consensus techniques, or from a literature search (Brown RL *et al*, 1992, Wigton RS, 1988 Streiner DL, Norman GR, 2001). The items chosen for the vignettes were based on a literature search (please see section 3.1).

The variables used in this study were the cardiac index, myocardial ischemia, age and sex as most studies have found the patients' hemoglobin concentration, age and sex to be the factors that are most commonly associated with increased transfusions (Lithmathe J *et al,* 2003, Scott BH *et al*, 2003, Covin R *et al*, 2003, Karkouti K *et al*, 2001, Isomatsu Y *et al,* 2001, Surgenor DM *et al*, 1998 Surgenor DM *et al* 1996, Magovern JA *et al*, 1996, Cosgrove DM *et al*, 1989, Bilfinger V Conti R, 1989). Although left ventricular dysfunction has been shown to be associated with increased transfusion rates (Covin R *et al*, 2003, Surgenor DM *et al*, 1996 Magovern JA *et al*, 1996), preoperative left ventricular function may not be predictive of left ventricular function intra-operatively and postoperatively. Since the cardiac index, a measure of the cardiac output to body surface area (Klein SL, 1993), is more reflective of intraoperative cardiac function than preoperative left ventricular function, we included the cardiac index in the vignettes. As the literature for the optimal hemoglobin threshold for patients with myocardial ischemia is conflicting (Wu W-C *et al*, 2002, Hebert PC *et al*, 2001 Hebert PC *et al*, 1999, Rao SV *et al*, 2004), and the pilot study identified myocardial ischemia as an important determinant in transfusion decisions, myocardial ischemia was added as a variable. Additionally, all possible combinations of the non-demographic variables were included in the vignettes i.e. the range of plausible hemoglobin concentrations, cardiac index and presence or absence of myocardial ischemia. This methodology of using all possible combinations of all variables has been referred to as a full factorial design (Wigton RS, 1988).

The variables were classified as continuous, dichotomous, or categorical based on what we considered to be clinically significant categories to allow for the assessment of different transfusion practices. The dependent variable was the hemoglobin concentration at which red blood cells are transfused (i.e. the hemoglobin threshold). The hemoglobin threshold values included in the vignettes were based on transfusion thresholds from the literature for coronary artery bypass patients that range from 60 g/L to 90 g/L (Lithmathe J *et al,* 2003, Scott BH *et al*, 2003, Karkouti K *et al*, 2001, Bracey AW *et al,* 1999, Bracey AW *et al*, 1995 Bilfinger V Conti R, 1989), but we broadened the choices somewhat by including values between 50 g/L to 100 g/L. Thus, the dependent variable, the hemoglobin threshold, was classified as a continuous variable.

The age variable was dichotomized for the vignettes (age 55 and age 75 years). Although dichotomizing a continuous variable may lead to inefficiency and information loss (Streiner DL and Norman GR, 2001), age had to be restricted to two categories because of limitations of questionnaire length with the vignette format. We included two plausible values for age, 55 and 75 years, since the mean/median age for cardiac bypass surgery is approximately 65 years with a standard deviation of 10 years (Covin R *et al*, 2003, Karkouti K *et al,* 2001, Surgenor DM *et al*, 1998 Surgenor DM *et al,* 1996, Magovern JA *et al*, 1996).

Lastly, cardiac index was classified as a categorical variable based on three categories that were considered clinically important in the classification of cardiac function that would impact on physicians' transfusion decisions.

The questionnaire also included questions about physician characteristics, since various physician variables may be associated with transfusion decisions. Some physician variables that have been included in other studies that have been shown to be associated with transfusion rates are the academic affiliation, specialty, the hospital, and the experience of the physician (Brown RL *et al*, 1992, Salem Schatz SR *et al*, 1990, Surgenor DM *et al*, 1998, Hebert PC *et al*, 1998 Vincent JL *et al*, 2002). The following physician variables were included: age and sex of the physician, academic affiliation, the specialty, the number of cardiac bypass surgeries performed by each physician and the number of cardiac surgeries performed at each centre. *Post hoc*, a hospital variable was added because the literature suggests that the hospital site affects transfusion rates (Surgenor DM *et al*, 1998), and the effect of the hospital site may be distinct from the number of cases performed per centre.

Table 3.3 The variables.

Dependent Variables	
Hemoglobin concentration at which red blood cells are transfused	Continuous (50, 60, 70, 80, 90, 100) g/L
Independent Variables	
Patient Demographics	
Age	Dichotomous (55 or 75 years)
Sex	Dichotomous (male/female)
Cardiac index	Categorical (less than 2, 2-2.5, greater than 2.5 L/min/m^2)
Clinical/Physiological Variables	
Myocardial ischemia	Dichotomous (yes/no)
Physician Variables	
Academic centre	Dichotomous (yes/no)
Years in practice	Continuous (years)
Number of CABG surgeries/centre/year	Continuous
Hospital	Categorical
Number of CABG surgeries/physician/year	Continuous
Physician sex	Dichotomous (male/female)
Physician age	Continuous (years)
Physician specialty	Dichotomous (Anaesthesia, Cardiac Surgery)

CABG=coronary artery bypass surgery

3.6.4 Missing Data

Missing data relates to items on the questionnaire that were not answered by the respondents. Missing data can affect the validity of a study, as it can reduce the sample size available for analysis, and, hence, reduce the power to detect significant differences (Streiner DL, 2002).

There are a number of ways that one can deal with missing data. The method for dealing with missing data should be pre-specified before analyzing the data (White IR, Thompson SG, 2005) and depends on the type of missing data (Streiner DL, 2002). Data that are missing can be categorized in three groups: data can be missing completely at random, implying that the probability that the data being missing is not related to any variable, such as non-response to questionnaires because questionnaires were not delivered; data can be missing at random, where data are related to some variables measured but not to the outcome, such as elderly people attending a clinic to measure blood pressure less than younger people because they do not have transportation means; and data can be missing not at random in that the probability of the values missing are dependent on a variable, such as patients dropping out of a trial because they are sicker (Streiner DL, 2002).

The data in this questionnaire were considered to be missing completely at random because the missing data were not related to any other demographic variable and there was no pattern to the missing variables. Table 3.4 illustrates the comparison between the physician characteristics for respondents with and without missing data. There was one statistically significant result, the subspecialty of physicians. There were more cardiac surgeons with missing responses. However, because there was no apparent pattern to the missing responses, the results were not considered significant. There were also two hospitals that had more than one individual with missing data, but again, there were no patterns to the missing data. The Kingston General Hospital had three of nine respondents with missing data. The first respondent did not answer the question regarding the number of cases he/she was involved with, the second respondent did not respond to three case scenarios and the last respondent did not answer the last case scenario. At the Institut de Cardiologie de Montreal, four of six respondents had missing responses. One respondent did not respond to the demographics or the last case scenario, the second respondent did not respond to the question regarding the third most significant factor affecting his/her transfusion decision, the third respondent did not complete his/her age and years in practice, and the last respondent did not respond to one case scenario. Additionally, there were three individuals in the intraoperative and postoperative case scenarios that we excluded in the analysis because they responded to only one question in each case scenario. We could not determine whether they misinterpreted the questions thus their data were excluded. Aside from these three individuals, there was no pattern to the missing data, thus the data were considered to be missing completely at random.

Table 3.4 Comparisons of demographics of respondents with and without missing responses.

Characteristic	Respondents With Missing Responses	Respondents With All Responses Completed	Statistical Test	P
Sex (M: F) (%)	83:17	85:15	Fisher's Exact Test	0.76
Specialty (A: CV) (%)	52:48	73:27	Chi-Square	0.04
Academic Institution (Y: N) (%)	91:9	89:11	Chi-Square	1.0
*Preoperative (Y: N)(%)	76:24	61:39	Chi-Square	0.24
*Intraoperative (Y: N) (%)	86:14	96:4	Fisher's Exact Test	0.06
*Postoperative (Y: N)(%)	76:24	63:37	Chi-Square	0.34
Mean Age (sd) (years)	47(10)	46(8)	Student's T-test	0.66
Cases/individual (mean (sd))	131(78)	120(77)	Student's T-test	0.55
Cases/centre (mean (sd))	842(416)	946(472)	Student's T-test	0.26

M=male, F=female, A=anesthesiologists, CV=cardiac surgeons, Y=yes, N=no, sd=standard deviation, * involvement in preoperative or intraoperative or postoperative transfusion decisions, There are several different analytic approaches for dealing with missing data. Generally, using multiple imputation yields unbiased estimates of means, variances and other parameters (Streiner DL, 2002). Multiple imputation is optimal when there is a large amount of missing data (Greenland S, Finkle WD, 1995, Harrell FE, 2001) and when missing data are not missing completely at random (Streiner DL, 2002). Complete case analysis, i.e. using data from only complete cases such as only including respondents responding to all questions in a questionnaire, is often inefficient since it leads to a loss of precision and bias (Little RJA, Rubin DB, 2000, White IR, Thompson SG, 2005). However, when the proportion of missing data are less than five percent, using complete case analysis is an appropriate method of dealing with the missing results (Harrell FE, 2001), as the loss of precision and bias is minimal when there is a large number of complete cases (Harrell FE, 2001, Little RJA, Rubin DB, 2000, Wood AM *et al*, 2005). Additionally, because the data in this questionnaire were considered to be missing completely at random, analyzing the available data without using imputation techniques should not affect the validity of the analysis (Streiner DL, 2002, Wood AM *et al*, 2005).

The missing data were handled as follows. For the dependent variable, the hemoglobin concentration, the missing data were left missing since the proportion missing was less than five percent. The proportion missing for the intraoperative and postoperative case scenarios were 1.3% (210/16368) and 1% (146/13968), respectively. For the independent variables, the proportion of missing data was also less than five percent. For intraoperative data, two data points (n=338)(n= total respondents) were missing for whether the respondent had "involvement in preoperative, intraoperative, or postoperative transfusion decisions", seven data points (n=338) were missing for "cases/centre", two data points (n=338) missing for the "hospital", four data points (n=338) were missing for "cases/individual", 12 data points (n=338) were missing for "years in practice", and eight data points (n=338) were missing for "age" of the physician. For postoperative data, two data points (n=288) were missing for whether the individual had "involvement in preoperative, intraoperative, or postoperative transfusion decisions", five data points (n=288) were missing for "cases/centre", four data points (n=288) were missing for "cases/individual", nine data points (n=288) were missing for "years in practice", and seven data points (n=288) were missing for "age" of the physician.

We used complete case analysis and various methods to impute data for the multivariable analyses. We used complete case analyses for determination of the mean hemoglobin thresholds for the case scenarios and for univariate analyses. However, since the secondary analyses involved repeated measures, excluding data from any respondent that had missing data for any of the independent variables would result in the exclusion of all the data for that respondent. In order to try to minimize the exclusion of respondent data, the following approaches were taken for the handling of missing data for the independent variables. Missing data for the variable "involvement in preoperative, intraoperative, or postoperative, transfusion decisions" were left as missing, as it would be difficult to impute data for this variable. For the variable, "cases per cardiac centre", the mean value for this variable from other respondents affiliated with the same centre was used to impute the missing data. For the variable "the number of cases per cardiac centre" mean imputation was used since mean imputation is an accepted method when the variable does not predict the outcome (Little RJA, Rubin DB, 2000). In one instance, the "cases per cardiac centre" variable was missing from a respondent who was the lone respondent from that centre, so this datum was left missing. For "age", "years in practice" and "cases/individual", regression equations were created to determine whether regression could be used to estimate the missing data. Table 3.5 lists the regression equations and the corresponding coefficients of determination, adjusted R squared (R^2). The adjusted R^2 for "age" and "years in practice" showed a strong linear relationship in that 82% of the variability among observed values for age is explained by the linear relationship between age and years in practise, thus the regression equations were used to impute the missing data. For "age" and "years in practice", the regression equations, age = years in practice, and years in practice = age, were selected, respectively, as the addition of the variable "cases/individual" did not change R^2 considerably. For three respondents (for intraoperative and postoperative data), data were missing for both "age" and "years in practice", and thus the data were left missing. Regression equations were not used for "cases/individual" as the adjusted R^2 squared ranged from less than 0.001 to 0.02, indicating that the models selected only explained two percent or less of the variation in the variable "cases per individual" and could not be used to predict the variable (Pagano M, Gauvreau K, 2000). Overall, seven respondents (n=338) were not included in the analysis (two of the respondents who had data missing for "cases /individual" also had data missing for "age" and "years in practice", and a respondent who had data missing for "cases/individual" also had data missing for "involvement in preoperative, intraoperative, or postoperative decisions").

Table 3.5 The regression models and adjusted R squared for the independent variables, age, years in practice and cases/individual.

Model	Adjusted R Squared
Age= years in practice (y=33.88 +0.904years in practice)	0.824
Age= years in practice + cases/individual (y=32.9 +0.9 years in practice + 0.008 cases/individual)	0.828
Years in practice=age (y=-28.427 +0.911age)	0.823
Years in practice=age + cases/individual	0.828
Cases/individual=age	0.02
Cases/individual =age +years in practice	0.002
Cases/individual =age*years in practice	<0.001
Cases/individual =age +cases/centre	0.007

3.7 Data management

All response categories to the items in the questionnaire were pre-coded. All data were entered into a database created using Microsoft Access™. Data entry was verified by double data entry for all data.

3.8 Ethics

The institutional review board at St. Michael's Hospital approved the study protocol. It also approved the correction to the typographical error in the questionnaire and the mailings of the corrected questionnaires. All data were kept confidential and anonymous and names were not transcribed to data sheets. Data were kept on a password-protected computer in a locked office. Identification numbers were used rather than respondent identifiers, and the file linking respondent names to identification numbers was kept separately from the database in a password-protected computer in a locked office.

Chapter 4

4.0 Results

4.1 Intraoperative Case Scenarios

4.1.1 Response Rate

Of the 545 anesthesiologists and surgeons who were mailed a survey questionnaire, 56 respondents either were not involved in coronary artery bypass surgery or had relocated. This left 489 eligible respondents. The response rate for the intraoperative case scenarios was 70.6% (345/489); 68.8% (243/353) of all anesthesiologists responded and 75% (102/136) of all cardiac surgeons responded. Responses were received from anesthesiologists from all 32 cardiac centres in Canada and from cardiac surgeons from 30/32 centres. The response rate by province is illustrated in Table 4.1. There was no difference in non-response rate by sex of the participant or province of practice (Table 4.1).

Two respondents were not involved in intraoperative transfusion decisions and did not complete the intraoperative case scenarios. Three respondents answered only one question in each case scenario. These three respondents were excluded from the analysis, as we could not determine whether the respondents misinterpreted the questions. Two respondents completed only the demographics portion of the questionnaire and were also excluded. Thus, there were 338 responses that were included in the analysis of the intraoperative case scenarios of the 489 eligible respondents (69.1%).

Table 4.1 Response rate by province for the intraoperative case scenarios.

Cardiac Centre	Proportion Responded (%)		Proportion Male/Female (%)		Proportion Respondents Male/Female (%)	
	A	**C**	**A**	**C**	**A**	**C**
British Columbia	65	56	85/15	94/6	71/33	67/0
Alberta	57	72	90/10	91/9	58/50	80/100
Saskatchewan	89	25	67/33	100/0	100/67	25
Manitoba	72	40	100/0	100/0	82	40
Ontario	74	84	77/23	93/7	67/64	88/33
Quebec	58	70	74/26	95/5	57/64	68/100
New Brunswick	100	100	75/25	100/0	100/100	100
Nova Scotia	73	89	91/9	100/0	80/0	89
Newfoundland	61	67	93/7	100/0	54/100	67

A=anesthesiologists, C=cardiac surgeons

4.1.2 The Study Group

Table 4.2 depicts the characteristics of the study group for the intraoperative case scenarios. The majority of physicians were male, belonged to an academic centre and were involved in preoperative, intraoperative, and postoperative transfusion decisions. Cardiac surgeons reported that they were involved in preoperative, intraoperative and postoperative transfusion decisions, whereas anesthesiologists were predominantly involved in intraoperative transfusion decisions.

Table 4.2 Characteristics of physicians for the intraoperative case scenarios.

Characteristic	All Physicians (n=338)	Anesthesiologists (n=241)	Cardiac Surgeons (n=97)
Mean age (sd)(years)	46.4 (8.6)	46.0 (8.3)	47.5 (9.5)
Male Sex (%)	286 (85)	193 (80)	93 (96)
Academic Centre (yes)(%)	299 (89)	215 (89)	84 (88)
Median years in practice (IQR)	13 (6,20)	13 (6,20)	13 (5,20)
Involved in Preoperative Transfusion Decisions (%)	208 (62)	130 (54)	78 (81)
Involved in Intraoperative Transfusion Decisions (%)	321 (96)	239 (99.6)	82 (85)
Involved in Postoperative Transfusion Decisions (%)	215 (64)	125 (52)	90 (94)
Median cases/physician (IQR)	100 (60,100)	80 (50,110)	200(150, 200)
Median cases/centre (IQR)	850 (400,1200)	800 (575,1200)	1000 (700,1200)

sd=standard deviation, IQR=interquartile range

4.1.3 Subgroup Analyses

The tables for the univariate and multivariable analyses for anesthesiologists and cardiac surgeons are illustrated in Appendix IV for the male and female case scenarios.

4.1.4 The Impact of Sex on Hemoglobin Thresholds

As the analyses for the female and male case scenario did not demonstrate significant differences for the intraoperative or postoperative case scenarios, the figures and the tables for the univariate and multivariable analyses for the male case scenarios are illustrated in Appendix IV for the subgroup analyses and Appendix V for all physicians.

