Blood transfusion in cardiac surgery: Primum non nocere

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Title: Blood transfusion in cardiac surgery: Primum non nocere
Issue Date: 2019-06-04

Tolerance of intraoperative hemoglobin decrease during cardiac surgery

CHAPTER 3

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Published in Transfusion; vol 54, 2014, pag 2696-2704

Abstract

Background
It has been suggested that a decrease of at least 50% from the preoperative hemoglobin (Hb) level during cardiac surgery is associated with adverse outcomes even if the absolute Hb level remains above the commonly used transfusion threshold of 7.0 g/dL. In this study the relation between intraoperative Hb decline of at least 50% and a composite endpoint was analyzed.

Study Design and Methods
This single-centre study comprised 11,508 patients who underwent cardiac surgery and had normal preoperative Hb levels (12.0-16.0 g/dL in women, 13.0-18.0 g/dL in men) between January 2001 and December 2011. Logistic regression modeling was used. The composite endpoint comprised in-hospital mortality, stroke, myocardial infarction and renal failure.

Results
Patients whose Hb did not decrease at least 50% and remained above 7 g/dL were used as reference (n=9672). A total of 363 (3.2%) patients had an intraoperative Hb of less than 7 g/dL during surgery but a Hb decrease less than 50%; 876 patients (7.4%) showed both a nadir Hb less than 7g/dL and a Hb decrease of at least 50%, while 597 (5.2%) had a Hb decrease of at least 50% and a nadir Hb of at least 7 g/dL. In this last group the incidence of the composite endpoint was higher than in patients in the reference group (adjusted odds ratio,1.27; 95 % confidence interval,1.14-1.41).

Conclusions
Our findings show that a decrease at least 50% from baseline Hb during cardiac surgery is associated with adverse outcomes, even if the absolute Hb level remains above the commonly used transfusion threshold 7.0 g/dL.

Introduction

Cardiac surgery is associated with intraoperative blood loss and hemoglobin (Hb) decrease, which can lead to an anemic state. Anemia is a recognized risk factor for operative mortality; additionally serious and invalidating postoperative morbidity like stroke, myocardial infarction, and renal failure have been described.[1–4] Transfusions with red cells (RBCs) serve to prevent the occurrence of anemia-related complications, but have also been associated with severe side effects.[5,6] Therefore, it is sometimes unclear whether an anemic patient will benefit from a RBC transfusion or not.

Measuring tissue oxygen delivery would be the best way to measure a critically low Hb level that may benefit from a RBC transfusion, but since this is not yet possible surrogate indications for transfusion are used. In cardiac surgery often a transfusion threshold of 7.0 g/dL is used. It has been suggested that the extent of an acute decrease in Hb might pose a greater risk for postoperative complications than a Hb decreasing below 7.0 g/dL.[7]

This could imply that a relative transfusion threshold might be more useful in preventing ischemia-related complications than an absolute transfusion trigger. This would especially be the case in patients with a 'higher' preoperative Hb level, because they must tolerate a larger Hb decrease before being transfused with RBCs when a fixed transfusion trigger is used. In the literature, the use of a relative transfusion trigger of 50% Hb decrease has led to fewer postoperative adverse events.[7]

Our primary objective was to examine the association between intraoperative acute anemia - defined as a Hb decrease of 50% or more – on a composite endpoint of postoperative complications. Our secondary objective was to analyze the relation between RBC transfusions and the composite endpoint in patients with an intraoperative Hb decrease of 50% or more with a nadir Hb of higher than 7 g/dL.

Materials and Methods

This study complied with the Declaration of Helsinki (2012-2013 revision. The local research ethics committee approved this study and the need for informed consent was waived.

Study population

We performed a single-centre cohort study that included 11,580 consecutive patients who underwent cardiac surgery in the Amphia Hospital in Breda, the Netherlands.

Annually, approximately 1500 patients undergo cardiac surgery at the Amphia Hospital. After surgery, patients were admitted at a 26-bed, level III intensive care unit.

Patients undergoing all types of on-pump cardiac surgery from January 1, 2001 until December 31, 2011 were included. To avoid bias of preexistent anemia and polycytemia, we excluded patients with an abnormal Hb level. Therefore, we only included patients with a preoperative Hb between 12.0 and 16.0 g/dL in women and 13.0 and 18.0 g/dL in men according to the definition of the World Health Organization (WHO).[8] All RBC transfusions prescribed to patients were allogeneic and leukoreduced. Patients of whom no perioperative Hb levels were available were excluded.

