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Is it the patient or the physician who cannot tolerate anemia? A prospective analysis in 1854 non-transfused coronary artery surgery patients

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Abstract

Background and objective: Low hematocrit level and transfusion may coexist during cardiopulmonary bypass and the actual impact of one on the outcome parameters may be counfounded or masked by the other. This study aims to determine the impact of the lowest hematocrit level during cardiopulmonary bypass on outcome parameters in non-transfused patients. Methods: Two thousand six hundred and thirty-two consecutive patients who underwent isolated coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass were evaluated prospectively: 1854 (70.4%) patients who did not receive any red blood cells during hospital stay were included in the study. Perioperative data and outcome parameters were recorded. Outcomes were evaluated in 2 groups according to the lowest level of hematocrit (>21%: high hematocrit group, n= 1680, (91.6%) and ≤21%: low hematocrit group, n=174, (9.4%)) during cardiopulmonary bypass. Results: Overall mean lowest hematocrit level of patients was 27.7±4.4% (19.7±1.9% in the low hematocrit group, 28.5±4.1% in the high hematocrit group). The comparison of outcome parameters regarding the time on ventilator, duration of intensive care unit stay, intensive care unit re-admission, hospital re-admission, reoperation for bleeding or tamponade, low cardiac output, postoperative atrial fibrillation, stroke, creatinine level at hospital discharge, new onset renal failure, mediastinitis, pulmonary complication and mortality rates were similar in both groups. Conclusions: Our findings suggest that a lowest hematocrit level of ≤21% during cardiopulmonary bypass has no adverse impact on outcome after isolated coronary surgery in non-transfused patients.

Keywords

cardiopulmonary bypass; coronary artery bypass grafts; outcomes; blood transfusion

Introduction

There remains controversy as to when patients undergoing cardiac surgery should receive a transfusion and whether a low hematocrit and its treatment with a transfusion of red cells influences outcome. For more than half a century, hemodilution has been an important tool in cardiac surgery. However, its safety range has always been questioned. The lowest hematocrit was found to be associated with prolonged intensive care unit and hospital stay,[1] increased postoperative renal failure,[2] stroke,[3] and even with increased operative mortality.[4] For that reason, almost half of the patients undergoing coronary artery bypass grafting in the United States still receive ≥1 unit packed red blood cells, with the most common number being 2 units, and the probability of receiving blood is greater when procedures are more complex.[5,6]

On the other hand, there is an increasing amount of evidence that correlates adverse outcome and transfusion during cardiac surgery.[7,8] Although the immediate impact on operative mortality is significantly greater, long-term survival is also affected.[9,10]

More than a decade ago, a task force of the American Society of Anesthesiologists (ASA) developed a consensus statement based mostly on level B and C evidence

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and concluded that, "red blood cell transfusions should not be dictated by a single hemoglobin 'transfusion trigger' but instead should be based on the patient's risk of developing complications of inadequate oxygenation".[11] However, the decisions to transfuse are still based on hemoglobin thresholds tailored to the patient's age and comorbidity. Moreover, these thresholds vary widely, both within and between institutions. No definite rule depending on physiological basis existed so far, thus, the overall decision process for transfusion might have been a choice of the physician more than the physiologic needs of the patient. Recently published guidelines for blood transfusion and conservation in cardiac surgery by The Society of Thoracic Surgeons recommend transfusion for an hemoglobin of <7 g/dl.[12] However, the level of evidence is 'C' with a recommendation of 'Class 2b', which means that supporting evidence is inadequate. This study aims to elucidate the sole impact of the lowest hematocrit level during cardiopulmonary bypass (CPB) on outcome parameters after isolated coronary artery bypass surgery in non-transfused patients. Our hypothesis was that the previously reported adverse outcomes in patients with low hematocrit levels during CPB might not be valid in the current era if anemia is tolerated and patients are not transfused.

Methods

This observational study used prospectively collected data from consecutive isolated on-pump coronary artery bypass procedures performed by one surgical and anesthesia team between 1999 and 2006. The use of these data for this study was approved by the Institutional Review Board. Complete data of 2632 patients were retrospectively reviewed. Patients who received red blood cells at any time during their hospital stay (peri/postoperatively) (n: 778; 29.6%) were excluded from the study; the remaining 1854 (70.4%) patients were further analyzed. Perioperative data and outcome parameters were recorded. Although there is no strong data available with regard to the cutoff point for hematocrit level for adverse outcome, the general tendency is to avoid hematocrit levels below 20-22%.[1-13,14] Additionally, Murphy and colleagues suggest a 21% hematocrit value as a practical 'restrictive' threshold for a randomized trial.[8] For that reason, the patients were allocated into two groups according to their lowest hematocrit levels during CPB; >21%: high hematocrit group, (n= 1680), (91.6%) and ≤21%: low hematocrit group (n=174), (9.4%).

During the hypothermic period, none of the patients was transfused based on hematocrit values. However, if the hematocrit value was below 17% during the hypothermic period and below 20% just before rewarming, red blood cells were given and these patients were excluded from the study.