4.1.5 The Hemoglobin Thresholds

Fifty four percent of physicians selected a hemoglobin concentration of 70 g/L as the hemoglobin at which they would transfuse patients described in the 55-year old patient having primary elective coronary artery bypass surgery, without any preoperative comorbid illnesses and who is euvolemic with a heart rate of 90, blood pressure of 110/70 and mixed venous oxygen saturation of 70% (Figure 4.1). The mean hemoglobin thresholds (i.e. the hemoglobin concentration which physicians selected to transfuse the simulated patient) for the male and female 55 year old base case scenarios were similar, 69 g/L (Table 4.3) and did not differ between anesthesiologists and cardiac surgeons (Table 4.4). The mean hemoglobin concentrations increased with decreasing cardiac index (69 g/L for a cardiac index greater than 2.5 L/min/m^2 and 79 g/L for a cardiac index less than 2 L/min/m^2) and the presence of myocardial ischemia (69 g/L without myocardial ischemia and 78 g/L with myocardial ischemia)(Table 4.3). For the 75-year old case scenarios, the mean hemoglobin thresholds were higher than for the 55-year old scenarios, (69 g/L for a the 55-year old case scenario compared to 74 g/L for the 75-year old case scenario), however similar results were found compared to the 55-year old scenarios in that the mean hemoglobin concentrations increased with decreasing cardiac index and the presence of myocardial ischemia. The subgroup analyses for anesthesiologists and cardiac surgeons did not differ compared to the analysis for all physicians (Table 4.4 and 4.5). Approximately 80% of physicians selected a hemoglobin concentration of 70 g/L or 80 g/L for the 75-year old case scenario (Figure 4.2).

Figure 4.1 The hemoglobin thresholds for the base case scenario, 55-year old woman in the intraoperative setting.

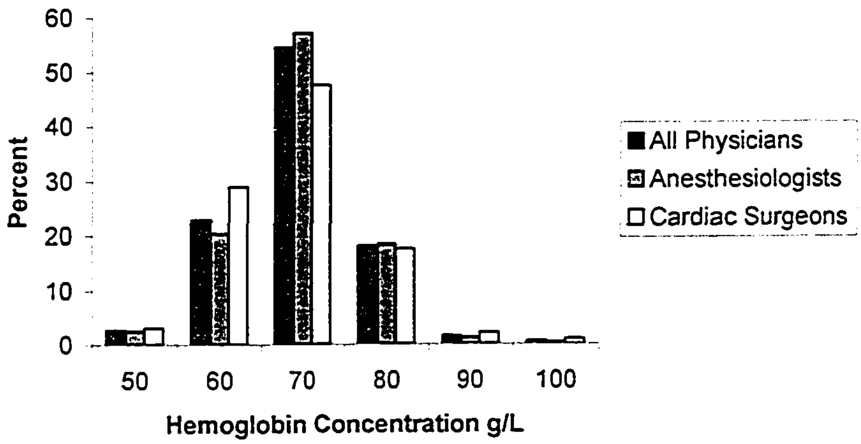


Table 4.3 The mean hemoglobin concentrations for the 55-year old patient according to cardiac index and presence of myocardial ischemia for the intraoperative case scenarios.

Variable	Mean Hemoglobin Concentration (SD)(g/L) for the 55-year old female	Mean Hemoglobin Concentration for the (SD) (g/L) 55-year old male
Cardiac index >2.5	69.5(7.9)	69.4(7.8)
Cardiac index 2-2.5	71.8(8.4)	71.7(8.2)
Cardiac index <2	78.8(10.2)	78.4(10.2)
MI and Cardiac index >2.5	78.1(10.4)	77.9(10.2)
MI and Cardiac index 2-2.5	80.2(10.7)	80.0(10.4)
MI and Cardiac index <2	84.7(10.8)	84.8(10.5)

SD=standard deviation, MI=myocardial ischemia

Table 4.4 Mean hemoglobin thresholds* for the intraoperative base case scenarios for all physicians, anesthesiologists and cardiac surgeons.

Case Scenario	Mean Hemoglobin Concentration (SD) (g/L)		
	All	Anesthesiologists	Cardiac Surgeons
55 year old female	69.5 (7.9)	69.7 (7.6)	69.0 (8.7)
55 year old male	69.4 (7.8)	69.6 (7.4)	69.0(8.8)
75 year old female	73.9 (8.4)	74.2 (8.3)	73.2(8.7)
75 year old male	73.8 (8.3)	74.1 (8.3)	73.2 (8.4)

SD=standard deviation

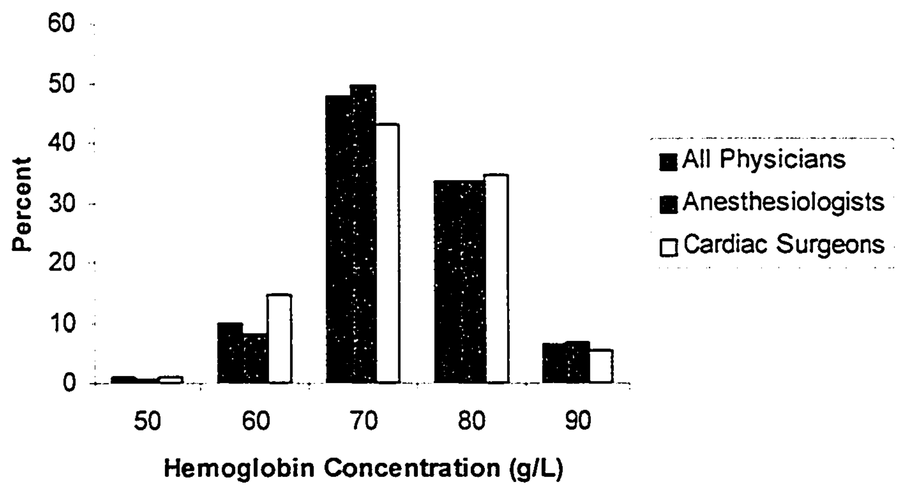
*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients

Table 4.5 The mean hemoglobin concentrations for the 75-year old patient according to cardiac index and presence of myocardial ischemia for the intraoperative case scenarios.

Variable	Mean Hemoglobin Concentration (SD)(g/L) for the 75-year old female	Mean Hemoglobin Concentration for the (SD) (g/L) 75-year old male
Cardiac index >2.5	73.9(8.4)	73.8(8.4)
Cardiac index 2-2.5	76.0(9.4)	76.0(9.4)
Cardiac index <2	82.2(10.4)	81.8(10.3)
MI and Cardiac index >2.5	80.6(10.4)	80.6(10.4)
MI and Cardiac index 2-2.5	82.6(10.4)	82.4(10.3)
MI and Cardiac index <2	86.5(10.1)	86.4(10.2)

SD=standard deviation, MI=myocardial ischemia

Figure 4.2 The hemoglobin thresholds for the base case scenario, 75-year old woman in the intraoperative setting.



4.1.6 Univariate Analyses

The univariate analysis identified seven variables that affected the hemoglobin thresholds: the age of the simulated patient, presence of myocardial ischemia, the cardiac index, the number of cardiac cases per individual physician and the hospital ($p<0.001$) (Table 4.6). As illustrated in Tables 4.3 to 4.5, the hemoglobin concentration selected by physicians increased with age of the simulated patient, a declining cardiac index and the presence of myocardial ischemia. As the number of cases per individual physician increased the hemoglobin concentration selected for transfusion decreased. The hemoglobin concentrations selected by physicians also varied by hospital. When the data were sorted according to the hospital where physicians practiced, we found that physicians at seventy percent of hospitals selected hemoglobin concentrations between 60 to 70 g/L for the base case scenario of a 55 year-old female. Physicians at only one hospital had a mean hemoglobin concentration of 80 g/L. Most of the standard deviations for the hospital variable ranged from 5 to 7 reflecting that the hemoglobin thresholds selected varied according to the hospital. The physician specialty, sex, age, academic affiliation, and years of practice did not affect the hemoglobin thresholds selected by physicians.

The subgroup analyses for anesthesiologists and cardiac surgeons also identified the same patient-related factors affecting transfusion thresholds (i.e. age of the patient, cardiac index and myocardial ischemia) ($p<0.0001$) (Appendix IV). The subgroup analyses for anesthesiologists, but not cardiac surgeons, demonstrated that preoperative involvement in transfusion decisions affected the transfusion threshold for both female and male case scenarios ($p=0.02$) (Appendix IV). If physicians were involved with preoperative transfusion decisions, they selected lower hemoglobin thresholds for transfusion.

Figure 4.6 Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55-year old woman in the intraoperative setting.

Characteristic	T value	Degrees of Freedom	p-value
Characteristics of the Simulated Patient:			
Sex	0.52	335	0.60
Age	14.01	334	<0.0001
Cardiac index (>2.5 vs. 2-2.5)	8.93	337	<0.0001
Cardiac index (>2.5 vs. <2)	21.07	336	<0.0001
Cardiac index (2-2.5 vs. <2)	19.45	337	<0.0001
Myocardial ischemia	19.51	333	<0.0001
Physicians' Characteristics:			
Specialty	0.69	157	0.49
Sex	1.22	78	0.22
Academic Centre	0.94	44	0.35
Age	0.85	334	0.40
Years in practice	0.97	334	0.33
Cases/physician	2.61	333	0.009
Hospital	F value=3.04	**33/335	<0.001
Involvement in transfusion decisions:			
Preoperatively	1.75	274	0.08
Intraoperatively	1.18	16	0.26
Postoperatively	1.82	238	0.07

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients.

**Degrees of freedom for the numerator/denominator

4.1.7 Repeated Measures Regression Models

The repeated measures regression model is illustrated in Table 4.7. The subgroup analyses for anesthesiologists and cardiac surgeons are illustrated in Appendix IV and only the interaction terms that were statistically significant are displayed. The repeated measures regression model for all physicians showed that with older age, presence of myocardial ischemia and lower cardiac indices, physicians increased the hemoglobin threshold for transfusion (i.e. chose a higher hemoglobin level at which they would transfuse) (Table 4.7). The repeated measures regression model also identified that the academic affiliation of the physician affected transfusion thresholds, and there was a trend for the number of cardiac cases to affect transfusion thresholds ($p=0.08$) (Table 4.7). Physicians working in an academic institution selected lower hemoglobin thresholds than physicians in a community setting. Similar results were found for the repeated measures regression model only including anesthesiologists ($p=0.06$ for academic affiliation and $p=0.08$ for the number of cases per physician) (Appendix IV). Three interaction terms were significant for the subgroup analyses for anesthesiologists, age and cardiac index, age and myocardial ischemia, and myocardial ischemia and cardiac index ($p<0.01$) (Appendix IV). The parameter estimates for the interaction terms were small except for age and myocardial ischemia, and myocardial ischemia and cardiac index less than 2 $L/min/m^2$. With increasing age and the presence of myocardial ischemia and with the presence of myocardial ischemia and a cardiac index less than 2 $L/min/m^2$, physicians increased the hemoglobin threshold for transfusion.

For the subgroup analyses for cardiac surgeons, the same patient-related factors (i.e. age, presence of myocardial ischemia and cardiac index ($p<0.001$)) were associated with the hemoglobin thresholds, but there were no physician related variables that affected transfusion decisions (Appendix IV). The significance of the interaction terms was similar to the subgroup analyses for anesthesiologists in that the parameter estimates for age and myocardial ischemia, and myocardial ischemia and a cardiac index less than 2 $L/min/m^2$ were statistically significant ($p<0.01$).

Table 4.7 Repeated measures regression model for all physicians for the intraoperative case scenarios.

Variable	Parameter Estimate	95% Confidence Interval	p value
Intercept	86.5	77.7-95.4	<0.0001
Characteristics of Simulated Patients:			
Sex (F: M)	0.14	-0.09-0.38	0.25
Age (55 years: 75 years)	-3.13	-3.1- -2.4	<0.0001
Cardiac index: 2-2.5:> 2.5	2.12	1.8-2.4	<0.0001
Cardiac index: >2.5: <2	-7.45	-6.3- -5.3	<0.0001
Cardiac index 2-2.5: <2	-5.33	-4.4- -3.4	<0.0001
Myocardial Ischemia (No: Yes)	-6.8	-4.9- -4.0	<0.0001
Physicians' Characteristics:			
Specialty (A: CV)	-0.28	-2.6-2.0	0.81
Sex (F:M)	1.7	0.6-50.1	0.14
Academic institution (No: Yes)	3.26	0.08-6.4	0.04
Age	0.02	-0.2-0.3	0.80
Years in Practice	-0.008	-0.2-0.2	0.95
Cases/physician	-0.01	-0.02-0.002	0.08
*Preoperative (No: Yes)	-0.10	-1.9-1.7	0.91
*Intraoperative (No: Yes)	-1.62	-5.8-2.5	0.44
*Postoperative (No: Yes)	1.40	-0.7-3.4	0.19

F=female, M=male, A=anesthesiologists, CV=cardiac surgeons, *involvement in transfusion decisions in the preoperative, intraoperative and postoperative settings.

4.1.8 Factors Physicians Identified as Being Most Significant in Transfusion Decisions

When physicians were asked to rank the three most significant factors that influenced their intraoperative transfusion decisions, the most significant factor selected by all physicians and the subgroup analyses for anesthesiologists was myocardial ischemia (Table 4.8). The hemoglobin concentration was selected as the second most significant factor, and the third most significant factors was blood loss. When the scores were summed for cardiac surgeons, blood loss was the most common factor selected affecting transfusion decisions, followed by myocardial ischemia and the hemoglobin concentration. Other factors that ranked highly were the mixed venous oxygen saturation and the cardiac index.

Factors listed in the "Other" category that physicians selected as affecting transfusion decisions include low ejection fraction, ongoing bleeding, congestive heart failure, hemodynamic instability, size, weight, mass, hypotension, and a low preoperative hemoglobin concentration. For the heading "Comorbid illness", diabetes, renal disease, and cerebrovascular disease were the most frequently cited conditions affecting transfusion decisions. Other comorbid illnesses cited were pulmonary disease and coronary artery disease.

Table 4.8 The three most significant variables that physicians identified as influencing their decision to transfuse red blood cells intraoperatively.*

Factor	All Physicians	Anesthesiologists	Cardiac Surgeons
Hemoglobin concentration	5	5	4
Age			
Cardiac index	1	2	1
Myocardial ischemia	7	7	5
Sex			
Blood loss	3	3	6
Mixed venous oxygen saturation	2	1	3

*For all physicians, there were 4 missing values for the most significant variable, 3 missing values for the second most significant variable, and 4 missing values for the third most significant variable affecting transfusion decisions.

For anesthesiologists, there were 4 missing values for the most significant variable, 3 missing values for the second most significant variable, and 3 missing values for the third most significant variable affecting transfusion decisions.

For cardiac surgeons, there was 1 missing values for the third most significant variable affecting transfusion decisions.

4.2 Postoperative Case Scenarios

4.2.1 Response Rate

The response rate for the postoperative case scenarios was 60.7% (297/489); 58% (205/353) of all anesthesiologists and 67.6% (92/136) of all cardiac surgeons responded. Responses were received from anesthesiologists from all 32 cardiac centres in Canada and from cardiac surgeons from 30/32 (93.8%) centres. As there was a typographical error in the postoperative case scenarios (please refer to Methods 3.4), we categorized responses to the postoperative case scenarios based on whether the respondents responded to the questionnaire with a typographical error or a questionnaire without the typographical error (Figure 4.3).

A number of respondents were excluded. Six respondents indicated that they were not involved in postoperative transfusions decisions and did not complete the postoperative case scenarios. Three respondents answered only one question in each case scenario. These nine respondents were excluded from the analysis, as we could not determine whether the respondents misinterpreted the questions. Two respondents completed only the demographics portion of the questionnaire and were also excluded. Thus, there were 288 responses that were included in the analysis of the postoperative case scenarios of the 489 eligible respondents (58.9%). Table 4.9 depicts the response rate by province. There was no difference in the non-response rate by sex of the physician or province of practice (Table 4.9).

Figure 4.3 Responses to the postoperative case scenarios.