Decisions regarding patient care or perioperative transfusions were left to the attending anesthesiologist and/or surgeon, according to the transfusion guidelines of the American Association of Anesthesiologists and the Dutch transfusion guideline.[9,10]
On the intensive care unit and the ward, transfusions were prescribed by the attending physician based on the assumed cardio and respiratory status of the patient. This Dutch guideline stated that RBC transfusion is usually indicated when the Hb level is < 7 g/dL and rarely higher than 9 g/dL. In case of Hb levels between 7 and 9 g/dL cardiopulmonary reserve, age, comorbidity and blood loss determines the transfusion threshold. In practice a transfusion trigger of 7 g/dL was applied.

Data collection

Data collection for this cohort started January 1, 1997. Intraoperative Hb data were not collected until 2001. To answer our specific research question, patients who underwent cardiac surgery prior to January 1, 2001, were therefore excluded. Thus, our cohort comprised patients who underwent on-pump cardiac surgery from January 1, 2001, until December 31, 2011. Data collection was compliant with the National Cardiac Surgery Registry and the National Intensive Care Registry.[11] All data were acquired from pre-, intra-, and postoperative routine blood draws and medical files.

Measurements

The preoperative Hb level was routinely measured in all patients and the last preoperatively measured Hb level was used as preoperative Hb in our study. Intraoperative Hb was measured at the induction of anesthesia, 30 minutes after the start of cardiopulmonary bypass (CPB), and after heparin reversal before chest closure. Additional Hb measurements were left to the discretion of the attending anesthesiologist and/or surgeon and were mostly performed when the patient's condition required strict monitoring. The lowest intraoperative Hb was taken as the nadir Hb. Only patients whose pre- as well as intraoperative Hb level were available were included in the present analysis.
The Hb decrease in percentage was calculated as: [(preoperative Hb – nadir Hb)/preoperative Hb] x 100.

Outcome definitions

Our primary aim was to analyze the effect of a Hb decrease of 50% or more during cardiac surgery on a composite endpoint of possible anemia-related complications comprising in-hospital death and/or stroke and/or acute kidney failure and/or myocardial infarction. Stroke was defined as a new persistent cerebrovascular event leading to neurological defaults and was diagnosed by a neurologist. Acute kidney failure was defined as the
need for postoperative renal replacement therapy when this was not indicated before and/or an increase in serum creatinine of more than 100%. The diagnosis postoperative myocardial infarction was made based on either the occurrence of new Q waves on the electrocardiogram or ischemic ST changes in combination with abnormal postoperative troponin T levels (troponin T level > 0.5 µ/L for coronary artery bypass grafting (CABG) surgery, troponin T level > 0.8 µ/L for valve surgery and troponin T level > 1.0 µ/L for combined CABG and valve procedures). Both serum

creatinine and troponin T were routinely measured in every patient postoperatively. A secondary aim was to analyze the association between RBC transfusion and the composite endpoint in the four different categories independently, in particular because we were interested in the effect of RBC transfusion in patients with a Hb decrease of 50% or more.

Statistical analyses

We divided our cohort in four categories based on absolute and relative Hb decrease using the cut off points described previously. Specifically, we analyzed the association between a 50% Hb decrease or more and the composite endpoint in the presence and in the absence of a Hb level of less than 7 g/dL as this is a commonly used transfusion trigger.

The first (reference) category consisted of patients who had an intraoperative Hb decrease less than 50% and whose intraoperative nadir Hb remained higher than 7 g/dL. Furthermore, the categories consisted of patients who only had a Hb level of less than 7 g/dL (second category), only an intraoperative Hb decrease of 50% or more (third category), and both an intra-operative Hb level of less than 7 g/dL and a Hb decrease of 50% or more (fourth category).

Multivariable logistic regression models were used and crude as well as adjusted results are presented. Covariates were included in the adjusted analysis if they were considered a risk factor for the composite endpoint and their incidence differed between the four categories. Because of the etiological nature of our research question we also included covariates related to the exposure and the outcome irrespectively if there were differences between the four categories.[12] We adjusted for the following pre- and intra-operative variables;