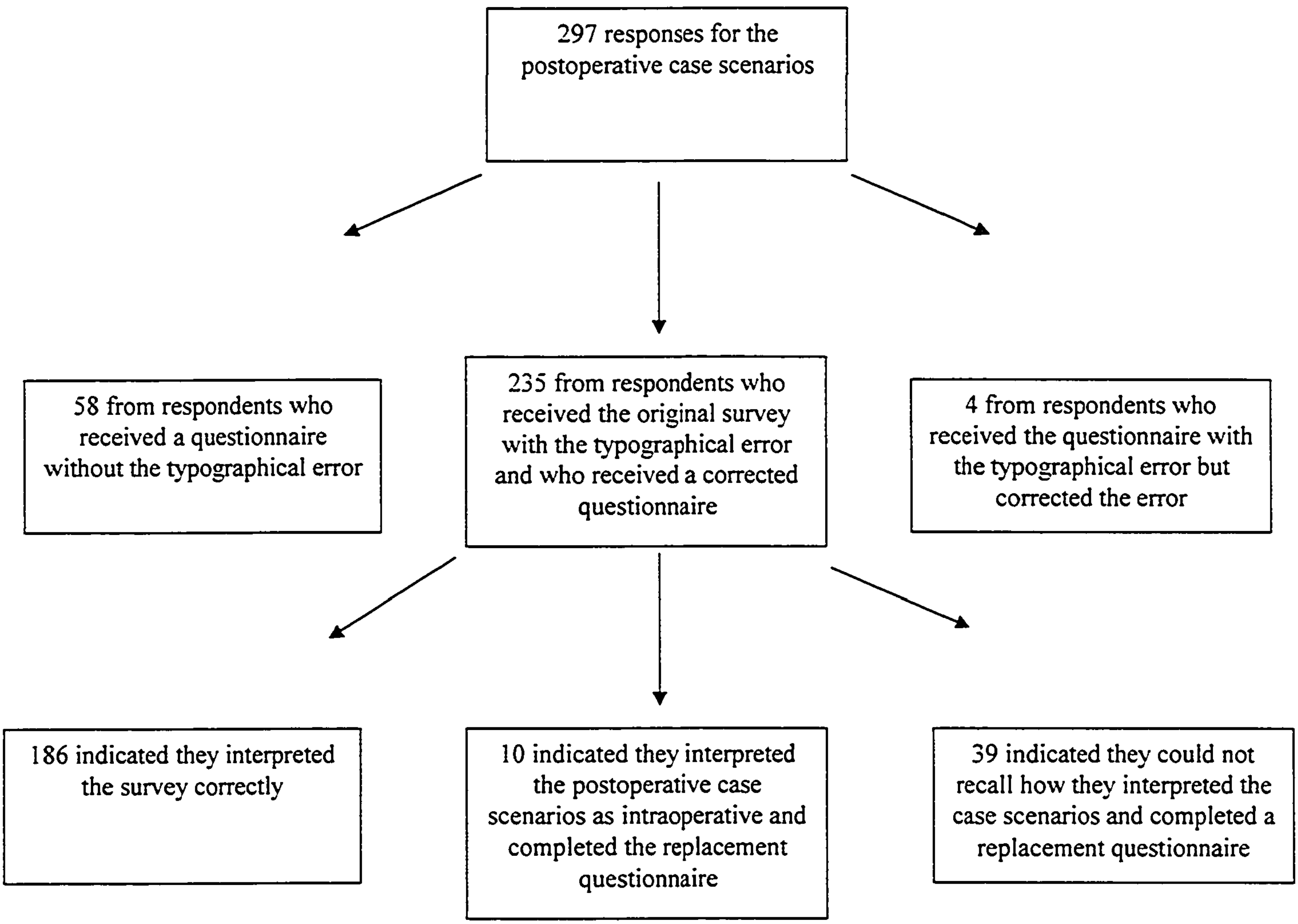


Table 4.9 Response rate by province for the postoperative case scenarios.

Cardiac Centre	Proportion responded (%)		Proportion Male/Female (%)		Proportion Responded Male/Female (%)	
	A	**C**	**A**	**C**	**A**	**C**
British Columbia	50	56	85/15	94/6	53/33	67/0
Alberta	48	72	90/10	91/9	47/50	80/100
Saskatchewan	89	25	67/33	100/0	100/67	25
Manitoba	72	40	100/0	100/0	82	40
Ontario	65	82	77/23	93/7	58/54	86/33
Quebec	48	62	74/26	95/5	47/54	60/100
New Brunswick	75	100	75/25	100/0	100/0	100
Nova Scotia	64	78	91/9	100/0	70/0	78
Newfoundland	50	67	93/7	100/0	46/100	67

A=anesthesiologists, C=cardiac surgeons

4.2.2 The Study Group

Table 4.10 depicts the characteristics of the study group for the postoperative case scenarios. Similar to the population who answered the intraoperative case scenarios, physicians were mostly male, belonged to an academic centre and were involved in transfusion decisions in the preoperative, intraoperative and postoperative settings.

Table 4.10 Characteristics of physicians for the postoperative case scenarios

Characteristic	All Physicians (n=288)	Anesthesiologists (n=198)	Cardiac Surgeons (n=90)
Median age (yrs)(IQR)	47 (40,52)	46(39,52)	48((40,53)
Male sex (%)	249 (86)	163(82)	86 (96)
Academic Centre (yes) (%)	257(90)	179 (90)	78(88)
Median years in practice(IQR)	14 (6,20)	13 (6,20)	14 (7,20)
Preoperative transfusion decisions (%)	170 (59)	101(51)	69(78)
Intraoperative Transfusion Decisions (%)	269(94)	196(99.5)	73(82)
Postoperative Transfusion Decisions (%)	188(66)	105(53)	83(93)
Median Cases/physician (IQR)	100(65,160)	190 (150,200)	80(50,110)
Median cases/centre (IQR)	858(600,1200)	1000(700,1200)	800(600,1200)

Yrs=years, IQR=interquartile range, M=male, F=female.

4.2.3 The Hemoglobin Thresholds

Sixty percent of physicians selected a hemoglobin concentration of 70 g/L as the hemoglobin at which they would transfuse patients described in the baseline scenario of the 55-year old patient having primary elective coronary artery bypass surgery. The baseline scenario stipulated that there were no comorbid illnesses and the patient was described as being euvolemic, with a heart rate of 90, blood pressure of 110/70 and mixed venous oxygen saturation of 70% (Figure 4.4). The mean hemoglobin thresholds (i.e. the hemoglobin concentration which physicians selected to transfuse the simulated patient) for the male and female 55-year old base case scenarios were similar

(Table 4.11) and did not differ between anesthesiologists and cardiac surgeons (Table 4.12). The mean hemoglobin thresholds increased with decreasing cardiac index (a hemoglobin concentration of 72 g/L for a cardiac index greater than 2.5 L/min/m^2 compared to a hemoglobin concentration of 80 g/L with a cardiac index less than 2L/min/m^2) and the presence of myocardial ischemia (a hemoglobin concentration of 72 g/L without myocardial ischemia compared to a hemoglobin concentration of 80 g/L with myocardial ischemia), similar to the results for the intraoperative case scenarios (Table 4.11). For the 75-year old case scenarios, the mean hemoglobin thresholds were higher than for the 55-year old scenarios (Tables 4.12 and 4.13) and the mean hemoglobin concentrations increased with decreasing cardiac index, and the presence of myocardial ischemia (Table 4.13). Additionally, the subgroup analyses for cardiac surgeons and anesthesiologists were similar to the analysis for all physicians (Table 4.12). Approximately 87% of physicians selected a hemoglobin concentration of 70 g/L or 80 g/L for the 75-year old case scenarios (Figure 4.5). Compared to the intraoperative case scenarios, more physicians selected a hemoglobin concentration of 80 g/L to transfuse a 55-year old patient for the postoperative case scenarios (approximately 25% for the postoperative case scenarios compared to 17% for the intraoperative case scenarios). Additionally, the mean hemoglobin concentrations were higher for the postoperative case scenarios compared to the intraoperative case scenarios (Tables 4.3 to 4.5 and 4.11 to 4.17).

Figure 4.4 The hemoglobin thresholds for the base case scenario, 55-year old woman in the postoperative setting.

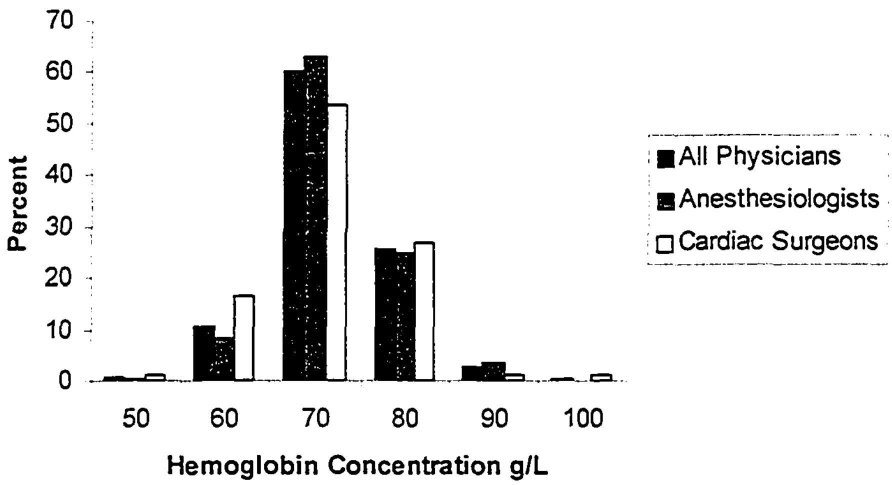


Table 4.11 The mean hemoglobin concentrations for the 55-year old patient according to cardiac index and presence of myocardial ischemia for the postoperative case scenarios.

Variable	Mean Hemoglobin Concentration (SD)(g/L) for the 55-year old female	Mean Hemoglobin Concentration for the (SD) (g/L) 55-year old male
Cardiac index >2.5	72.0(7.0)	71.8(7.0)
Cardiac index 2-2.5	74.3(7.7)	73.9(7.5)
Cardiac index <2	80.4(9.2)	80.1(9.1)
MI and Cardiac index >2.5	80.8(9.3)	80.4(9.2)
MI and Cardiac index 2-2.5	82.5(9.3)	82.4(9.3)
MI and Cardiac index <2	87.1(9.4)	86.8(9.4)

SD=standard deviation, MI=myocardial ischemia

Table 4.12 Mean hemoglobin thresholds* for the postoperative base case scenarios.

Case Scenario	Mean Hemoglobin Concentration (SD) (g/L)		
	All	**Anesthesiologists**	**Cardiac Surgeons**
55 year old female	71.9(7.0)	72.2(6.6)	71.3(7.9)
55 year old male	71.8(6.9)	72.1(6.6)	71.2(7.8)
75 year old female	75.7(7.2)	76.0(7.0)	75.2(7.7)
75 year old male	75.5(7.0)	75.8(6.9)	74.8(7.2)

SD=standard deviation

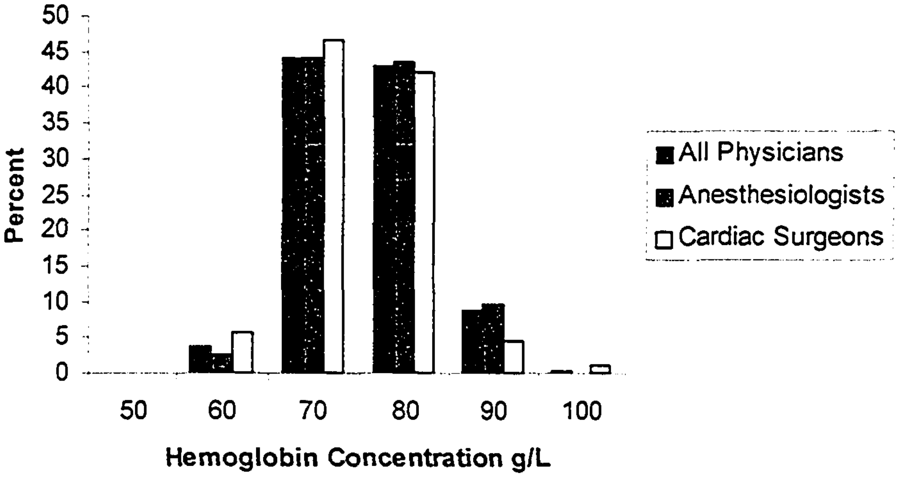
*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients.

Table 4.13 The mean hemoglobin concentrations for the 75-year old patient according to cardiac index and presence of myocardial ischemia for the postoperative case scenarios.

Variable	Mean Hemoglobin Concentration (SD)(g/L) for the 75-year old female	Mean Hemoglobin Concentration for the (SD) (g/L) 75-year old male
Cardiac index >2.5	75.7(7.1)	75.5(7.1)
Cardiac index 2-2.5	77.8(8.2)	77.5(8.0)
Cardiac index <2	83.8(9.4)	83.3(9.5)
MI and Cardiac index >2.5	83.3(9.2)	83.0(9.3)
MI and Cardiac index 2-2.5	85.1(9.1)	84.8(9.2)
MI and Cardiac index <2	88.8(8.9)	88.6(9.1)

SD=standard deviation, MI=myocardial ischemia

Figure 4.5 The hemoglobin thresholds for the base case scenario, 75-year old woman in the postoperative setting.



4.2.4 Univariate Analyses

The univariate analyses identified the same seven variables that affected the hemoglobin thresholds in the intraoperative case scenario: the age of the simulated patient, presence of myocardial ischemia, the cardiac index, the hospital and the number of cardiac cases per individual physician (Tables 4.14). Tables 4.11 to 4.13 illustrate that with increasing age, a declining cardiac index and the presence of myocardial ischemia, the hemoglobin thresholds detected increased. In contrast to the intraoperative case scenarios where the mean hemoglobin concentration selected by 70% of hospitals ranged between 60 to 70 g/L, 70% of hospitals for the postoperative case scenarios selected a hemoglobin concentration between 70 g/L to 80 g/L. Only three hospitals selected a hemoglobin concentration of approximately 65 g/L for the postoperative base case scenario. The standard deviations were also narrow indicating that hemoglobin thresholds selected by physicians vary by the hospital where they practice. The physician specialty, sex, age, academic affiliation, and years of practice did not affect the hemoglobin thresholds selected by physicians.

The subgroup analyses for anesthesiologists and cardiac surgeons also identified the same patient-related factors affecting transfusion thresholds (i.e. age of the patient, cardiac index and myocardial ischemia (Appendix V)). The subgroup analysis for anesthesiologists (Appendix IV) demonstrated that involvement in preoperative and postoperative transfusion decisions affected hemoglobin thresholds for the female and male base case scenarios ($p<0.05$), whereas the subgroup analysis for cardiac surgeons demonstrated that the number of cardiac cases per surgeon affected transfusion thresholds ($p<0.05$)(Appendix IV). The associations were similar as for the intraoperative case scenarios in that with involvement in preoperative and postoperative transfusion decisions and increasing cases per surgeon, the hemoglobin threshold decreased.

Table 4.14 Univariate analysis of the variables affecting the hemoglobin threshold[*] for the base case scenario, 55-year old woman in the postoperative setting.

Characteristic	T value	Degrees of Freedom	p value
Characteristics of Simulated Patient:			
Sex	0.89	286	0.37
Age	12.10	286	<0.0001
Cardiac index (>2.5: 2-2.5)	8.68	286	<0.0001
Cardiac index (>2.5: <2)	19.10	286	<0.0001
Cardiac index (2-2.5: <2)	16.79	286	<0.0001
Myocardial ischemia	20.25	283	<0.0001
Physicians' Characteristics:			
Specialty	0.97	147	0.33
Sex	0.51	64.7	0.61
Academic Centre	1.28	35	0.20
Age	1.23	284	0.21
Years in practice	1.34	284	0.18
Cases/physician	94.78	283	0.01
Hospital	F value=3.18	**33/286	<0.0001
Involvement in transfusion decisions :			
Preoperatively	2.71	266	0.007
Intraoperatively	1.31	20	0.20
Postoperatively	2.48	200	0.01

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients.

**Degrees of freedom for the numerator/denominator.

4.2.5 Repeated Measures Regression Models

The repeated measures regression models are illustrated in Tables 4.15 and Appendix V for the subgroup analyses. Only the interaction terms that were statistically significant are displayed. The repeated regression models for all physicians and for the subgroup analyses for patient related factors demonstrated similar results as for the intraoperative case scenarios (Tables 4.15 and Appendix V); with older age, presence of myocardial ischemia and lower cardiac indices, physicians increased the hemoglobin threshold for transfusion (i.e. chose a higher hemoglobin level at which they would transfuse). The three regression models demonstrated statistically significant interactions between age of the patient and presence of myocardial ischemia, and presence of myocardial ischemia and cardiac index less than 2 L/min/m^2. The analysis of all patients and the subgroup analysis of anesthesiologists also showed that the interaction of cardiac index less than 2 L/min/m^2 compared to a cardiac index greater than 2.5 L/min/m^2 and age affected transfusion thresholds significantly ($p<0.0001$)(Tables 4.15 and Appendix V). With increasing age and the presence of myocardial ischemia, and with the presence of myocardial ischemia and lower cardiac indices, physicians selected higher transfusion thresholds. The repeated measures regression model also identified involvement in postoperative transfusion decisions as affecting transfusion thresholds for all physicians ($p=0.01$) and for the subgroup analysis for anesthesiologists ($p=0.03$), with physicians involved in postoperative transfusion decisions selecting lower hemoglobin thresholds for transfusion (Tables 4.15 and Appendix IV). In the intraoperative case scenarios, involvement in postoperative transfusion decisions did not affect transfusion thresholds (Tables 4.7 and Appendix IV). Academic affiliation did not impact transfusion thresholds for the postoperative case scenarios ($p=0.10$) (Tables 4.15 and Appendix IV).

Table 4.15 Repeated measures regression model for the postoperative scenarios for all physicians.

Variable	Parameter Estimate	95% Confidence Interval	p value
Intercept	84.8	76.2-93.4	<0.0001
Characteristics of Simulated Patients:			
Sex (F: M)	0.25	-0.2-0.7	0.32
Age (55 years: 75 years)	-1.93	-2.4—1.4	<0.0001
Cardiac index: 2-2.5: > 2.5	1.73	1.1-2.3	<0.0001
Cardiac index: >2.5: <2	-5.61	-5.9--4.8	<0.0001
Cardiac index: 2-2.5: <2	-3.87	-4.5—3.3	<0.0001
MI (No: Yes)	-5.4	-5.9--4.8	<0.0001
Age and MI (No: Yes)	-1.21	-1.7—0.7	<0.0001
Age and Cardiac Index:>2.5: <2	-0.65	-1.2--0.04	0.04
MI and Cardiac Index: >2.5: <2	-2.22	-2.8--1.6	<0.0001
MI and Cardiac Index: 2-2.5: <2	-1.94	-2.5—1.3	<0.0001
Physicians' Characteristics			
Specialty (A: CV)	0.09	-2.0 -2.1	0.92
Sex (F: M)	20.2	-6.2-46.7	0.13
Academic institution (No: Yes)	2.5	-2.0-2.1	0.10
Age	0.08	-0.1-0.3	0.45
Years in Practice	-0.05	-0.3-0.2	0.65
Cases/physician	-0.007	-0.02--0.004	0.22
*Preoperative (No: Yes)	-0.06	-1.8-1.6	0.94
*Intraoperative (No: Yes)	2.4	-1.1-5.9	0.17
*Postoperative (No: Yes)	2.7	0.7-4.7	0.01
Years in Practice and Sex	0.73	-0.01-1.5	0.05

F=female, M=male, A=anesthesiologists, CV=cardiac surgeons, MI= myocardial ischemia.