Preoperative variables

Preoperative variables included age (as a continuous variable), sex, current smoking, preoperative Hb (g/dL), vascular disease (defined as having previous vascular surgery and/or intermittent claudication), liver cirrhosis (diagnosed by a positive biopsy and documented portal hypertension or previous periods of upper gastrointestinal bleeding due to portal hypertension or previous episodes of liver failure, coma or encephalopathy), hematologic malignancy (as diagnosed by a hematologist), left ventricle hypertrophy (diagnosed on echocardiography), atrial fibrillation, endocarditis (according to the Duke criteria), hypertension (diagnosis retrieved from patient’s history and/or treatment with antihypertensive drug therapy), chronic obstructive pulmonary disease (COPD; diagnosis retrieved from patient’s history and treatment with bronchodilators and/or corticosteroids), diabetes (defined as receiving any antidiabetic drug therapy), myocardial infarction (as diagnosed by the referring cardiologist), aspirin use, clopidogrel use, use of anticoagulant drugs (heparin, low-molecular-weight heparin, coumarines or a combination), creatinine clearance (as a continuous variable), fibrinogen (g/dl; as categorical variable; <2 / > 2 g/dl), New York Heart association (NYHA) class, respiratory failure (defined as the need for mechanical ventilation), previous cardiac surgery, emergency surgery, type of surgery (CABG, CABG plus valve surgery, CABG plus other, valve surgery or other), cardiopulmonary resuscitation (CPR) 24h before surgery.

Intra-operative variables

Intraoperative variables included use of antifibrinolytics (aprotinin, tranexamic acid, other), lowest intraoperative temperature (as continuous variable), CPB duration and operation duration (both as continuous variables), fresh frozen plasma (FFP) and platelet (PLT) transfusion (as binary variables), circulatory arrest, number of coronary arteries affected and cell-saver blood returned to patient (as binary variable). Missing data in the database were
imputed using a multiple imputations model.[13]
RBC transfusions were not included in the overall model because the relationship between RBC transfusions and the composite endpoint in the four patient groups was analyzed separately.
Effect modification occurs when the magnitude of the effect of the primary exposure on an outcome differs depending on the level of a third variable. In this situation, computing an overall estimate of association has little meaning. One common way of dealing with effect modification is to examine the association separately for each
level of the third variable.[14,15] To analyze if there was any effect modification present in our study sample we did separate analyses, stratifying sex and type of surgery, for all patients with a Hb decrease of at least 50%.

Results

Characteristics of the study population

Data of 16,352 patients were collected of which 11,508 patients were included in the analysis. Figure 1 presents a flow chart of patient exclusions and number of patients available for analysis. Perioperative Hb data were missing for 3341 patients, so they were excluded. A total of 181 patients were excluded because of missing intraoperative Hb data. An additional 1322 were excluded because they underwent off-pump surgery. A total of 1473 (12.8%) patients had a Hb decrease of 50% or more.

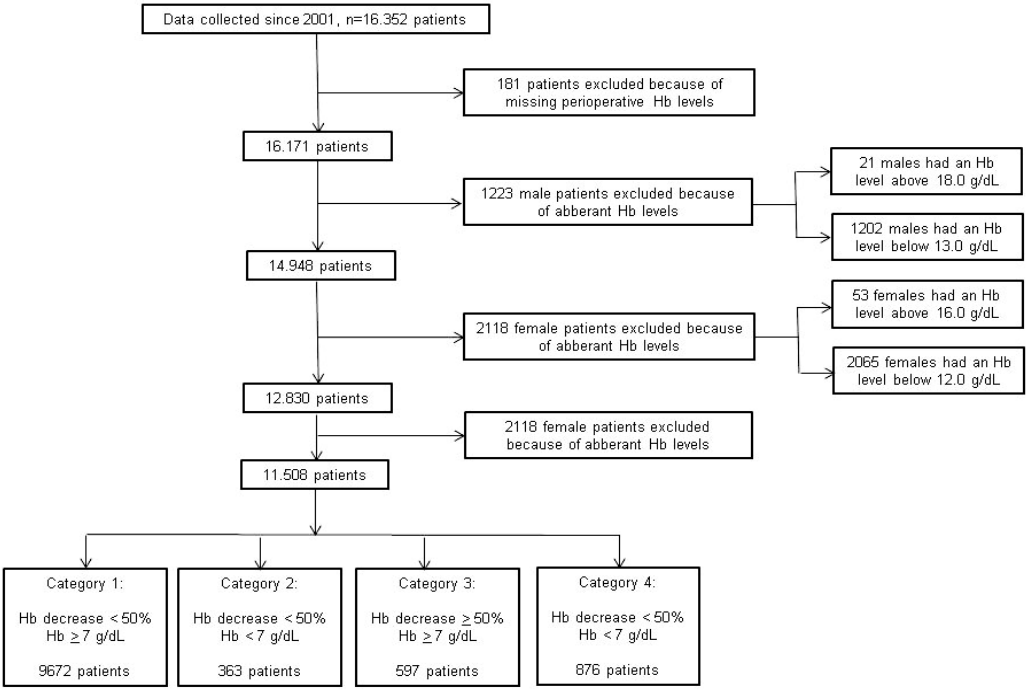

Figure 1. *In- and exclusion flowchart*

Perioperative characteristics of the included patients according to Hb loss of 50% or more and/or nadir Hb below 7 g/dL are shown in Table 1. As expected comorbidities, demographics, and risk factors differed between patients with different amounts of blood loss. For example patients with an intraoperative Hb loss of 50% or more and a nadir Hb of higher than 7 g/dl were more often male, had less often emergency surgery performed, had a higher preoperative Hb and were less frequently transfused. Also, they received less inotropic drugs.