* involvement in transfusion decisions in the preoperative, intraoperative and postoperative settings.

4.2.6 Factors Physicians Identified as Being Most Significant in Transfusion Decisions

The summations of the three most significant factors that physicians were asked to rank are illustrated in Table 4.16. Myocardial ischemia was selected as the most important factor in guiding transfusion decisions for all physicians and the subgroup analysis of anesthesiologists similar to the most significant factor chosen intraoperatively (Table 4.16). The most significant factor for cardiac surgeons was the hemoglobin concentration whereas blood loss was the most significant factor chosen intraoperatively. Blood loss was the second most significant factor for all physicians and the subgroup analysis of cardiac surgeons, and the hemoglobin concentration was ranked second for anesthesiologists. The third most important factor differed for the analysis of physicians and the subgroup analyses, in that the third most significant factor selected was the hemoglobin concentration for all physicians, blood loss for anesthesiologists and age and myocardial ischemia for cardiac surgeons. The mixed venous oxygen saturation was also one of the higher ranked variables affecting transfusion decisions. These results coincide with the intraoperative case scenarios in that the same factors were ranked highly, i.e. myocardial ischemia, the hemoglobin concentration and blood loss.

Characteristics affecting transfusion decisions listed in the "Others" category included weight, ongoing bleeding, volume status, hemodynamic instability, and hemoglobinopathies. Renal dysfunction was the most commonly cited comorbid condition that affected transfusion decisions. Other comorbid illnesses that physicians cited as affecting transfusion decisions included congestive heart failure, liver disease, cerebrovascular disease, and success of the bypass procedure, peripheral vascular disease, debility, ischemic organ injury, sex, obesity and vasculopathy.

Table 4.16 The three most significant variables that physicians identified as influencing their decision to transfuse red blood cells postoperatively.*

Factor	All Physicians	Anesthesiologists	Cardiac Surgeons
Hemoglobin concentration	3	5	6
Age			4
Cardiac index	2		3
Myocardial ischemia	7	7	4
Sex			
Blood loss	4	4	5
Mixed venous oxygen saturation	2	2	1

*For the analysis of all physicians, there were 5 missing values for the most significant variable, 5 missing values for the second most significant variable, and 6 missing values for the third most significant variable affecting transfusion decisions. For the analysis of anesthesiologists, there were 3 missing values for the most significant variable, 3 missing values for the second most significant variable, and 3 missing values for the third most significant variable affecting transfusion decisions. For the analysis of cardiac surgeons, there were 2 missing values for the most significant variable, 2 missing values for the second most significant variable, and 3 missing values for the third most significant variable affecting transfusion decisions.

4.3 Comparison of the Intraoperative and Postoperative Case Scenarios

The mean hemoglobin concentrations were lower for all the intraoperative case scenarios in comparison to the postoperative case scenarios. (The results for the male case scenarios are illustrated in Appendix V.) Table 4.17 illustrates the results of the univariate analysis for intraoperative and postoperative case scenarios for the base case scenario and the scenarios declining cardiac index, with the presence of myocardial ischemia and increasing age. All the differences were statistically significant.

Additionally, there appeared to be a trend in what physicians selected for the intraoperative and postoperative case scenarios (Table 4.18). Physicians who selected low hemoglobin thresholds for the intraoperative case scenarios selected low hemoglobin thresholds for the postoperative case scenarios.

Table 4.17 Results of the univariate analysis of the intraoperative and postoperative case scenarios.

Case Scenario	T-Value	Degrees of Freedom	P-value
55-year old female	6.97	327	<0.0001
55-year old female with a cardiac index <2	6.15	321	<0.0001
55- year old female with myocardial ischemia	3.1	328	0.002
75-year old female	4.42	325	<0.0001

Table 4.18 The mean hemoglobin concentrations selected by physicians for the *55-year old woman* postoperatively as classified by hemoglobin concentrations selected intraoperatively.

Hemoglobin Concentration (g/L) Selected Intraoperatively	Mean Hemoglobin Concentration (SD) (g/L) Selected Postoperatively
50	64.4(11.3)
60	66.3(5.9)
70	71.6(4.1)
80	78.5(4.8)
90	86.0(5.5)
100	95.0(7.1)

SD=standard deviation

4.4 Comparison of Corrected and Uncorrected Questionnaires

For the postoperative case scenarios, we compared the results of the questionnaire with the typographical errors (i.e. referring to the postoperative scenarios as being intraoperative) with the corrected questionnaire (Appendix VI). All analyses demonstrated similar results except for the repeated measures regression analysis where the interaction term years of practice and sex of the physician was statistically significant for the uncorrected questionnaires.

5.0 The Discussion

The decision to transfuse red blood cells to patients having coronary artery bypass surgery is based on many factors. The hemoglobin threshold (the hemoglobin concentration at which to transfuse red blood cells) is the most common transfusion trigger and is modified by various physiological and clinical variables. What hemoglobin threshold is chosen and the variables that modify the threshold are dependent on individual physicians' decisions based on clinical experience, hospital policies and/or reports from the literature. The objectives of this study were: 1. To determine the hemoglobin concentration that physicians select to transfuse coronary artery bypass patients intraoperatively and postoperatively. 2. To determine the factors that are actively being used by physicians to guide transfusion decisions and to determine whether these factors are the same as those that have been reported in the literature to be associated with increased transfusion rates. The ultimate goal is to determine whether the variables identified in this study are appropriate in guiding transfusion decisions and whether transfusion based on these factors impact on patient morbidity and mortality.

5.1. Major Outcomes

5.1.1 The Hemoglobin Threshold

For the scenarios of a 55-year old male or female vignette this study found that the mean hemoglobin transfusion thresholds were 69 g/L for the intraoperative scenarios and 72 g/L for the postoperative scenarios. These values were similar for the analysis including all physicians and in the subgroup analyses for anesthesiologists and cardiac surgeons and the results were statistically significant from each other. The distribution of hemoglobin thresholds differed intraoperatively and postoperatively in that a greater proportion of physicians transfused at a hemoglobin concentration of 60 g/L in the intraoperative compared to the postoperative setting. Intraoperatively 23% of all physicians transfused at a hemoglobin concentration of 60 g/L compared to 11% of all physicians in the postoperative period. In contrast, more physicians selected a hemoglobin concentration of 80 g/L postoperatively, 25%, compared to the intraoperative setting, 18%. Nonetheless, one to four percent of physicians continue to transfuse at hemoglobin concentrations of 90 g/L and 100 g/L perioperatively. Thus, the hemoglobin concentrations selected for the intraoperative case scenarios were lower, but there are individuals who transfuse at higher hemoglobin concentrations.

The lower hemoglobin thresholds for the intraoperative versus the postoperative period that were noted in this study are largely consistent with prior reports that describe transfusion policies as part of their studies (Karkouti K *et al*, 2001, Bilfinger V and Conti VR, 1989, Scott BH *et al,* 2003, Isomatsu Y *et al*, 2001, Litmathe J *et al*, 2003). The rationale for the lower hemoglobin threshold intraoperatively is that during surgery, while patients are on cardiopulmonary bypass, oxygen requirements are reduced.

The mean hemoglobin threshold identified for the intraoperative period in this study are also consistent with prior studies. The published mean hemoglobin thresholds in cohort studies for the intraoperative period range from 60 g/L to 67 g/L (Karkouti K *et al*, 2001, Bilfinger V and Conti VR, 1989, Scott BH *et al,* 2003, Isomatsu Y *et al*, 2001, Litmathe J *et al*, 2003). The mean hemoglobin concentrations for the postoperative period in this study were lower than the hemoglobin concentration described in previous publications. Cohort studies assessing factors associated with increased transfusion rates in patients having coronary artery bypass surgery describe a hemoglobin threshold of approximately 80 g/L for the postoperative period (Bracey AW *et al*, 1995, Karkouti K *et al*, 2001, Bilfinger V and Conti VR, 1989, Scott BH *et al*, 2003, Isomatsu Y *et al*, 2001, Litmathe J *et al*, 2003). Surveys based on case scenarios of hemoglobin thresholds for transfusion for critically ill patients (patients who have had coronary artery bypass surgery are often included in studies of critically ill patients) demonstrated that physicians selected hemoglobin concentrations of 80 g/L to 100 g/L (Hebert PC *et al*, 1998, Boralessa H *et al*, 2002). Only one study (Hebert PC *et al*, 2005) reported that more physicians were adopting a hemoglobin threshold of 70 g/L in critically ill patients. The lower hemoglobin threshold for the postoperative period selected by physicians in this study may be explained by a social desirability bias in our study, in that respondents may have responded based on how they think others would have wanted them to respond (Bowling A, 2000). This is because the study of transfusion triggers in critical care showed that there was no difference in mortality in patients transfused at a hemoglobin concentration of 70 g/L compared to a hemoglobin concentration of 100 g/L (Hebert PC *et al*, 1999). The result may also be secondary to the Hawthorne effect, where physicians provided responses that differ from their actual practice because they were being "tested" (Bowling A, 2000). Alternatively, physicians may be using lower hemoglobin thresholds as a result of the study by Hebert and colleagues (Hebert PC *et al*, 1999, Hebert PC *et al*, 2001) that demonstrated that a hemoglobin transfusion threshold of 70 g/L does not result in increased morbidity and mortality compared to a hemoglobin transfusion threshold of 100 g/L.

5.1.2 Variables Affecting Hemoglobin Concentrations in the Vignettes

The variables in the vignettes that affect the hemoglobin concentrations selected for transfusion are consistent with reports of factors that are associated with increase transfusion rates. The analyses of the vignettes demonstrated that the mean hemoglobin concentrations selected for transfusions increased with the presence of myocardial ischemia, with decreasing cardiac index, and with increase in the patient's age. The effect of these variables on the hemoglobin concentration was statistically significant. These are similar to reports of the factors associated with increased transfusion rates both in cohort studies and in questionnaires (Hebert PC *et al*, 2005 Hebert PC *et al*, 2005, Rao SV *et al*, 2004, Vincent JL *et al*, 2002, Mathoulin-Pelissier S *et al*, 2000, Friedman BA *et al*, 1979, Lithmathe J *et al*, 2003, Magovern JA *et al*, 1996 Scott BH *et al*, 2003, Covin R *et al*, 2003, Karkouti K *et al*, 2001, Isomatsu Y *et al*, 2001, Surgenor DM *et al*, 1996 Cosgrove DM *et al*, 1989, Bilfinger V Conti R, 1989,Hebert PC *et al*, 1998, Boralessa H *et al*, 2002, Brown RL *et al*, 1992).

This study described significant changes in hemoglobin concentrations selected for transfusion, ranging from 5 g/L to 10 g/L, when the variables myocardial ischemia, cardiac index and age were added to the case scenarios. The presence of myocardial ischemia and a cardiac index less than 2 L/min/m^2 resulted in the greatest increment in the hemoglobin threshold. With the addition of myocardial ischemia, and when the cardiac index decreased from a normal value of 2.5 L/min/m^2 to less than 2L/min/m^2, the hemoglobin transfusion threshold increased by approximately 10 g/L. When the age in the case scenarios increased from 55 to 75 years, the hemoglobin transfusion threshold increased approximately 5 g/L. The absolute changes in hemoglobin concentrations selected for transfusion that are associated with each factor have not been described in prior published reports, and need to be confirmed.

Sex was not found to be a significant factor that affected hemoglobin thresholds. Contrary to this finding, several studies assessing transfusion rates in patients having coronary artery bypass surgery have shown that female patients do have higher transfusion rates (Friedman BA *et al*, 1979, Rao SV *et al*, 2004 Shevde K *et al*, 2000, Lithmathe J *et al*, 2003, Scott BH *et al*, 2003, Covin R *et al*, 2003, Engstrom KG *et al*, 2002, Karkouti K *et al*, 2001, Surgenor DM *et al*, 1998 Surgenor DM *et al* 1996, Magovern JA *et al*, 1996, Cosgrove DM *et al*, 1989, Bilfinger V Conti R, 1989). Some authors suggest that the different rates of transfusion by sex may be due to different blood volumes between men and women, with women having lower blood volumes and hence requiring more transfusions in response to blood loss (Karkouti K *et al*, 2001). However, other investigators found that both sex and blood volume independently affected transfusion rates (Cosgrove DM *et al*, 1985). The fact that this study did not find sex to be a significant factor in affecting the hemoglobin concentration contributes to the literature by suggesting that the increased transfusion rates observed for women may not be attributed to physicians actively selecting different hemoglobin concentrations simply on the basis of the sex of the patient. As this study is a survey, these findings need to be confirmed by exploring actual practices.

5.2 Secondary Outcomes

5.2.1 Interactions of Variables

This study identified a number of significant interactions between variables that have not been previously reported. There were significant interactions between age and myocardial ischemia, cardiac index and myocardial ischemia and age and cardiac index. These interactions were associated with increases of hemoglobin concentrations from 10 g/L to 15 g/L. The significance of these interactions need to be substantiated in other studies but they possibly represent how physicians integrate various factors in their decision-making.

5.2.2 Physician Variables Affecting the Hemoglobin Thresholds

Few physician variables affected the hemoglobin transfusion thresholds in the multivariable model; for the intraoperative case scenarios, only the physicians' academic affiliation, and for the postoperative case scenarios, only the physicians' involvement in postoperative transfusion decisions. Intraoperatively, physicians in academic institutions transfused patients at lower hemoglobin thresholds, and postoperatively, physicians who were involved with transfusion decisions transfused patients at lower hemoglobin thresholds. Prior reports have shown that physicians in an academic institution selected higher transfusion thresholds (Hebert PC *et al,* 1998) or had higher transfusion rates (Vincent JL *et al*, 2002). The difference between our results and previous reports may be secondary to the physician population sampled, in that this study focused on anesthesiologists and cardiac surgeons whereas the previous studies assessed critical care physicians (Hebert PC *et al,* 1998, Vincent JL *et al*, 2002). The difference may also be due to the fact that surveys such as the one used in the study reflect attitudes of physicians compared to studies addressing actual clinical practice (Vincent JL *et al*, 2002). The age, sex, specialty and experience of physicians did not affect hemoglobin thresholds selected, although the specialty of the physician and experience of the physicians have been shown to affect transfusion decisions in other studies (Matot I *et al*, 2003, Brown RL *et al*, 1992, Salem Schatz *et al*, 1990). Involvement in postoperative transfusion decisions affecting the hemoglobin concentrations has not been previously described.

The only variable that affected both intraoperative and postoperative case scenarios was the hospital. The mean hemoglobin concentration used at each hospital ranged from 60 to 80 g/L and was largely consistent within that hospital. Previous cohort studies have described that transfusion rates are associated with the hospital where the surgery was conducted (Surgeoner DM *et al*, 1998, Stover EP *et al*, 1998). The association between the hospital and hemoglobin thresholds may be due to hospital policies regarding transfusions.

5.2.3 Factors Identified by Physicians As Influencing Transfusion Decisions

When physicians were asked to select the three most important factors that affected their intraoperative transfusion decisions, myocardial ischemia, the hemoglobin concentration, and blood loss were the most frequently selected factors. All physicians combined and anesthesiologists identified myocardial ischemia as the most important factor while cardiac surgeons identified blood loss as the most significant factor.

For the postoperative case scenarios, the three most important factors that affected their transfusion decisions were the same as for the intraoperative case scenarios except for cardiac surgeons. Myocardial ischemia was selected by all physicians combined and anesthesiologists as the most important factor whereas cardiac surgeons identified the hemoglobin concentration as the most important factor.

Considering all case scenarios, other highly ranked factors that were identified as impacting on transfusion decisions were the cardiac index (intraoperative and postoperative), the mixed venous oxygen saturation (intraoperative and postoperative), and age (postoperative only).

This is the first survey that asked physicians to rank the important factors that influenced their transfusion decisions so there are no direct published results to compare. Compared with reports addressing factors affecting transfusion rates and surveys on transfusions, our results are comparable. Myocardial ischemia, blood loss, the hemoglobin concentration and cardiac function have been shown to be associated with increased transfusion rates in cohort studies (Lithmathe J *et al*, 2003, Magovern JA *et al*, 1996 Scott BH *et al*, 2003, Covin R *et al*, 2003, Karkouti K *et al*, 2001, Isomatsu Y *et al*, 2001, Surgenor DM *et al* 1996 Cosgrove DM *et al*, 1989, Bilfinger V Conti R, 1989) and in previous transfusion surveys, (Nuttal GA *et al*, 2003, Stehling LC *et al*, 1987, Salem-Schatz SR *et al*, 1990, Brown RL *et al*, 1992, Hebert PC *et al*, 1998, Boralessa H *et al*, 2002). These results are also in agreement with the findings based in the vignettes that the presence of myocardial ischemia is a factor that significantly influences transfusion decision-making.

Several comorbidities were listed by respondents as important factors that affected transfusion decisions. However, comorbidities were not ranked as highly as the other variables described above. The presence of renal insufficiency, diabetes, cerebrovascular disease and congestive heart failure were often included as factors affecting transfusion rates. Other factors that were included are weight, and hemodynamic instability. Renal insufficiency, diabetes, congestive heart failure, weight, and hemodynamic instability have all been described to be associated with increased transfusion rates in previous studies (Lithmathe J *et al*, 2003 Scott BH *et al*, 2003 Covin R *et al*, 2003 Karkouti K *et al*, 2001 Magovern JA, *et al*, 1996 Bracey AW *et al*, 1995 Bilfinger V *et al*, 1989 Cosgrove DM, *et al*, 1989).

5.2.4 Subgroup Analyses

The results of the subgroup analyses for anesthesiologists and cardiac surgeons were not considerably different, unlike a previous survey demonstrating that the specialty of physicians affects transfusion rates (Brown RL *et al*, 1992). The same patient associated factors and interaction of factors in the vignettes were found to affect the hemoglobin thresholds for anesthesiologists and cardiac surgeons for the postoperative and intraoperative case scenarios. Although, based on the vignettes, anesthesiologists and cardiac surgeons incorporated similar factors into their transfusion decisions, there were some differences that arose when they were asked to identify the most significant factors affecting their transfusion decisions. Cardiac surgeons identified blood loss and the hemoglobin concentration as significant factors more often than anesthesiologists, and anesthesiologists identified myocardial ischemia as a significant factor more often than cardiac surgeons. This difference between cardiac surgeons and anesthesiologists in the important factors that affect transfusion decisions has not been previously described. A possible explanation is that cardiac surgeons may base transfusion decisions based on blood loss as they may focus more on blood loss in a surgical field whereas anesthesiologists are monitoring tissue oxygenation and physiological parameters such as myocardial ischemia.

5.3 Limitations

There are several limitations associated with the questionnaire used in this study. There are general limitations that are associated with all questionnaire designs and specific limitations associated with the questionnaire used in this study. General limitations associated with all questionnaire designs include sampling bias (the sample is not representative of the population), measurement error (inaccurate answers due to poor questionnaire construction), and non-response error (the characteristics of non-responders differ from responders potentially limiting the conclusions of the study) (Dillman DA, 2000). Additionally responses to questionnaires may not correlate well with actual clinical practice. Specific limitations to the questionnaire used in this study relate to the descriptions of the case scenarios.

Sampling bias was reduced by sampling all anesthesiologists and cardiac surgeons involved in coronary bypass surgery in Canada. However, the population that was sampled did not include all the physicians that are involved in making postoperative transfusion decisions for coronary bypass surgery patients. Other specialists who practice in intensive care units, such as general internists and respirologists, were not included in the survey. The study group was limited to anesthesiologists and cardiac surgeons because it would have been extremely difficult to track all other specialists that provide intensive care to patients that undergo coronary bypass surgery, and the focus of this study was specifically on transfusions in the perioperative period. Only anesthesiologists and cardiac surgeons are involved in transfusion decisions both intraoperatively and postoperatively. The study group, however, was representative of all the centres in Canada that conduct coronary artery bypass surgery, as responses were received from anesthesiologists from all cardiac centers and from cardiac surgeons from 30/32 centers.

We extensively pre-tested the questionnaire to try to reduce measurement error. However, due to the typographical error that occurred with the first mailing of the questionnaire, measurement error was introduced. We tried to reduce this potential measurement error by re-sending a corrected questionnaire to those who responded to the original version of the survey. Analyses based on responses from persons who answered the corrected questionnaire were essentially the same compared to the analyses based on responses from persons who answered the questionnaire with the typographical error, suggesting that this was not a significant source of measurement error.

We attempted to reduce non-response error by using established methods for increasing response rates (Dillman D, 2000, Edwards P, *et al* 2002). These included five techniques to enhance response rates: a respondent friendly questionnaire, personalization (i.e. real stationary, real names instead of Dear Sir/Madam, and real signatures), stamped self-addressed envelopes, a token pre-paid financial incentive not conditional on response, five contacts with each subject, and the use of coloured ink (Dillman D, 2000, Edwards P *et al,* 2002). The result was a response rate of 70.6% for the intraoperative case scenarios and 60.7% for the postoperative case scenarios. In addition, there were no significant differences between respondents and non-respondents with respect to their sex or province of origin.

Although this study has external validity because responses were received from anesthesiologists from all cardiac centres and from cardiac surgeons in 30/32 cardiac centres in Canada, our results may not be generalizable to French speaking physicians. We did not translate the questionnaire into French, so there may have been some French-speaking physicians who did not complete the survey because of this.

There are concerns that use of a questionnaire methodology with simulated cases may lack criterion validity. There have been some reports that results from questionnaires do not correlate with actual behaviour. (Page GP, Fielding DW, 1980, Hartley RM, 1985, Jones V, 1990, Morrell DC, Roland MO, 1990, Eccles *et al*, 1999), and that responses to simulated vignettes may over-estimate actual performance (Sandvik H, 1995, Rethans JJE van Boven CPA, 1987). Differences in responses to case simulations compared to real patients can be due to poor questionnaire design (Hartley RM, 1985). To improve the criterion validity of a questionnaire, questionnaires can be constructed to simulate patient encounters so that the questionnaire corresponds to the behaviour of interest (Jones V, 1990). We attempted to develop vignettes that simulate real patients and pilot tested them to ensure that they seemed relevant to physicians. We also ensured that our questionnaire was valid because the variables selected for the case scenarios were chosen from several studies that described an association between the variables selected and transfusion rates. In addition, the questionnaire was extensively pre-tested, and modifications were made based on pre-testing.

Ideally, the criterion validity of the questionnaire should be assessed, i.e. the responses of the questionnaire should be compared with actual clinical transfusion decisions based on data abstraction from clinical records or clinical databases or based on the use of standardized patients (gold standard). It would have been difficult to correlate results from this study with retrospective data about transfusion decisions. This is because intraoperatively it would be difficult to determine whether the anesthesiologist or the cardiac surgeon was responsible for the transfusion. It would be also difficult to determine what was used as the trigger for transfusion. Postoperatively, resident physicians, or intensive care physicians who are not anesthesiologists or cardiac surgeons may be responsible for transfusions. It is also not well documented in medical charts why a transfusion is administered (e.g. because of blood loss, a low hematocrit, etc.). In addition, using standardized patients is not feasible for coronary artery bypass surgery.

The vignettes we developed did not include comorbidities. Since the presence of comorbidities can affect transfusion decisions, we designed the vignettes to reflect a patient without comorbidities to ensure that transfusion decisions would be based on the factors that we were varying in the questionnaire and not on the presence of comorbidities (Covin R *et al*, 2003, Brown RL *et al*, 1992, Surgenor DM *et al*, 1996). Although the exclusion of comorbidities likely enhanced the internal validity of the study, it may have reduced the external validity, as we cannot generalize our results to the large proportion of coronary artery bypass surgery patients that have comorbidities.

The sample size of this study may have limited our ability to detect differences in transfusion decisions for the subgroup analyses. Although we sampled all physicians involved in coronary artery bypass surgery in Canada, and our response rate was high, the sample size for cardiac surgeons was 102 for the intraoperative case scenarios and 92 for the postoperative case scenarios. Nonetheless, the same patient variables that were selected by all physicians as affecting the hemoglobin thresholds for the case scenarios, i.e. myocardial ischemia, cardiac index and age were also found to affect the hemoglobin thresholds selected by cardiac surgeons.

Lastly, the intraoperative vignettes did not specify whether the patient was on cardiopulmonary bypass. There may be two hemoglobin thresholds for the intraoperative period, one threshold that applies during cardiopulmonary bypass (when the heart is arrested with cardioplegia and there is a lower metabolic rate), and one threshold that applies when the patient is off of cardiopulmonary bypass. Since the case scenarios described patients with heart rates and blood pressures, and a heart rate and blood pressure are not detected while a patient is on cardiopulmonary bypass, it was assumed that the respondent would interpret the simulated patient as not being on cardiopulmonary bypass.

5.4 Relevance

The hemoglobin thresholds that physicians selected for the intraoperative and postoperative case scenarios and the factors that increased the hemoglobin thresholds can potentially impact on patient morbidity and mortality and red blood cell utilization if the attitudes in this survey reflect actual practice. Based on various factors, the hemoglobin transfusion thresholds varied by 10 g/L to 15 g/L. Although this change in hemoglobin threshold reflects what physicians think they do and may not reflect actual practice, this range in hemoglobin concentrations for transfusion represents a considerable difference that could markedly effect utilization and clinical outcomes.

5.4.1 The Impact of a Change in Hemoglobin Threshold on Morbidity and Mortality Based on Cardiac Index, Age, Myocardial Ischemia, and Sex

5.4.1.1 Cardiac Index

The finding in this study of a 10 g/L change in the hemoglobin transfusion threshold when the cardiac index decreased from 2.5 L/min/m^2 to less than 2 L/min/m^2 has important clinical implications since reduced cardiac function is common in patients having coronary artery bypass surgery. Although the cardiac index is a measure of cardiac function, cardiac index is not routinely used to describe cardiac function in reports of patients having coronary artery bypass surgery. Left ventricular dysfunction and congestive heart failure are often the descriptor used to characterize patients with a low cardiac index. To appreciate the significance of optimizing hemoglobin thresholds in patients with a depressed cardiac index having coronary artery bypass surgery, it is necessary to be aware of the importance of left ventricular dysfunction in patients having cardiac bypass surgery and the importance of anemia in patients with left ventricular dysfunction.

Congestive heart failure is the most common morbidity after coronary artery bypass surgery (Geraci JM *et al*, 1993) and is associated with a high mortality. In one study, 65% of deaths in patients following coronary artery bypass surgery were attributed to heart failure (O'Connor GT *et al*, 1998). Additionally, congestive heart failure increases with age (O'Connor CM *et al*, 1997), and age is a predictor of death from heart failure following coronary artery bypass surgery (70 to 79 years of age compared to younger patients, odds ratio 1.53 (95% confidence interval, 1.16 to 2.02); older than 80 years of age, odds ratio 2.74 (95% confidence interval 1.64 to 4.56) (Surgenor SD *et al*, 2001). As more cardiac bypass procedures are performed on elderly individuals (Zaidi AM *et al*, 1999, Kumar P *et al*, 1999, Peterson ED *et al*, 1995, Wenger NK *et al*, 1988), congestive heart failure is a significant morbidity in cardiac bypass patients.

Anemia is common in patients with heart failure (Ezekowitz JA *et al*, 2003, Kosiborod M *et al*, 2003). Anemia has been demonstrated to occur in 17% to 37% of patients with heart failure (Ezekowitz JA *et al*, 2003, Kosiborod M *et al*, 2003) and has been shown to be associated with an increased mortality in these patients (Felker GM *et al*, 2003, Ezekowitz JA *et al*, 2003 Horwich TB *et al*, 2002, McClellan WM *et al*, 2002). A hematocrit level of less than 27% (a hemoglobin concentration of 90 g/L) has been shown to be associated independently with one year mortality (hazard ratio, 1.4, (95% confidence interval, 1.02 to 1.92, p=0.04 of a hematocrit 27% compared to greater than 42% (hemoglobin concentration of 140 g/L) (Kosiborod M *et al*, 2003).

Because the level of hemoglobin concentration may impact on mortality in patients with left ventricular dysfunction, it is apparent that the hemoglobin transfusion threshold for patients with depressed cardiac function (i.e. a low cardiac index) has the potential to impact on patient outcomes following cardiac bypass surgery. On the one hand, transfusions can exacerbate the left ventricular dysfunction leading to pulmonary edema (Hebert PC *et al*, 1999). On the other hand, the hemoglobin transfusion threshold for patients with a cardiac index less than 2 L/mim/m^2 was 80 g/L, and this concentration may be too low for these patients. A hemoglobin concentration of 90 g/L compared to 140 g/L has been associated with increased mortality in patients with heart failure (Kosiborod M *et al*, 2003). In addition, a small group of patients with heart failure who were treated with erythropoietin and iron to maintain hemoglobin levels between 100 to 115 g/L (much higher than the hemoglobin transfusion threshold derived from the case scenarios in this study) had significant improvements in classification of left ventricular ejection fraction, a decrease in hospitalizations, and a decrease in the use of intravenous diuretics (Silverberg DS *et al*, 2001). Caveats to the above studies are that they had small sample sizes or did not adequately control for confounding. Nonetheless, should anemia be definitively associated with increased morbidity and mortality in patients with depressed cardiac function who have coronary artery bypass surgery, then a hemoglobin concentration of 80 g/L may not be adequate for patients with a low cardiac index. The impact of transfusing at this hemoglobin concentration for patients with depressed cardiac function needs to be studied further.

5.4.1.2 Myocardial Ischemia

As was found for cardiac index, the presence of myocardial ischemia resulted in an increase in the hemoglobin transfusion threshold by 10 g/L. However, this change in the hemoglobin threshold may also not be optimal for patients experiencing myocardial ischemia. The hemoglobin transfusion threshold selected for all case scenarios with the presence of myocardial ischemia was approximately 80 g/L. Recent reports describe conflicting data regarding the hemoglobin concentration at which to transfuse patients with acute coronary syndromes (Rao SV *et al*, 2004, Wu W-C *et al*, 2001 Hebert PC *et al*, 2001). One study reports a decreased mortality with transfusions below a hemoglobin concentration of 83 g/L and an increased mortality above this concentration (Rao SV *et al*, 2004). Other studies have found a reduction in mortality among patients transfused at a hemoglobin concentration less than 100 g/L compared to those transfused at higher hemoglobin concentrations (Wu W-C *et al*, 2001 Hebert PC *et al*, 2001). Further studies are needed to define the optimal hemoglobin concentration at which to transfuse patients having myocardial ischemia following bypass surgery, as they may require transfusions at higher hemoglobin concentrations than were identified in this study.

5.4.1.3 Age

Should hemoglobin concentrations for transfusion change based solely on the age of the patient? This study showed that age significantly changed the hemoglobin concentration for physicians selected for transfusion. It has been demonstrated that anemia is commonly found in elderly individuals (Ania BJ *et al*, 1997, Izaks GJ *et al*, 1999 Penninx BWJH *et al*, 2003, Ezekowitz JA *et al*, 2003, Beghe C *et al*, 2004, Guralnik JM *et al*, 2004). Anemia has also been shown to be associated with an increased mortality in elderly patients (Chaves PHM *et al*, 2004, Kikuchi M *et al*, 2001). However, anemia has not been shown to affect outcomes in elderly patients following coronary bypass surgery. Given that more cardiac bypass procedures are performed on elderly individuals (Zaidi AM *et al*, 1999, Kumar P *et al*, 1999, Peterson ED *et al*, 1995, Wenger NK *et al*, 1988), and given that there are several risks associated with transfusion (Kleinman S *et al*, 2003, Silliman CC *et al*, 2005), it is important to determine whether age alone should guide transfusion decisions as increasing age has been associated with increased transfusion rates in cohort studies (Lithmathe J *et al*, 2003, Scott BH *et al*, 2003, Covin R *et al*, 2003, Engstrom KG *et al*, 2002 Isomatsu Y *et al*, 2001, Karkouti K *et al*, 2001, Surgeoner DM *et al*, 1996, Magovern JA *et al*, 1996, Cosgrove DM *et al*, 1989)

5.4.1.4 Sex

The fact that the hemoglobin transfusion thresholds based on the case scenarios did not differ according to sex also has potentially important clinical implications. Several reports have shown that women are transfused more than men (Lithmathe J *et al*, 2003, Magovern JA *et al*, 1996 Scott BH *et al*, 2003, Covin R *et al*, 2003, Karkouti K *et al*, 2001, Surgenor DM *et al,l* 1996 Cosgrove DM *et al*, 1989, Bilfinger V Conti R, 1989). The apparently discordant results between this study's findings and reports demonstrating that women are transfused more than men may not be discordant at all. If men and women were transfused at the same hemoglobin thresholds, women would be expected to receive more transfusions because they tend to have lower preoperative hemoglobin concentrations. However, as women have a higher overall mortality after cardiac surgery compared to men (Vaccarino V *et al*, 2002, Edwards FH *et al*, 1998 O'Connor GT *et al*, 1993, Nalysnyk L *et al*, 2003), and a higher mortality rate secondary to congestive heart failure (O'Connor GT *et al*, 1993, Surgenor SD *et al*, 2001); the issue of selecting the same hemoglobin thresholds for men and women needs to be resolved since women may be at increased risk of transfusion-related heart failure, and possibly subsequent mortality.

5.4.2 The Impact of Increasing Hemoglobin Thresholds on Red Cell Utilization

The hemoglobin transfusion thresholds selected can affect red cell utilization. This study showed that there was an increase of 10 g/L in the hemoglobin threshold selected in the presence of a low cardiac index and in the presence of myocardial ischemia. It has been demonstrated in previous studies that left ventricular dysfunction (or a low cardiac index) is common after bypass surgery (Geraci JM *et al*, 1993) and that anemia is common in patients with heart failure (Ezekowitz JA *et al*, 2003, Kosiborod M *et al*, 2003). Thus, a considerable proportion of coronary bypass surgery patients will receive transfusions. An increase in the hemoglobin transfusion threshold of 10 g/L in patients having coronary bypass surgery has been shown to be associated with a 20% increase of red cell use (Bracey AW *et al*, 1999).

In addition, red cell utilization may also be affected by the trend towards conducting coronary bypass surgery on older persons. In this study, the hemoglobin transfusion threshold increased by 5 g/L as age increased from 55 to 75 years. Given that more cardiac bypass procedures are performed on elderly individuals (Zaidi AM *et al*, 1999, Kumar P *et al*, 1999, Peterson ED *et al*, 1995, Wenger NK *et al*, 1988) and that patients who are older are more likely to be transfused (Mathoulin-Pélissier S *et al*, 2000, Wells AW *et al*, 2002, Lithmathe J *et al*, 2003, Magovern JA *et al*, 1996 Scott BH *et al*, 2003, Covin R *et al*, 2003, Karkouti K *et al*, 2001, Isomatsu Y *et al*, 2001, Surgenor DM *et al*, 1996 Cosgrove DM *et al*, 1989, Bilfinger V Conti R, 1989), an increase in hemoglobin transfusion thresholds would significantly impact red cell utilization. This in turn would lead to significantly higher overall costs for coronary artery bypass patients, especially in light of the rising cots of blood products (Amin M *et al*, 2004).