Blood loss and anemia-related complications

Overall, anemia-related complications occurred in 2322 (20.7%) patients, of who 254 (2.2%) died, 952 (8.3%) had a stroke, 569 (5.0%) developed postoperative renal failure requiring renal replacement therapy and/or an increase in serum creatinine of more than 100% and 1176 (10.3%) suffered a postoperative myocardial infarction. Some patients suffered more than one complication.

Compared to patients who did not lose 50% or more of their Hb and who remained higher than 7 g/dl (reference group, Category 1), patients in Category 3 with a Hb loss of 50% or more whose intraoperative nadir Hb remained higher than 7 g/dL did suffer more anemia-related complications (adjusted OR [aOR], 1.26; 95% Confidence Interval [CI] 1.13-1.41; table 2). In patients who had a Hb decrease of 50% or more and an intraoperative nadir Hb of less than 7 g/dL there was also a positive association with the composite endpoint (aOR 1.12; 95% CI 1.02-1.22). Patients who had a Hb decrease of less than 50% but who did experience a nadir Hb of less than 7 g/dL during surgery had roughly the same odds to suffer from the composite endpoints as the patients in the reference category (aOR, 0.93; 95% CI, 0.82-1.06).

Effect modification and stratification

To examine potential effect modification by sex and type of surgery, we performed stratified analyses for males and females as well as for type of surgery (CABG and CABG in combination with other surgical procedures vs. remaining non-CABG surgeries). Patients with an isolated Hb level of less than 7 g/dL despite less than 50% Hb decrease were more often female (85%), which is often a cause of a different profile of comorbidities and outcomes. When we stratified our analysis for sex, a more distinct association between a Hb decrease of at least 50% and the composite endpoint was found in women. This could be explained by the fact that for a woman to reach a Hb decrease of 50% or more, it means that a much lower nadir Hb must be reached compared to men, even though, this association was not statistical significant (aOR, 1.40; 95% CI, 1.09-1.81). When we examined CABG or combined surgery with CABG combined versus other surgical procedures, no apparent modifications of the effect of Hb decrease on the composite endpoint were found. These results are displayed in table 2A.

Table 1. Patient characteristics (N= 11508)