5.4.3 Mixed Venous Oxygen Saturation

We used the mixed venous oxygen saturation (which is used to detect inadequate tissue oxygenation) as a descriptive variable in the case scenarios as this measure is used at one of the study centres to guide transfusion decisions. Interestingly, we found that the mixed venous oxygen saturation was one of the important factors selected to guide transfusion decisions. Yet, the use of mixed venous oxygen saturation to guide transfusion decisions has never been established. Since this factor appeared to be influencing transfusion decisions, it would be useful to determine its value compared to hemoglobin concentrations in guiding transfusions. This would be of particular interest because there has not yet to be a physiological measure that can be used instead of the hemoglobin concentration to guide transfusions in patients having coronary artery bypass surgery.

5.5 Future Research

This study identified that anesthesiologists and cardiac surgeons selected slightly higher hemoglobin thresholds postoperatively versus intraoperatively (69 g/L and 72 g/L, respectively), and that hemoglobin concentration, myocardial ischemia, cardiac index, and age, but not sex, were important factors in influencing their transfusion decisions. The ultimate goal of future studies should be to identify the most appropriate intraoperative and postoperative transfusion thresholds, and to verify whether transfusions based on the factors identified in this study affect patient morbidity and mortality. The morbidity outcomes of interest for future studies are those that relate to over-transfusion, such as congestive heart failure, and under-transfusion, such as cardiac ischemia and myocardial infarction. Ultimately, a randomized controlled trial should be performed to determine optimal hemoglobin concentrations for transfusion in coronary artery bypass patients. However, there are a number of questions that need to be answered before proceeding to a randomized controlled trial. The following proposed studies are uncontrolled retrospective and prospective cohort studies. Although an uncontrolled research design cannot determine causation due to confounding, and retrospective studies cannot define the reason for transfusion, retrospective and prospective cohort studies can be used to determine associations that can be used in future controlled trials.

In order to determine the factors that influence transfusion decisions, the results of this study can be confirmed by conducting a study using a mixed qualitative and quantitative research design. The qualitative aspect would involve conducting interviews with anesthesiologists and cardiac surgeons immediately after surgical procedures to determine whether transfusions were administered and the rationale for the transfusions. The same group of physicians would be interviewed regarding transfusions administered in the postoperative period in the intensive care unit and the rationale for these transfusions would be elicited. Concurrently, a chart-based review of a cohort of patients that had coronary artery bypass surgery could be conducted to determine whether the factors identified by the interviews were consistent with the factors predicting transfusion based on the chart reviews. These factors could then be compared with the factors identified in this study (i.e. hemoglobin concentration, presence of myocardial ischemia, cardiac index and age).

To determine whether hemoglobin concentrations for transfusion differ according to cardiac index, myocardial ischemia and age and whether they affect patient outcomes for coronary artery bypass surgery, a retrospective database review can be conducted to look at these associations. The Cardiac Care Network Database contains clinical and physiological characteristics and morbidity and mortality data for coronary artery bypass surgery patients in Ontario. This database can be linked to the Canadian Institute for Health Information database that contains transfusion data for these patients. Alternatively, the University Health Network also has a database that has physiological and clinical characteristics of patients, transfusion data, and morbidity and mortality data. The main objectives would be: 1. To determine how the cardiac index and the presence of myocardial ischemia affect hemoglobin transfusion thresholds. 2. To determine whether age affects hemoglobin transfusion thresholds and 3. To determine the impact of transfusion decisions based on cardiac index, myocardial ischemia and age on morbidity and mortality.

A more rigorous, but more expensive and time-consuming approach to determine whether the hemoglobin transfusion thresholds identified in this study affect patient outcomes would involve a prospective multi-centre inception cohort study. This would involve a large cohort of coronary artery bypass surgery patients that would be followed over time. Data would be collected about hemoglobin levels, transfusions, patient variables and patient outcomes.

Although our study did not identify that sex impacts on transfusion decisions, the fact that women are reported to have higher transfusion rates than men and that physicians in this questionnaire selected the same hemoglobin concentrations to transfuse both sexes needs to be investigated further. By using the same hemoglobin transfusion thresholds for men and women, men may be at increased risk of ischemic events, i.e. angina, myocardial infarction, ischemic nephropathy, if the hemoglobin concentration used for transfusion is too low for an individual with coronary artery disease. Alternatively, women, who have a lower blood volume, may be predisposed to developing heart failure if the hemoglobin transfusion threshold is too high. Because women have a higher mortality rate than men following coronary bypass surgery (Vaccarino V *et al*, 2002, Edwards FH *et al*, 1998 O'Connor GT *et al*, 1993, Nalysnyk L *et al*, 2003) and because female sex has been shown to be a predictor of death from heart failure following coronary artery bypass surgery (O'Connor GT *et al*, 1993Surgenor SD *et al*, 2001), the impact of transfusions on outcomes according to sex need to be determined. In order to assess whether using the same hemoglobin transfusion threshold for men and women impacts on patient outcomes, a subgroup analysis of a prospective cohort study looking at the impact of transfusions on different hemoglobin concentrations can be undertaken.

Ultimately, results from the above trials should they confirm the results of the survey can be used to design a randomized controlled trial in patients undergoing coronary artery bypass surgery. Randomization would be based on hemoglobin concentrations identified in the prospective cohort study and outcomes can be stratified according to factors identified in the retrospective database study as impacting on transfusions, e.g. cardiac index and myocardial ischemia.

Lastly, to assess whether the mixed venous oxygen saturation can be used to guide transfusion decisions, a retrospective study needs to be conducted initially to determine whether there is an association between mixed venous oxygen saturation, the hemoglobin threshold, transfusions and outcomes. Based on the findings of this preliminary study, more definitive studies can be conducted to explore the use of this variable as a transfusion trigger.

5.6 Conclusion

This is the only questionnaire that focused on transfusion decisions exclusively in coronary artery bypass surgery patients, a group of patients who are at high risk of receiving a transfusion. It is the only questionnaire that focused on physicians who commonly administer transfusions both in the intraoperative and postoperative periods. In addition, this is the only study that directly asked physicians what factors influence their transfusions decisions. This study identified that myocardial ischemia, cardiac index, and age increased the hemoglobin concentrations physicians selected to transfuse coronary artery bypass patients. Future studies should address whether the hemoglobin thresholds selected actually reflect clinical practice and if so, whether the hemoglobin concentrations selected and the modification of hemoglobin thresholds based on the cardiac index, myocardial ischemia and age affect transfusion related morbidity (i.e. congestive heart failure and ischemia) and mortality. Ultimately, transfusion decision-making can be optimized for coronary artery bypass surgery patients.

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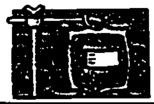
Red Cell Transfusions in Coronary Artery Bypass Surgery Questionnaire



Does part of your practice involve coronary artery bypass surgery? Please check. ☐Yes ☐No If **NO**, please **DO NOT** complete this questionnaire but **DO** return it in the stamped self-addressed envelope, and we will not contact you again.

The first 4 case vignettes examine INTRAOPERATIVE transfusion decisions.
Each case vignette has 2 sections (1&2) and each section has 3 cardiac index scenarios (a,b & c). For each cardiac index scenario, please indicate below what hemoglobin concentration you would transfuse red blood cells. The 4 case vignettes describe patients with different ages and sex.
All responses will be kept confidential.

Vignette 1: FACTORS AFFECTING RED CELL TRANSFUSIONS *INTRAOPERATIVELY* in women.

55 year old FEMALE	**Below what hemoglobin concentration would you transfuse red cells in the following INTRAOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)**	**Hemoglobin Concentration (g/L)**					
		50	**60**	**70**	**80**	**90**	**100**
Primary elective CABG	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
No preoperative morbidity	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
Heart rate=90	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
Blood pressure=110/70	2. If she has intraoperative myocardial ischemia and						
Euvolemic	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
Mixed venous oxygen	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
saturation=70%	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 2: FACTORS AFFECTING RED CELL TRANSFUSIONS *INTRAOPERATIVELY* in women.

75 year old FEMALE	**Below what hemoglobin concentration would you transfuse red cells in the following INTRAOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)**	**Hemoglobin Concentration (g/L)**					
		50	**60**	**70**	**80**	**90**	**100**
Primary elective CABG	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
No preoperative morbidity	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
Heart rate=90	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
Blood pressure=110/70	2. If she has intraoperative myocardial ischemia and						
Euvolemic	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
Mixed venous oxygen	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
saturation=70%	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 3:FACTORS AFFECTING RED CELL TRANSFUSIONS *INTRAOPERATIVELY* in men.

55 year old MALE	**Below what hemoglobin concentration would you transfuse red cells in the following INTRAOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)**	**Hemoglobin Concentration (g/L)**					
		50	**60**	**70**	**80**	**90**	**100**
Primary elective CABG	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
No preoperative morbidity	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
Heart rate=90	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
Blood pressure=110/70	2.If he has intraoperative myocardial ischemia and						
Euvolemic	a)Cardiac index <2.5	☐	☐	☐	☐	☐	☐
Mixed venous oxygen	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
saturation=70%	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Red Cell Transfusions in Coronary Artery Bypass Surgery
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Vignette 4:FACTORS AFFECTING RED CELL TRANSFUSIONS ***INTRAOPERATIVELY*** **in men.**

75 year old MALE Primary elective CABG No preoperative morbidity Heart rate=90 Blood pressure=110/70 Euvolemic Mixed venous oxygen saturation=70%	**Below what hemoglobin concentration would you transfuse red cells in the following INTRAOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)**	**Hemoglobin concentration (g/L)** 50	60	70	80	90	100
	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
	2. If he has intraoperative myocardial ischemia and						
	a)Cardiac index <2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

The last 4 case vignettes examine POSTOPERATIVE transfusion decisions in the intensive care unit (ICU).

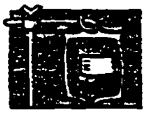
Vignette 5:FACTORS AFFECTING RED CELL TRANSFUSIONS ***POSTOPERATIVELY (ICU ONLY)*** **in women.**

55 year old FEMALE Primary elective CABG No preoperative morbidity Extubated Heart rate=90 Blood pressure=110/70 Euvolemic Mixed venous oxygen saturation=70%	**Below what hemoglobin concentration would you transfuse red cells in the following INTRAOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)**	**Hemoglobin Concentration (g/L)** 50	60	70	80	90	100
	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
	2.If she has postoperative myocardial ischemia and						
	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 6:FACTORS AFFECTING RED CELL TRANSFUSIONS ***POSTOPERATIVELY (ICU ONLY)*** **in women.**

75 year old FEMALE Primary elective CABG No preoperative morbidity Extubated Heart rate=90 Blood pressure=110/70 Euvolemic Mixed venous oxygen saturation=70%	**Below what hemoglobin concentration would you transfuse red cells in the following INTRAOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)**	**Hemoglobin Concentration (g/L)** 50	60	70	80	90	100
	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
	2.If she has postoperative myocardial ischemia and						
	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Red Cell Transfusions in Coronary Artery Bypass Surgery
Questionnaire



Vignette 7:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in men.

55 year old MALE Primary elective CABG No preoperative morbidity Extubated Heart rate=90 Blood pressure=110/70 Euvolemic Mixed venous oxygen saturation=70%	**Below what hemoglobin concentration would you transfuse red cells in the following INTRAOPERATIVE scenarios?** **(CHECK ONE IN EACH SCENARIO)**	**Hemoglobin Concentration (g/L)**					
		50	**60**	**70**	**80**	**90**	**100**
	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
	2.If he has postoperative myocardial ischemia and a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 8:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in men.

75 year old MALE Primary elective CABG No preoperative morbidity Extubated Heart rate=90 Blood pressure=110/70 Euvolemic Mixed venous oxygen saturation=70%	**Below what hemoglobin concentration would you transfuse red cells in the following INTRAOPERATIVE scenarios?** **(CHECK ONE IN EACH SCENARIO)**	**Hemoglobin Concentration (g/L)**					
		50	**60**	**70**	**80**	**90**	**100**
	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
	2.If he has postoperative myocardial ischemia and a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Please rank the 3 most significant factors that affect your decision to transfuse red blood cells in the intraoperative setting. Place the numbers that appear next to these 3 factors in their respective ranking boxes.

Intraoperative Factor	**Rank**
1.Intraoperative blood loss 2.Age 3.Sex 4.Cardiac index 5.Intraoperative hemoglobin concentration 6.Myocardial ischemia 7.Lactic Acidosis 8.Mixed venous oxygen saturation 9.Comorbid illness: PLEASE SPECIFY__________________ 10.Other: PLEASE SPECIFY__________________	☐ Most significant ☐ Second ☐ Third

The last 4 case vignettes examine POSTOPERATIVE transfusion decisions in the intensive care unit (ICU).

Vignette 5:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in women.

55 year old FEMALE Primary elective CABG No preoperative morbidity Extubated Heart rate=90 Blood pressure=110/70 Euvolemic Mixed venous oxygen saturation=70%	Below what hemoglobin concentration would you transfuse red cells in the following POSTOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)	Hemoglobin Concentration (g/L) 50	60	70	80	90	100
	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
	2.If she has postoperative myocardial ischemia and						
	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 6:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in women.

75 year old FEMALE Primary elective CABG No preoperative morbidity Extubated Heart rate=90 Blood pressure=110/70 Euvolemic Mixed venous oxygen saturation=70%	Below what hemoglobin concentration would you transfuse red cells in the following POSTOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)	Hemoglobin Concentration (g/L) 50	60	70	80	90	100
	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
	2.If she has postoperative myocardial ischemia and						
	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 7:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in men.

55 year old MALE Primary elective CABG No preoperative morbidity Extubated Heart rate=90 Blood pressure=110/70 Euvolemic Mixed venous oxygen saturation=70%	Below what hemoglobin concentration would you transfuse red cells in the following POSTOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)	Hemoglobin Concentration (g/L) 50	60	70	80	90	100
	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
	2.If he has postoperative myocardial ischemia and						
	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 8:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in men.

75 year old MALE Primary elective CABG No preoperative morbidity Extubated Heart rate=90 Blood pressure=110/70 Euvolemic Mixed venous oxygen saturation=70%	Below what hemoglobin concentration would you transfuse red cells in the following POSTOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)	Hemoglobin Concentration (g/L) 50	60	70	80	90	100
	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
	2.If he has postoperative myocardial ischemia and						
	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Appendix III- The Corrected Questionnaire Package

Replacement Letter

Dear Dr.

Many thanks for completing the transfusion questionnaire.

Unfortunately there was an error noted in part of the questionnaire sent to you. The questionnaire included 4 intraoperative followed by 4 postoperative vignettes. The description above the 4 postoperative vignettes described the vignettes as "POSTOPERATIVE" case scenarios, but within the wording of each of these vignettes they were described as intraoperative cases. We are concerned that this error may have mistakenly caused you to believe that the second set of 4 vignettes also represented intraoperative scenarios, and, therefore, your answers may not reflect your views about transfusion decisions in the postoperative period.

We are writing to ask you if you can clarify for us your interpretation of the second set of 4 vignettes as INTRAOPERATIVE or POSTOPERATIVE scenarios. We have enclosed your questionnaire to remind you of your responses. Please check one of the boxes on the attached form.

We appreciate the time that you have taken to help ensure the validity of your responses and we apologize for any inconvenience that this has caused. We thank you again for your time and effort in helping us analyze the factors that affect transfusion decisions in coronary artery bypass patients in Canada.

Yours sincerely,

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Interpretation of Postoperative Vignettes

Please check the appropriate box:

☐ I interpreted the second set of 4 vignettes as **POSTOPERATIVE** scenarios.

If you interpreted the second set of vignettes as postoperative, *would you please return this page with your original questionnaire in the stamped, self-addressed envelope.*

☐ I interpreted the second set of 4 vignettes as **INTRAOPERATIVE** scenarios.

If you interpreted the second set of 4 vignettes as intraoperative, *would* you *please complete the questions about the 4* ***POSTOPERATIVE*** *vignettes on the* ***new form*** *that is enclosed and return it with this page and your original questionnaire in the stamped, self-addressed envelope.*

☐ I don't remember how I interpreted the vignettes.

If you do not remember how you interpreted the 4 vignettes, *would you please complete the questions about the 4* ***POSTOPERATIVE*** *vignettes on the* ***new form*** *that is enclosed and return it with this page and your original questionnaire in the stamped, self-addressed envelope.*

We thank you again for your important contribution to this study and apologize for the inconvenience this may have caused.

The last 4 case vignettes examine POSTOPERATIVE transfusion decisions in the intensive care unit (ICU).

Vignette 5:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in women.

55 year old FEMALE Primary elective CABG	Below what hemoglobin concentration would you transfuse red cells in the following POSTOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)	Hemoglobin Concentration (g/L)					
		50	60	70	80	90	100
No preoperative	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
morbidity	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
Extubated	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
Heart rate=90							
Blood pressure=110/70	2.If she has postoperative myocardial ischemia and						
Euvolemic	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
Mixed venous oxygen	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
saturation=70%	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 6:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in women.

75 year old FEMALE Primary elective CABG	Below what hemoglobin concentration would you transfuse red cells in the following POSTOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)	Hemoglobin Concentration (g/L)					
		50	60	70	80	90	100
No preoperative	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
morbidity	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
Extubated	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
Heart rate=90							
Blood pressure=110/70	2.If she has postoperative myocardial ischemia and						
Euvolemic	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
Mixed venous oxygen	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
saturation=70%	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 7:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in men.

55 year old MALE Primary elective CABG	Below what hemoglobin concentration would you transfuse red cells in the following POSTOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)	Hemoglobin Concentration (g/L)					
		50	60	70	80	90	100
No preoperative	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
morbidity	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
Extubated	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
Heart rate=90							
Blood pressure=110/70	2.If he has postoperative myocardial ischemia and						
Euvolemic	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
Mixed venous oxygen	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
saturation=70%	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Vignette 8:FACTORS AFFECTING RED CELL TRANSFUSIONS *POSTOPERATIVELY (ICU ONLY)* in men.

75 year old MALE Primary elective CABG	Below what hemoglobin concentration would you transfuse red cells in the following POSTOPERATIVE scenarios? (CHECK ONE IN EACH SCENARIO)	Hemoglobin Concentration (g/L)					
		50	60	70	80	90	100
No preoperative	1.a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
morbidity	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
Extubated	c)Cardiac index <2	☐	☐	☐	☐	☐	☐
Heart rate=90							
Blood pressure=110/70	2.If he has postoperative myocardial ischemia and						
Euvolemic	a)Cardiac index >2.5	☐	☐	☐	☐	☐	☐
Mixed venous oxygen	b)Cardiac index between 2 and 2.5	☐	☐	☐	☐	☐	☐
saturation=70%	c)Cardiac index <2	☐	☐	☐	☐	☐	☐

Appendix IV: Subgroup Analyses for Anesthesiologists and Cardiac Surgeons

Table IV.1 Subgroup analysis for anesthesiologists.
Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55-year old woman in the intraoperative setting:

Characteristic	T value	Degrees of Freedom	p value
Characteristics of the Simulated Patient:			
Sex	0.58	239	0.56
Age	12.20	239	<0.0001
Cardiac index (>2.5vs. 2-2.5)	8.77	240	<0.0001
Cardiac index (>2.5:<2)	17.1	240	<0.0001
Cardiac index (2-2.5 vs.<2)	15.31	240	<0.0001
Myocardial ischemia	18.93	239	<0.0001
Physicians' Characteristics:			
Sex	1.25	77	0.21
Academic Centre	0.83	28	0.41
Age	0.14	240	0.89
Years in practice	0.68	240	0.49
Cases/physician			0.04
Hospital	F value=2.59	33/239	<0.0001
Involvement in transfusion decisions:			
Preoperatively	2.43	226	0.02
Intraoperatively	NA	NA	0.90***
Postoperatively	1.41	222	0.16

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients.
**Degrees of freedom for the numerator/denominator.
*** n=1 for no involvement in intraoperative transfusion decisions
NA=not available

Table IV.2 Subgroup analysis for anesthesiologists.
Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55-year old man in the intraoperative setting.

Characteristic	T value	Degrees of Freedom	p value
Characteristics of Simulated Patient:			
Sex	0.58	239	0.56
Age	11.68	238	<0.0001
Cardiac index (>2.5vs. 2-2.5)	8.95	239	<0.0001
Cardiac index (>2.5: <2)	17.25	239	<0.0001
Cardiac index (2-2.5 vs.<2)	15.34	239	<0.0001
Myocardial ischemia	18.8	238	<0.0001
Physicians' Characteristics:			
Sex	1.35	75	0.18
Academic Centre	0.88	28	0.38
Age	0.78	239	0.89
Years in practice	1.25	239	0.50
Cases/physician	1.76	237	0.04
Hospital	F value =2.32	**33/238	0.002
Involvement in transfusion decisions:			
Preoperatively	2.30	220	0.02
Intraoperatively	NA	NA	1.0***
Postoperatively	1.09	223	0.28

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients.
**Degrees of freedom for the numerator/denominator.
*** n=1 for no involvement in intraoperative transfusion decisions
NA=not available

Table IV.3 Subgroup analysis for cardiac surgeons.
Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55-year old woman in the intraoperative setting:

Characteristic	T value	Degrees of Freedom	p value
Characteristics of Simulated Patient:			
Sex	0.22	95	0.82
Age	6.91	94	<0.0001
Cardiac index (>2.5vs. 2-2.5)	2.97	96	0.004
Cardiac index (>2.5vs.<2)	12.49	95	<0.0001
Cardiac index (2-2.5 vs. <2.5)	12.43	95	<0.0001
Myocardial ischemia	7.92	93	<0.0001
Physicians' Characteristics:			
Sex	0.58	4	0.60
Academic Centre	0.45	14	0.66
Age	1.25	93	0.21
Years in practice	0.67	93	0.50
Cases/physician	1.78	94	0.08
Hospital	F value =2.52	**33/95	0.001
Involvement in transfusion decisions:			
Preoperatively	1.04	29	0.30
Intraoperatively	-0.97	20	0.34
Postoperatively	2.02	7	0.08

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients.
**Degrees of freedom for the numerator/denominator.

Table IV.4 Subgroup analysis for cardiac surgeons.
Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55- year old man in the intraoperative setting.

Characteristic	T value	Degrees of Freedom	p value
Characteristics of Simulated Patient:			
Sex	0.22	95	0.82
Age	6.71	94	<0.0001
Cardiac index (>2.5vs. 2-2.5)	2.52	95	0.013
Cardiac index (>2.5vs. <2)	10.22	95	<0.0001
Cardiac index (2-2.5 vs. <2.5)	10.59	95	<0.0001
Myocardial ischemia	7.78	95	<0.0001
Physicians' Characteristics:			
Sex	0.57	4	0.60
Academic Centre	0.56	14	0.58
Age	0.44	92	0.66
Years in practice	0.50	92	0.63
Cases/physician	1.63	93	0.10
Hospital	F value =2.76	**33/94	0.0004
Involvement in transfusion decisions:			
Preoperatively	0.71	31.2	0.48
Intraoperatively	0.60	22	0.34
Postoperatively	2.02	7	0.08

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients.
**Degrees of freedom for the numerator/denominator.

Table IV.5 Repeated measures regression model for anesthesiologists for the intraoperative case scenarios.

Variable	Parameter Estimate	95% Confidence Interval	p value
Intercept	84.9	74.5-95.4	<0.0001
Characteristics of Simulated Patients:			
Sex (F: M)	-0.10	-0.6-0.5	0.73
Age (55 years: 75 years)	-1.6	-2.1—1.0	<0.0001
Cardiac index: 2-2.5: >2.5	1.8	1.1-2.5	<0.0001
Cardiac index: >2.5:<2	-5.6	-6.2- -4.9	<0.0001
Cardiac index: <2: 2-2.5	-3.7	-4.3- -3.1	<0.0001
MI (No: Yes)	-5.1	-5.7—4.5	<0.0001
Age and Cardiac Index: 2-2.5:>2.5	0.37	-0.41.7	0.29
Age and Cardiac Index: >2.5: <2	-1.03	-1.7—0.3	0.003
Age and Cardiac Index: 2-2.5: <2	-0.66	-1.3-0.01	0.06
Age and MI (No: Yes)	-1.90	-2.4—1.3	<0.0001
MI and Cardiac Index: 2-2.5:>2.5	0.52	-0.2-1.2	0.1
MI and Cardiac Index: >2.5: <2	-2.57	-3.2-1.9	<0.0001
MI and Cardiac Index: 2-2.5: <2	-2.05	-2.7—1.4	<0.0001
Physicians' Characteristics:			
Sex (F:M)	25.2	-1.3-51.7	0.06
Academic institution (No: Yes)	3.74	0.1-7.4	0.04
Age	0.04	-0.2-0.3	0.80
Years in Practice	0.03	-0.2-0.3	0.84
Cases/physician	-0.01	-0.03-0.003	0.06
*Preoperative (No: Yes)	-0.26	-2.3-1.8	0.80
*Intraoperative (No: Yes)	-5.03	-19.8-9.8	0.50
*Postoperative (No: Yes)	0.76	-1.5-3.0	0.51

F=female, M=male, MI=myocardial ischemia * involvement in transfusion decisions in the preoperative, intraoperative and postoperative settings.

Table IV.6 Repeated measures regression model for cardiac surgeons for the intraoperative case scenarios.

Variable	Parameter Estimate	95% Confidence Interval	p value
Intercept	76.4	54.2-98.7	<0.0001
Characteristics of Simulated Patients:			
Sex (F: M)	0.80	-0.1-1.7	0.08
Age (55 years: 75 years)	-1.8	-2.7—0.9	<0.0001
Cardiac index: 2-2.5: > 2.5	2.2	1.3-3.2	0.0001
Cardiac index:>2.5: <2	-6.4	-7.5- -5.3	<0.0001
Cardiac index: 2-2.5: <2	-4.2	-5.3- -3.1	<0.0001
MI (No: Yes)	-2.7	-3.7—1.8	<0.0001
Age and MI (No: Yes)	-1.6	-2.5—0.7	0.0007
MI and Cardiac Index: 2-2.5:>2.5	-0.7	-1.8-0.4	0.20
MI and Cardiac Index: >2.5: <2	-1.6	-2.7—0.5	0.004
MI and Cardiac Index: 2-2.5: <2	-2.4	-3.5—1.3	<0.0001
Physicians' Characteristics			
Sex	-148.1	-8.8-9.4	0.33
Academic institution (No: Yes)	1.6	-5.0-8.2	0.63
Age	0.29	-0.3-0.9	0.36
Years in Practice	-0.31	-0.9- 0.3	0.30
Cases/physician	-0.008	-0.04-0.02	0.63
*Preoperative (No: Yes)	0.41	-4.0- 4.8	0.86
*Intraoperative (No: Yes)	-1.29	-6.7-4.1	0.64
*Postoperative (No: Yes)	3.6	-4.3-11.6	0.36

F=female, M=male, MI= myocardial ischemia, * involvement in transfusion decisions in the preoperative, intraoperative and postoperative settings.

Table IV.7 Subgroup analysis for anesthesiologists.
Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55- year old woman in the postoperative setting:

Characteristic	T value	Degrees of Freedom	p value
Characteristics of Simulated Patient:			
Sex	0.77	197	0.44
Age	10.20	197	<0.0001
Cardiac index (>2.5: 2-2.5)	8.06	197	<0.0001
Cardiac index (>2.5: <2)	15.59	197	<0.0001
Cardiac index (2-2.5: <2.5)	13.42	197	<0.0001
Myocardial ischemia	18.72	196	<0.0001
Physicians' Characteristics			
Sex	0.34	70	0.73
Academic Centre	1.8	21	0.08
Age	0.26	197	0.79
Years in practice	0.51	197	0.61
Cases/physician	1.42	195	0.16
Hospital	F value= 2.26	**33/197	0.0005
Involvement in transfusion decisions:			
Preoperatively	2.75	195	0.007
Intraoperatively	NA	NA	0.73***
Postoperatively	2.27	183	0.02

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients,
**Degrees of freedom for the numerator/denominator.
NA=not available
* **n=1 for no involvement in intraoperative transfusion decisions

Table IV.8 Subgroup analysis for anesthesiologists.
Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55- year old man in the postoperative setting.

Characteristic	T value	Degrees of Freedom	p value
Characteristics of Simulated Patient:			
Sex	0.34	70	0.65
Age	10.09	197	<0.0001
Cardiac index (>2.5: 2-2.5)	7.62	197	<0.0001
Cardiac index (>2.5: <2)	15.59	197	<0.0001
Cardiac index (2-2.5: <2.5)	13.56	197	<0.0001
Myocardial ischemia	18.04	196	<0.0001
Physicians' Characteristics			
Sex	1.24	70	0.33
Academic Centre	1.17	20	0.22
Age	0.16	197	0.87
Years in practice	0.67	197	0.50
Cases/physician	1.15	195	0.25
Hospital	F value= 2.00	**33/197	0.003
Involvement in transfusion decisions:			
Preoperatively	2.2	195	0.03
Intraoperatively	NA	NA	0.75***
Postoperatively	2.14	183	0.03

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients,
**Degrees of freedom for the numerator/denominator.
NA=available
** n=1 for no involvement in intraoperative transfusion decisions

Table IV.9 Subgroup analysis for cardiac surgeons.
Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55- year old woman in the postoperative setting:

Characteristic	T value	Degrees of Freedom	p value
Characteristics of Simulated Patient:			
Sex	0.45	88	0.66
Age	6.51	88	<0.0001
Cardiac index (>2.5: 2-2.5)	3.64	88	<0.0005
Cardiac index (>2.5: <2)	11.03	88	<0.0001
Cardiac index (2-2.5: <2)	10.28	88	<0.0001
Myocardial ischemia	9.00	86	<0.0001
Physician Characteristics:			
Sex	1.41	2	0.28
Academic Centre	0.22	14	0.83
Age	1.65	86	0.10
Years in practice	1.42	86	0.16
Cases/physician	2.37	87	0.02
Hospital	F value=3.00	**33/88	0.0002
Involvement in transfusion decisions :			
Preoperatively	0.46	36	0.65
Intraoperatively	1.85	36	0.07
Postoperatively	0.93	7	0.38

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients
**Degrees of freedom for the numerator/denominator.

Table IV.10 Subgroup analysis for cardiac surgeons.
Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55- year old man in the postoperative setting.

Characteristic	T value	Degrees of Freedom	p value
Characteristics of Simulated Patients:			
Sex	0.45	88	0.65
Age	6.86	89	<0.0001
Cardiac index (>2.5: 2-2.5)	2.78	89	<0.007
Cardiac index (>2.5: <2)	10.15	89	<0.0001
Cardiac index (2-2.5: <2)	10.43	89	<0.0001
Myocardial ischemia	8.61	88	<0.0001
Physician Characteristics:			
Sex	1.48	4	0.22
Academic Centre	0.33	16	0.75
Age	1.49	86	0.14
Years in practice	1.20	86	0.24
Cases/physician	2.73	87	0.008
Hospital	F value= 3.34	**33/89	<0.0001
Involvement in transfusion decisions:			
Preoperatively	0.16	34	0.87
Intraoperatively	1.49	38	0.14
Postoperatively	0.25	8	0.81

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients
**Degrees of freedom for the numerator/denominator.

Table IV.11 Repeated measures regression model for anesthesiologists for the postoperative scenarios.

Variable	Parameter Estimate	95% Confidence Interval	p value
Intercept	88.1	78.5-97.7	<0.0001
Characteristics of Simulated Patients:			
Sex (F: M)	0.12	-0.5-0.7	0.69
Age (55 years: 75 years)	-1.6	-2.2--1.0	<0.0001
Cardiac index: 2-2.5:>2.5	1.5	0.8-2.3	<0.0001
Cardiac index: >2.5: <2	-5.2	-5.9 - -4.4	<0.0001
Cardiac index: 2-2.5: < 2	-3.6	-4.4- -2.9	<0.0001
MI (No: Yes)	-6.3	-7.0 --5.7	<0.0001
MI and Age	-1.3	-1.8—0.7	<0.0001
Age and Cardiac Index: >2.5: <2	-0.81	-1.5--0.9	0.03
MI and Cardiac Index: >2.5: <2	-2.2	-2.9—1.4	<0.0001
MI and Cardiac Index: 2-2.5: <2	-1.6	-2.3—0.9	<0.0001
Physicians' Characteristics			
Sex (F: M)	20.7	-7.4-48.8	0.14
Academic institution (No: Yes)	1.6	-1.8-5.1	0.35
Age	-0.002	-0.2-0.2	0.98
Years in Practice	0.03	-0.2-0.3	0.78
Cases/physician	-0.006	-0.02--0.008	0.38
*Preoperative (No: Yes)	0.20	-1.7-2.1	0.84
*Intraoperative (No: Yes)	-8.4	-20.9-4.1	0.19
*Postoperative (No: Yes)	2.3	0.22-4.4	0.03

F=female, M=male, MI=myocardial ischemia * involvement in transfusion decisions in the preoperative, intraoperative and postoperative settings.

Table IV.12 Repeated measures regression model for cardiac surgeons for the postoperative scenarios.

Variable	Parameter Estimate	95% Confidence Interval	p value
Intercept	82.1	62.3-101.8	<0.0001
Characteristics of Simulated Patients:			
Sex (F: M)	0.53	-0.4-1.4	0.24
Age (55 years: 75 years)	-2.7	-3.6--1.8	<0.0001
Cardiac index: 2-2.5:>2.5	2.2	1.1-3.3	<0.0001
Cardiac index: >2.5: < 2	-6.6	-7.6--5.5	<0.0001
Cardiac index: 2-2.5: < 2	-4.4	-5.5--3.3	<0.0001
MI (No: Yes)	-2.7	-4.1--2.2	<0.0001
MI and Age	-1.1	-2.0—0.2	0.02
MI and Cardiac Index: >2.5: <2	-2.3	-3.4—1.2	<0.0001
MI and Cardiac Index: 2-2.5: <2	-2.6	-3.7—1.5	<0.0001
Physicians' Characteristics:			
Sex (F:M)	-128.3	-386.3-129.6	0.32
Academic institution (No: Yes)	3.4	-2.4-9.1	0.24
Age	0.22	-0.3-0.8	0.41
Years in Practice	-0.21	-0.7-0.3	0.42
Cases/physician	-0.02	-0.04-0.01	0.22
*Preoperative (No: Yes)	-0.35	-4.2-3.4	0.86
*Intraoperative (No: Yes)	2.71	-1.8-7.2	0.24
*Postoperative (No: Yes)	1.04	-5.9-8.0	0.77

F=female, M=male, MI=myocardial ischemia, * involvement in transfusion decisions in the preoperative, intraoperative and postoperative settings.

Appendix V: Results for the Male Case Scenarios for All Physicians

Figure V.1 The hemoglobin thresholds for the base case scenario, 55-year old man in the intraoperative setting.