	Total	Missing	Hb decrease <50% & Hb > 7 g/dL (n=9672)	Hb decrease <50% & Hb < 7 g/dL (n=363)	Hb decrease >50% & Hb > 7 g/dL (n=597)	Hb decrease >50% & Hb < 7 g/dL (n=876)
Pre-operative variables:						
Female, N (%)	3202 (27.8)	-	2304 (23.8)	310 (85.4)	86 (14.4)	502 (57.3)
Age (year), median (IQR)	67 (59-73)	-	67 (59-73)	71 (64-77)	65 (57-71)	69 (61-74)
Weight (kg), median (IQR)	80 (71-89)	1	81 (72-90)	70 (63-79)	79 (73-87)	72 (64-81)
Aspirin use, N (%)	6489 (57.3)	182	5445 (57.0)	208 (59.1)	360 (62.2)	476 (56.7)
Clopidogrel use, N (%)	2183(17.1)	58	1950 (17.9)	59(16.3)	72(12.0)	102(11.6)
Anticoagulant drug use, N (%)*	3476 (30.3)	35	3009 (31.2)	99 (27.3)	126 (21.2)	242 (27.8)
Pre-operative fibrinogen level <2, N (%)	26 (0.5)	6068	23 (0.5)	1 (0.8)	1 (0.8)	1 (0.6)
Diabetes	2085 (18.2)	19				
Diabetes I, N (%)	365 (3.2)		296 (3.1)	19 (5.2)	12 (2.0)	38 (4.3)
Diabetes II, N (%)	1720 (15.0)		1415 (14.7)	82 (22.6)	77 (12.9)	146 (16.7)
Hypertension, N (%)	6494 (56.4)	3	5449 (56.4)	229 (63.1)	318 (53.3)	498 (56.8)
Cerebro-vascular disease (history of stroke, transient ischaemic attack, other), N (%)	1089 (9.5)	7	878 (9.1)	53 (14.6)	58 (9.7)	100 (11.4)
Hematological malignancy, N (%)	29 (0.3)	7	23 (0.2)	2 (0.6)	2 (0.3)	2 (0.2)
Atrial fibrillation, N (%)	1392 (12.1)	15	1220 (12.6)	46 (12.7)	49 (8.2)	77 (8.8)
History of myocardial infarction, N (%)	1894 (19.7)	1916	1698 (20.8)	40 (12.7)	55 (12.4)	101 (14.9)
Left ventricular hypertrophy, N (%)	2815 (24.6)	68	2368 (24.6)	99 (27.3)	119 (20.0)	229 (26.4)
Previous cardiac surgery, N (%)	747 (6.5)	1	573 (5.9)	22 (6.1)	46 (7.7)	106 (12.1)
No. coronary arteries affected, median (IQR)	3 (1-3)	26	3 (1-3)	3 (0-3)	3 (2-3)	3 (2-3)
Ejection Fraction, N (%)		187				
- >50%	8896 (78.6)		7443 (78.2)	287 (80.2)	486 (82.9)	680 (79.5)
- 25-50%	1928 (17.0)		1637 (17.2)	59 (16.5)	84 (14.3)	148 (17.3)
- < 25%	497 (4.4)		442 (4.6)	12 (3.4)	16 (2.7)	27 (3.2)
Creatinine clearance (ml/min), median (IQR)	82 (65-102)	20	84 (67-104)	64 (50-78)	82 (66-102)	68 (55-86)
Chronic renal failure (creatinine> 177), N (%)	131 (1.1)	3	93 (1.0)	12 (3.3)	4 (0.7)	22 (2.5)
Acute renal failure N (%)	99 (0.9)	7	86 (0.9)	1 (0.3)	2 (0.3)	10 (1.1)
Type of surgery, N (%)		-				
- CABG	7028 (61.1)		5885 (60.8)	187 (51.5)	419 (70.2)	537 (61.3)
- CABG + valve	1584 (13.8)		1276 (13.2)	78 (21.5)	68 (11.4)	162 (18.5)
- CABG + other	87 (0.8)		67 (0.7)	4 (1.1)	4 (0.7)	12 (1.4)
- Valve replacement	2397 (20.8)		2123 (21.9)	84 (23.1)	82 (13.7)	108 (12.3)
- Other	412 (3.6)		321 (3.3)	10 (2.8)	24 (4.0)	57 (6.5)
Emergency surgery, N (%)	672 (5.8)	3	562 (5.8)	22 (6.1)	18 (3.0)	70 (8.0)
Euroscore I, median (IQR)	5 (3-7)		5 (3-7)	7 (5-9)	4 (2-6)	6 (4-9)

Table 1. Patient characteristics (N= 11508)

Intra-operative variables:						
Time in surgery in minutes, median (IQR)	240 (205-281)	14	235 (205-275)	252 (210-305)	245 (207-295)	270 (225-340)
CPB duration (min), median (IQR)	97 (78-125)	-	95 (77-122)	104 (80-136)	99 (79-127)	111 (85-160)
Circulatory arrest, N (%)	141 (1.2)		86 (0.9)	5 (1.4)	12 (2.0)	38 (4.3)
IABP, N (%)	485 (4.2)	-	379 (3.9)	16 (4.4)	19 (3.2)	71 (8.1)
Inotropic drug use, N (%)	4494 (39.4)	88	3786 (39.5)	156 (43.1)	161 (27.1)	391 (44.8)
Anti-fibrinolytic drug use, N (%)	7671 (67.2)	92	6774 (70.5)	213 (59.7)	269 (45.5)	415 (48.0)
Cellsaver blood returned during surgery, N (%)	11495 (99.9)	-	9666 (99.9)	362 (99.7)	595 (99.7)	872 (99.5)
≥ 1 unit RBC during surgery, N (%)	1300 (11.3)	1	703 (7.3)	157 (43.3)	47 (7.9)	393 (44.9)
≥ 1 unit FFP during surgery, N (%)	598 (5.2)	-	395 (4.1)	22 (6.1)	39 (6.5)	142 (16.2)
≥ 1 unit platelets during surgery, N (%)	569 (4.9)	-	373 (3.9)	24 (6.6)	43 (7.2)	129 (14.7)
Hb measurements:						
Pre-operative Hb (g/dl), median (IQR)	14.3 (13.5-15.1)	-	14.3 (13.7-15.1)	12.7 (12.4-13.0)	15.5 (15.0-16.1)	13.8 (13.2-14.5)
Lowest Hb during surgery (g/dl), median (IQR)	8.5 (7.6-9.3)	-	8.7 (8.1-9.7)	6.7 (6.6-6.9)	7.4 (7.2-7.7)	6.4 (6.0-6.7)
Hb at hospital discharge, median (IQR)	10.5 (9.7-11.4)	220	10.5 (9.7-11.4)	10.3 (9.7-10.9)	10.6 (10.0-11.6)	10.5 (9.7-11.3)
In hospital mortality, N (%)	254 (2.2)	-	167 (1.7)	17 (4.7)	11 (1.8)	59 (6.7)
Acute kidney injury, N (%) †	569 (5.0)	236	435 (4.6)	23 (6.5)	27 (4.6)	84 (9.8)
Stroke, N (%) ‡	952 (8.3)	14	759 (7.9)	34 (9.4)	52 (8.7)	107 (12.2)
Acute myocardial infarct, N (%)	1176 (10.3)	1916	953 (9.9)	38 (10.5)	63 (10.6)	122 (14.0)
Composite endpoint, N (%)	2322 (20.7)	303	1865 (19.8)	85 (24.2)	124 (21.2)	248 (29.2)

** Heparin, low molecular weight heparin (LMWH), coumarines or a combination*

† Defined as the postoperative need for renal replacement therapy or a creatinine rise > 100%

‡ Defined as a new persistent cerebro-vascular event leading to neurological defaults.

Table 2. Composite endpoint in relation to intraoperative Hb decrease (N = 11508)

Patient category	Number	Hb decrease ≥ 50%	Hb < 7 g/dL	OR (crude)	95% CI	p value	OR* (adjusted)	95% CI	p value
1 (ref)	9672	–	–	1			1		
2	363	–	+	1.28	1.16-1.42	<0.001	0.93	0.82-1.06	0.309
3	597	+	–	1.08	0.99-1.17	0.064	1.26	1.13-1.41	<0.001
4	876	+	+	1.65	1.55-1.75	<0.001	1.12	1.02-1.22	0.017

**Adjusted for acetylsalicylic acid, clopidogrel and anticoagulant drug use, preoperative fibrinogen of less than 2 g/dL, hematologic malignancy, antifibrinolytic use, cell-saver blood returned to patient, lowest temperature intraoperative, previous cardiac surgery, preoperative Hb (g/dL), emergency surgery, CPB duration, operation duration, type of surgery, FFP and PLT transfusion during surgery, liver cirrhosis, preoperative circulation arrest, number of coronaries affected, age, sex, creatinine clearance, NYHA class, left ventricle hypertrophy, respiratory failure, smoking, atrial fibrillation, endocarditis, hypertension, COPD, diabetes, vascular disease, preoperative myocardial infarction, and CPR 24 hours before surgery.*

Table 2A: Patients with more than 50% Hb decrease in relation to the composite endpoint stratified for gender & type of surgery

Intra-operative Hb:		N	Hb decrease >50%	Hb < 7 g/dl	OR (crude)	95% CI	P-value	OR* (adjusted)	95% CI	P-value
Category 3	Male	511	+	-	1.12	1.02-1.22	0.016	1.22	1.08-1.39	0.002
Category 4	Male	374	+	+	1.67	1.51-1.83	<0.001	1.13	0.98-1.31	0.092
Category 3	Female	86	+	-	1.04	0.84-1.27	0.735	1.40	1.09-1.81	0.009
Category 4	Female	502	+	+	1.44	1.32-1.57	<0.001	1.05	0.93-1.19	0.444
Category 3	CABG	491	+	-	1.07	0.97-1.19	0.170	1.24	1.07-1.43	0.003
Category 4	CABG	711	+	+	1.46	1.34-1.59	<0.001	1.10	0.97-1.24	0.153
Category 3	Non-CABG	106	+	-	1.19	1.03-1.37	0.015	1.26	1.05-1.51	0.013
Category 4	Non-CABG	165	+	+	1.95	1.77-2.14	<0.001	1.19	1.04-1.36	0.014