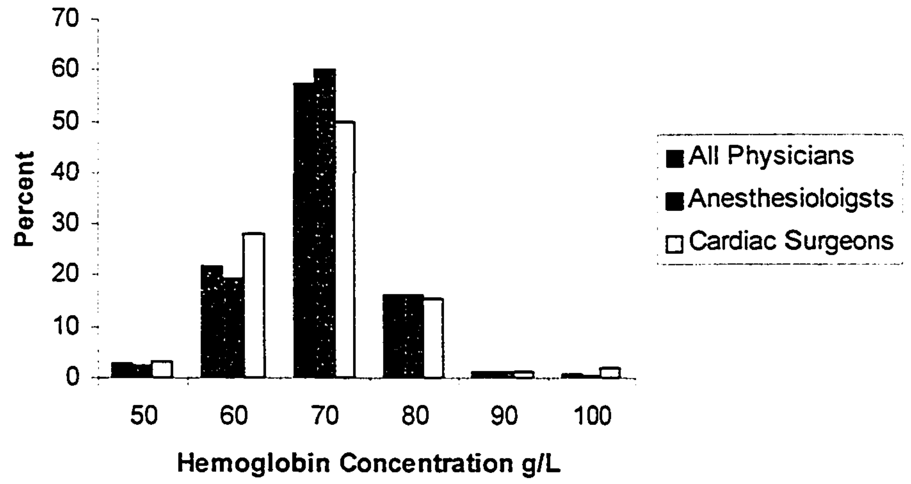

Figure V.2 The hemoglobin thresholds for the base case scenario, 75-year old man in the intraoperative setting.

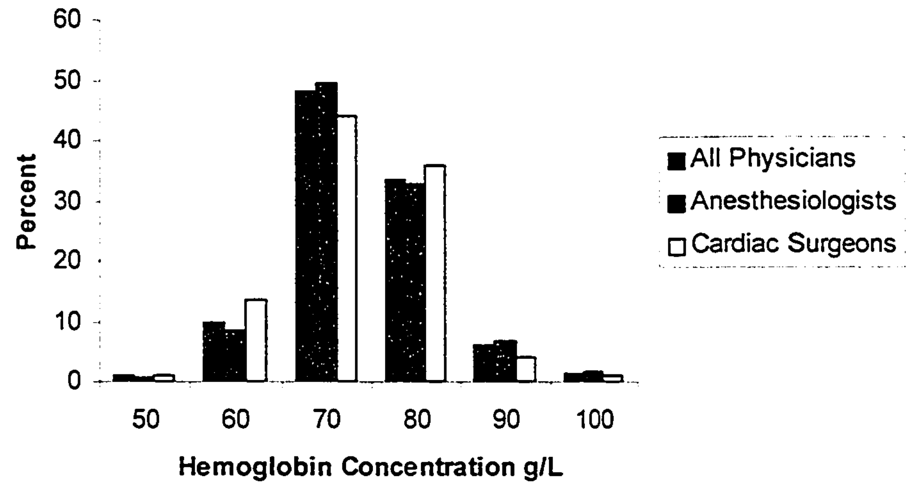

Table V.1 Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55-year old man in the intraoperative setting.

Characteristic	T value	Degrees of Freedom	p value
Characteristics of the Simulated Patient:			
Sex	0.52	335	0.60
Age	13.7	333	<0.0001
Cardiac index (>2.5vs. 2-2.5)	8.77	335	<0.001
Cardiac index (>2.5:<2)	20.06	335	<0.0001
Cardiac index (2-2.5 vs.<2)	18.63	335	<0.0001
Myocardial ischemia	19.71	334	<0.0001
Physicians' Characteristics:			
Specialty	0.61	150	0.54
Sex	1.29	77	0.20
Academic Centre	0.41	43	0.68
Age	0.83	332	0.41
Years in practice	1.30	332	0.19
Cases/physician	2.3	331	0.02
Hospital	F value= 2.78	**33/333	<0.001
Involvement in transfusion decisions:			
Preoperatively	1.74	273	0.08
Intraoperatively	0.80	16	0.44
Postoperatively	1.54	246	0.12

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients.

**Degrees of freedom for the numerator/denominator

Figure V.3 The hemoglobin thresholds for the base case scenario, 55-year old man in the postoperative setting.

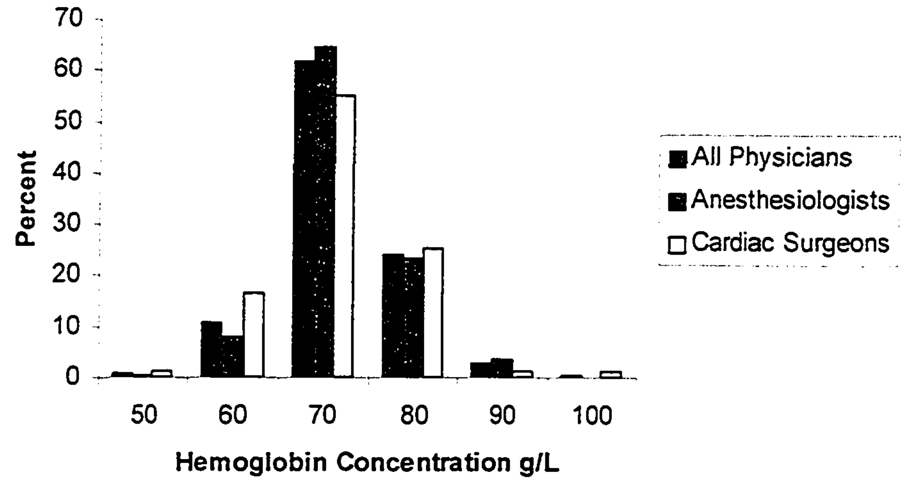

Figure V.4 The hemoglobin thresholds for the base case scenario, 75-year old man in the postoperative setting.

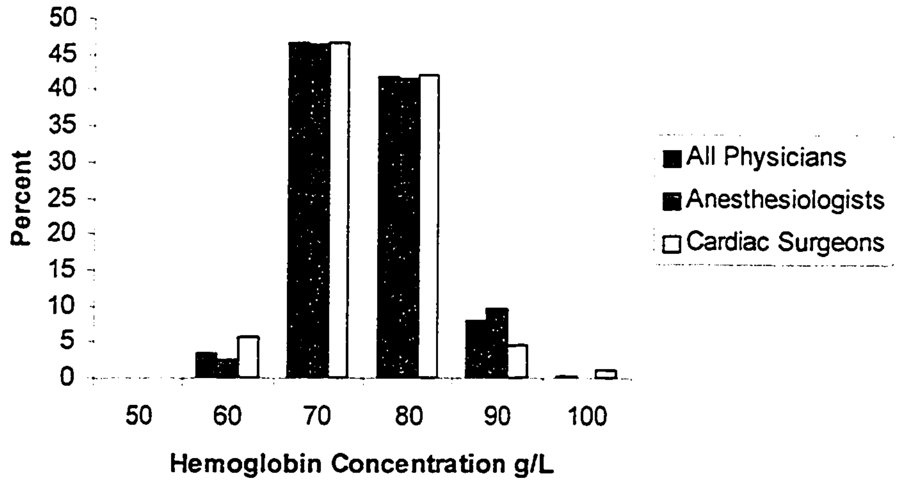

Table V.2 Univariate analysis of the variables affecting the hemoglobin threshold* for the base case scenario, 55-year old man in the postoperative setting.

Characteristic	T value	Degrees of Freedom	p value
Characteristics of Simulated Patient:			
Sex	0.89	286	0.37
Age	12.22	287	<0.0001
Cardiac index (>2.5: 2-2.5)	7.81	287	<0.001
Cardiac index (>2.5: <2)	18.59	287	<0.0001
Cardiac index (2-2.5: <2)	17.02	287	<0.0001
Myocardial ischemia	19.39	285	<0.0001
Physician Characteristics:			
Specialty	0.95	149	0.34
Sex	1.38	69	0.17
Academic Centre	1.15	35	0.26
Age	1.06	284	0.29
Years in practice	1.32	284	0.18
Cases/physician	2.49	283	0.01
Hospital	F value= 2.86	**33/287	<0.0001
Involvement in transfusion decisions:			
Preoperatively	1.94	266	0.05
Intraoperatively	0.98	21	0.33
Postoperatively	2.21	202	0.03

*Hemoglobin threshold = the hemoglobin concentration selected by physicians to transfuse the simulated patients

**Degrees of freedom for the numerator/denominator.

Table V.3 Results of the univariate analysis for the intraoperative and postoperative case scenarios.

Case Scenario	T-Value	Degrees of Freedom	P-value
55-year old male	7.0	326	<0.0001
55-year old male with a cardiac index <2	3.6	329	0.0004
55- year old male with myocardial ischemia	6.2	324	<0.0001
75-year old male	4.5	324	<0.0001

Table V.4 The mean hemoglobin concentrations selected by physicians for the 55-year old man postoperatively as classified by hemoglobin concentrations selected intraoperatively.

Hemoglobin Concentration (g/L) Selected Intraoperatively	Mean Hemoglobin Concentration (SD) (g/L) Selected Postoperatively
50	66.7 (5.8)
60	68.0 (7.1)
70	72.9 (5.1)
80	79.0 (5.2)
90	86.7 (4.8)
100	90.0 (7.1)

SD=standard deviation

Appendix VI: Comparison of Corrected and Uncorrected Questionnaires

For the postoperative case scenarios, we compared the results of the questionnaire with the typographical errors (i.e. referring to the postoperative scenarios as being intraoperative) with the corrected questionnaire (Tables 1 to 9). All analyses demonstrated similar results except for the repeated measures regression analysis where the interaction term years of practice and sex of the physician was statistically significant for the uncorrected questionnaires.

Table VI.1 Comparison of the mean hemoglobin concentration for the 55-year old patient according to cardiac index and presence of myocardial ischemia for the corrected postoperative case scenarios and the case scenarios with the typographical error.

Variable	Mean Hemoglobin Concentration (SD)(g/L) for the 55-year old female		Mean Hemoglobin Concentration for the (SD) (g/L) 55-year old male	
	Corrected	Not corrected	Corrected	Not Corrected
Cardiac index >2.5	72.0(7.0)	71.9(6.9)	71.8(7.0)	71.8(6.8)
Cardiac index 2-2.5	74.3(7.7)	74.2(7.8)	73.9(7.5)	73.9(7.5)
Cardiac index <2	80.4(9.2)	80.2(9.4)	80.1(9.1)	80.0(9.1)
MI and Cardiac index >2.5	80.8(9.3)	80.8(9.6)	80.4(9.2)	80.5(9.5)
MI and Cardiac index 2-2.5	82.5(9.3)	82.7(9.7)	82.4(9.3)	82.5(9.7)
MI and Cardiac index <2	87.1(9.4)	87.0(9.6)	86.8(9.4)	86.7(9.6)

SD=standard deviation, MI=myocardial ischemia

Table VI.2 Comparison of the mean hemoglobin concentrations for the 75-year old patient according to cardiac index and presence of myocardial ischemia for the corrected postoperative case scenarios and the case scenarios with the typographical error.

Variable	Mean Hemoglobin Concentration (SD)(g/L) for the 75-year old female		Mean Hemoglobin Concentration for the (SD) (g/L) 75-year old male	
	Corrected	Not Corrected	Corrected	Not Corrected
Cardiac index >2.5	75.7(7.1)	75.6(7.3)	75.5(7.1)	75.5(7.2)
Cardiac index 2-2.5	77.8(8.2)	77.8(8.3)	77.5(8.0)	77.4(8.2)
Cardiac index <2	83.8(9.4)	83.4(9.6)	83.3(9.5)	83.0(9.5)
MI and Cardiac index >2.5	83.3(9.2)	83.2(9.6)	83.0(9.3)	83.1(9.4)
MI and Cardiac index 2-2.5	85.1(9.1)	85.1(9.4)	84.8(9.2)	84.8(9.5)
MI and Cardiac index <2	88.8(8.9)	88.7(9.1)	88.6(9.1)	88.5(9.2)

SD=standard deviation, MI=myocardial ischemia

Table VI.3 The hemoglobin thresholds selected by physicians for the base case scenario, 55-year old woman in the postoperative setting for the corrected case scenario and the case scenario with the typographical error (not corrected).

Hemoglobin Concentration (g/L)	Corrected (%) No. (%)	Not corrected No. (%)
50	2(0.7)	2(0.6)
60	31(10.8)	37(11.2)
70	172(60.0)	199(60.1)
80	73(25.4)	84(25.4)
90	8(2.8)	8(2.4)
100	1(0.4)	1(0.3)

Table VI.4 The hemoglobin thresholds selected by physicians for the base case scenario, 55-year old man, in the postoperative setting for the corrected case scenario and the case scenario with the typographical error (not corrected).

Hemoglobin Concentration (g/L	Corrected No. (%)	Not corrected No. (%)
50	2(0.7)	2(0.6)
60	31(10.8)	35(10.6)
70	177(61.5)	205(61.9)
80	69(24.0)	80(24.2)
90	8(2.8)	8(2.4)
100	1(0.4)	1(0.3)

Table VI.5 The hemoglobin thresholds selected by physicians for the base case scenario, 75-year old woman, in the postoperative setting for the corrected case scenario and the case scenario with the typographical error (not corrected).

Hemoglobin Concentration (g/L)	Corrected No. (%)	Not corrected No. (%)
50	0(0.0)	0(0.0)
60	11(3.8)	15(4.5)
70	127(44.2)	148(44.7)
80	123(42.9)	137(41.4)
90	25(8.7)	30(9.1)
100	1(0.4)	1(0.3)

Table VI.6 The hemoglobin thresholds selected by physicians for the base case scenario, 75 year old man, in the postoperative setting for the corrected case scenario and the case scenario with the typographical error (not corrected).

Hemoglobin Concentration (g/L	Corrected No. (%)	Not corrected No. (%)
50	0(0.0)	0(0.0)
60	10(3.5)	13(3.9)
70	134(46.5)	154(46.5)
80	120(41.7)	135(40.8)
90	23(8.0)	28(8.5)
100	1(0.4)	1(0.3)

Table VI.7 Comparison of univariate analysis of the independent variables on the hemoglobin concentration for the base case scenario, 55-year old woman, in the postoperative setting for the corrected case scenario and the case scenario with the typographical error (not corrected).

Characteristic	p value (Corrected)	p value (Not corrected)
Characteristics of the Simulated Patient:		
Sex	0.37	0.68
Age	<0.0001	<0.0001
Cardiac index (>2.5vs. 2-2.5)	<0.0001	<0.0001
Cardiac index (>2.5vs.<2)	<0.0001	<0.0001
Cardiac index (2-2.5 vs.<2)	<0.0001	<0.0001
Myocardial ischemia	<0.0001	<0.0001
Physicians' Characteristics:		
Specialty	0.30	0.27
Sex	0.70	0.76
Academic centre	0.17	0.2
Age	0.21	0.18
Years in practice	0.18	0.13
Cases/physician	0.01	0.006
Hospital	<0.0001	<0.0001
Involvement in transfusion decisions:		
Preoperatively (yes/no)	0.009	0.006
Intraoperatively (yes/no)	0.34	0.30
Postoperatively (yes/no)	0.01	0.02

Table VI.8 Comparison of univariate analysis of the predictor variables on the hemoglobin concentration for the base case scenario, *55-year old man*, in the postoperative setting for the corrected case scenario and the case scenario with the typographical error (not corrected).

Characteristic	p value (Corrected)	p value (Not corrected)
Characteristics of Simulated Patient:		
Sex	0.37	0.68
Age	<0.0001	<0.001
Cardiac index (>2.5vs. 2-2.5)	<0.001	<0.001
Cardiac index (>2.5: <2)	<0.0001	<0.0001
Cardiac index (2-2.5 vs.<2)	<0.0001	<0.0001
Myocardial ischemia	<0.0001	<0.001
Physicians' Characteristics:		
Specialty	0.31	0.16
Sex of the physician	0.30	0.61
Academic Centre	0.21	0.20
Age of the physician	0.29	0.35
Years in practice	0.18	0.20
Cases/physician	0.01	0.006
Hospital	<0.001	<0.0001
Involvement in transfusion decisions:		
Preoperatively	0.06	0.04
Intraoperatively	0.49	0.5
Postoperatively	0.03	0.02

Table VI.9 Repeated measures regression model for the postoperative scenarios with the typographical error for all physicians.

Variable	Parameter Estimates	95% Confidence Interval for β	p value
Intercept	83.9	75.5-92.3	<0.0001
Characteristics of Simulated Patients:			
Sex (F: M)	0.24	-0.01-0.8	0.05
Age (55 years: 75 years)	-1.8	-2.3--1.3	<0.0001
Cardiac index: 2-2.5:>2.5	2.1	1.1-2.9	<0.0001
Cardiac index: >2.5: <2	-5.5	-6.4--4.6	<0.0001
Cardiac index: 2-2.5: <2	-3.7	-4.3--2.5	<0.0001
MI (No: Yes)	-5.4	-5.9--5.0	<0.0001
MI and Age	-1.3	-1.7—0.8	<0.0001
Age and Cardiac Index: >2.5:<2	-0.7	-1.3—0.1	<0.0001
MI and Cardiac Index: >2.5: <2	-2.1	-2.7—1.6	<0.0001
MI and Cardiac Index: 2-2.5: <2	-1.8	-2.4—1.3	<0.0001
Physicians' Characteristics:			
Specialty (A: CV)	0.37	-1.6-2.4	0.72
Sex (F: M)	18.7	-3.6-40.7	0.10
Academic institution (No: Yes)	2.66	-0.2-5.5	0.06
Age	0.11	-0.1-0.3	0.28
Years in Practice	-0.12	-0.3-0.1	0.27
Cases/physician	-0.01	-0.02-0.001	0.07
*Preoperative (No: Yes)	0.20	-1.4-1.8	0.80
*Intraoperative (No: Yes)	2.2	-1.2-5.7	0.20
*Postoperative (No: Yes)	2.3	-0.4-4.2	0.01
Years in Practice and sex	0.74	0.1-1.4	0.02

A=anesthesiologists, CV=cardiac surgeons, F=female, M=male, MI= myocardial ischemia, * involvement in transfusion decisions in the preoperative, intraoperative and postoperative settings.