** Adjusted for: acetylic salicylic acid, clopidogrel and anti-coagulant drug use, preoperative fibrinogen <2 g/dl, haematological malignancy, anti-fibrinolytic use, cell saver blood returned to patient, lowest temperature intra-operative, previous cardiac surgery, pre-operative Hb (g/dL) emergency surgery, CPB duration, operation duration, type of surgery, FFP and platelet transfusion during surgery, liver cirrhosis, preoperative circulation arrest, number of coronaries affected, age, sex, creatinine clearance, NYHA class, left ventricle hypertrophy, respiratory failure, smoking, Atrial fibrillation, endocarditis, hypertension, COPD, diabetes, vascular disease, preoperative myocardial infarction, CPR 24h before surgery.*

Red cell transfusions

As shown in Table 1, 7.3 and 7.9% of patients in categories 1 and 3 received red blood cell transfusions though their nadir Hb remained higher than 7 g/dl. This is most often the result of clinical judgment by the attending physician or intraoperative events, which indicated the need of a blood transfusion despite the Hb level higher than the transfusion trigger of 7 g/dl. Table 3 presents the association between RBC transfusions and the composite endpoint within each of the four categories of Hb decrease. In Category 1 where there was neither a Hb decrease of at least 50 % nor a Hb level of less than 7 g/dL, the adjusted odds of acquiring the composite endpoint was

1.51 (95% CI, 1.38-1.66) in transfused patients compared with non-transfused patients. In patients from Categories 2 and 4, 43.3 and 44.9% received red cell transfusions. Among these patients transfusion was associated with a decreased odds of developing the composite endpoint (aOR 0.57, 95% CI 0.42-0.77, for Category 2; and aOR 0.95, 95% CI 0.78-1.16 for Category 4).
Among patients who had a Hb decrease of more than 50% but had an intraoperative nadir Hb of more than 7 g/dL, 47 (7.9%) patients received RBC transfusions. Among these patients transfusion was associated with a nonsignificant lower odds of developing composite endpoints (aOR, 0.88; 95% CI, 0.55-1.41).

Table 3: Composite endpoint in relation to RBC transfusion (n=11,508)

RBC transfusion	Number	Number (%) transfused	Hb decrease ≥ 50%	Hb < 7 g/dL	OR crude	95% CI	P value	OR* adjusted	95% CI	P value
Category 1	9672	703 (7.3)	–	–	2.67	2.50-2.86	<0.001	1.26	1.17-1.36	<0.001
Category 2	363	157 (43.3)	–	+	0.91	0.74-1.11	0.348	0.57	0.42-0.77	<0.001
Category 3	597	47 (7.9)	+	–	3.00	2.33-3.86	<0.001	0.88	0.55-1.41	0.590
Category 4	876	393 (44.9)	+	+	1.64	1.45-1.84	<0.001	0.95	0.78-1.16	0.618

** Adjusted for acetylsalicylic acid, clopidogrel and anticoagulant drug use, preoperative fibrinogen of less than 2 g/dL, hematologic malignancy, antifibrinolytic use, cell-saver blood returned to patient, lowest temperature intraoperative, previous cardiac surgery, preoperative Hb (g/dL), emergency surgery, CPB duration, operation duration, type of surgery, FFP and PLT transfusion during surgery, liver cirrhosis, preoperative circulation arrest, number of coronaries affected, age, sex, creatinine clearance, NYHA class, left ventricle hypertrophy, respiratory failure, smoking, atrial fibrillation, endocarditis, hypertension, COPD, diabetes, vascular disease, preoperative myocardial infarction, and CPR 24 hours before surgery.*

Discussion

In our cohort of cardiothoracic surgery patients an intraoperative Hb decrease of 50% or more was associated with a higher incidence of postoperative complications including in-hospital mortality and/or stroke and/or kidney failure and/or myocardial infarction, even if their Hb concentration remained higher than 7 g/dL. Males with higher preoperative Hb were overrepresented in this category , but when the analysis was stratified for gender these findings also applied to females with a higher preoperative Hb.
This finding is in agreement with a previous study performed by Karkouti and colleagues who analyzed the degree of acute anemia that patients can safely tolerate during cardiac surgery.[7] That study also showed that a Hb decrease of more than 50% during surgery was associated with in-hospital mortality, stroke and kidney failure (OR 1.53, 95% CI, 1.12-2.08).[7] In this study we combined two cut-off points creating four categories. This way we were able to analyze the association between absolute and relative Hb loss in more detail. We chose a broader definition of the composite endpoint; in addition to in-hospital mortality and/or stroke and/or renal failure our endpoint also comprised postoperative myocardial infarction.
Approximately 8% of the patients with more than 50% Hb loss were transfused RBCs despite Hb levels above 7 g/dL. In these patients, as well in patients who reached a nadir Hb below 7g/dL,

transfusion was associated with fewer postoperative complications, suggesting that transfusion might be efficacious in these patients. Yet, given the limited number of transfused patients in this subgroup and the lack of statistical significance, these findings have to be interpreted with caution.

To appreciate these findings, some issues need to be discussed. One of the strengths of our study was the large number of consecutive patients. The outcome variables of all patients were known and therefore selection bias was avoided. Also, due to the large amount of detailed covariates we were able to correct thoroughly for possible confounding caused by differences in preoperative patient characteristics. While seeking causal inferences between exposure and outcome, we chose to adjust for risk factors for the outcome and differences in baseline patient characteristics independent of their significance.[12]

A limitation of our study was that we only took intra-operative Hb and transfusion into account; this does not allow us to convey the conclusions to the whole perioperative period. The complexity of unravelling whether the complications that occur after cardiac surgery are caused by blood loss or by the events leading to excessive blood loss is well recognized. Although we tried to be as thorough as possible (for instance, by excluding re- sternotomies from our analysis) we cannot distinguish between the cause of Hb loss more than 50% and the acute anemia itself to explain the increased risk for the composite endpoint in this category.

A further limitation is that the number and timing of Hb measurements during surgery were not documented (besides the four standard measurements). Additional Hb measurements were performed on request by the attending anesthesiologist when deemed needed. This meant that the 'correct' lowest intraoperative Hb level might have been missed and that patients could have been misclassified. The risk of missing the 'correct' nadir Hb is a general problem in this type of study, since continuous measurement of Hb is not accurate enough for clinical use, especially in patients who have a low perfusion state.[16,17]

Our findings are biologically plausible, because it is known that an acute decrease in Hb level could have adverse consequences on end-organ function, especially on oxygen dependent organs as the kidney, heart and brain.[18]

An acute reduction in Hb level will be sensed on a cellular level which leads to adaptive cardiovascular and respiratory responses to optimize tissue oxygen delivery.[13,18–21] These adaptive responses include an increase in cardiac output, a reduction in systemic vascular resistance with organ specific vasodilatation, and an increase in tissue oxygen extraction.[18] Although these adaptive mechanisms can keep homeostatic balance intact for some time, depending on the extent and timing of Hb loss adaptive mechanisms may fail and eventually lead to end-organ damage.

The amount of Hb decrease that can be safely tolerated is highly debated. As long as cellular oxygen content measurements cannot be applied routinely to define whether or not a RBC transfusion is indicated, it is of great importance to define the most beneficial transfusion policy. In critically ill patients and in patients undergoing cardiothoracic surgery, a restrictive transfusion strategy is propagated, with the purpose of reducing the risks associated with the (inappropriate) transfusion of RBCs, as those risks are well put forward in literature.[22–25]

Interestingly, a pilot trial in patients with symptomatic coronary artery disease, comparing a restrictive (8 g/dL) versus a liberal (10 g/dL) transfusion threshold, showed that the liberal transfusion strategy was associated with a trend for fewer major cardiac events and deaths.[26] This underscores that the optimal transfusion threshold depends on the clinical situation and therefore differs for individual patients, which is corroborated by the results of an international forum in which 38 hospitals answered a questionnaire regarding their transfusion triggers and the use of guidelines. In those hospitals, target Hb on CPB differed, ranging from 6.0 till 8.0 g/dL.[25,27,28]

Also the appropriate acceptable amount of hemodilution is uncertain. Several studies have addressed the adverse effects of a low nadir Hct.[29–31] But if and when exactly volume and/or Hb replacement during cardiac surgery is indicated needs to be addressed in future studies.[18,32]

The results of our study imply that a fixed transfusion trigger might not be in the best interest of patients with a 'higher' preoperative Hb. Patients with a high preoperative Hb level must lose a greater Hb volume before reaching the transfusion triggers currently described in the guidelines.[9,10] Therefore, these patients are more likely to suffer from anemia-related complications. It is unknown whether RBC transfusions decrease the risk of anemia-related complications in patients with an intraoperative Hb decrease of 50% or more. In our study we found that RBC transfusions were associated with a lower incidence of the composite endpoint in patients with a Hb decrease of 50% while their nadir Hb remained higher than 7 g/dL. The previously mentioned questionnaire shows that the transfusion threshold described in guidelines or local protocols is not the leading reason for transfusions, as additional variables also serve as important triggers.[28] Taken into account the results of our study, a Hb decrease of 50% or more poses one of these additional variables.

In conclusion, patients with an intraoperative Hb decrease of 50% or more may suffer from anemia-related complications even if their Hb remains higher than 7 g/dL.

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