Anesthesia and Operative Technique

The night prior to the operation, all patients received alprazolam 0.5 mg PO (Xanax). Midazolam 125 μg/kg IM was given 30 minutes before the operation. A 16 gauge (G) IV cannula was inserted into all patients in the operating room. Anesthetic induction consisted of midazolam 50 μg/kg, pancronium 0.15 mg/kg, and fentanyl 25 to 35 μg/kg. After endotracheal intubation, 50% O_2, 50% N_2O, and 3-4% desflurane was used for all hemodynamically stable patients. Desflurane and N_2O were discontinued at times of hemodynamic instability. Maintenance anesthesia and muscle relaxation were accomplished with midazolam and vecuronium 80 μg/kg/hr. Furosemide 0.5 mg/kg was administered routinely. Priming solution for CPB included 900 ml Ringer's lactate solution, 150 ml 20% mannitol, and 60 ml sodium bicarbonate (8.4%). During CPB, mean arterial pressure and pump flow were kept between 50-80 mmHg, and 2.2-2.5 L/m^2, respectively. Adequacy of tissue perfusion was monitored with arterio-venous partial carbon dioxide difference (Pv-a CO_2), lactate level, urine output, and base deficit. Moderate hypothermia (32 °C) was used during CPB. Myocardial viability was preserved with antegrade cold hyperkalemic crystalloid cardioplegia (Plegisol®, Abbott Laboratories, IL, USA) except in patients with a left ventricular ejection fraction less than 0.25 in whom antegrade + retrograde blood cardioplegia associated with terminal warm blood cardioplegia was used. In patients with an ejection fraction <30 %, levosimendan infusion was used for 24 hours (0.2 mcg/kg/min) starting 4 hours preoperatively. After the termination of CPB, midazolam and vecuronium doses were decreased to 50 μg/kg/hr and discontinued at skin closure.

Postoperative Clinical Management

On arrival in the ICU, the ventilator mode was switched to synchronized intermittent mandatory ventilation (SIMV) plus pressure support and ventilator settings were adjusted as follows; respiratory rate 12/min, tidal volume 8-10 ml/kg, FiO_2:0.6, PEEP 0-5 mmHg, pressure support 10mmHg, and trigger sensitivity -2cmH_20. All patients were warmed with forced air warming until the rectal temperature reached 37°C. Basic fluid substitution during the first 20 postoperative hours was 40 ml/kg/day. Six hundred to 800 ml of this solution was the autologous blood derived from the CPB circuit and the rest was balanced crystalloid solution. Meperidine, 0.4 mg/kg IV to a total dose of 50 mg over 6 hours, was used to treat shivering. All patients were evaluated for extubation every half an hour. As soon as spontaneous breathing resumed, respiratory rate was gradually decreased to 4/min and pressure support to 4 mmHg. If there were

no contraindications for the use of beta-blockade, metoprolol was used intravenously to control hypertension. All hemodynamically stable patients without excessive chest tube drainage and $PaCO_2$ < 48 mmHg, pH > 7.30, and PaO_2/FiO_2 > 250 were extubated. After the patient was extubated, 40% to 50% oxygen was administered by face mask. Oxygen hemoglobin saturation and the respiratory rate were continuously monitored. Arterial blood gases were obtained at 30, 60, and 120 minutes postextubation. Repeated doses of diclofenac sodium 1.25 mg/kg IM was used for postoperative analgesia.

We aimed to discharge all patients on the fifth postoperative day. The decision to discharge is based on a satisfactory routine checkup on day 4, consisting of clinical examination, full blood cell count, urea and electrolyte levels, electrocardiogram, and chest roentgenogram. If the patient is medically unfit on day 5, hospitalization is prolonged, and further investigations may be performed, depending on the clinical status.

Data Source and Definitions

Our clinical database was used for outcome analysis. It is a prospectively collected database, containing relevant demographic data, comorbidities, intraoperative variables, and postoperative outcomes, including postoperative drainage, ventilation time, intensive care unit stay time, hospital stay time, transfusion rate, new onset postoperative renal failure, postoperative stroke, reoperation, arrhythmia, rate of re-admission to the intensive care unit, rate of re-admission to the hospital, and mortality.

Hematocrit measurements during the operation were performed with blood gas analysis before the induction of anesthesia, every 10 minutes during CPB, just before rewarming, and at the end of CPB. The ABL 700 (Radiometer America Inc.) blood gas analyzer was used for hematocrit measurements. This device offers a computerized spectrophotometric analysis. In the spectrum taken of a sample, the absorption recorded at each wavelength contains contributions from each of the compounds in the sample. The task then is to determine the magnitude of that contribution and, thereby, the concentration of each compound in the sample. The measurements were repeated at any time, depending on the hemodynamic or metabolic status. The lowest measured level of the hematocrit during CPB in these analyses was accepted as the lowest hematocrit. All patients were managed by the same transfusion strategy as described above.

Hospital mortality included all deaths within 30 days of operation irrespective of where the death occurred and all deaths in the hospital after 30 days among patients who had not been discharged after the operation. Postoperative blood loss was defined as total chest tube drainage. Renal complication included acute renal failure, defined as the requirement of hemodialysis postoperatively. Stroke included postoperative neurological dysfunction that was assessed by a neurologist and documented with radiologic imaging. Cranial imaging was performed when suggested by the neurologist. Delirium was not included in this definition.

Low cardiac output included patients who needed high dose inotropes (dopamine >5 μg/kg/min) for more than 4 hours and the ones who needed an intra-aortic balloon pump (IABP). Inotropic agents were used when the systolic blood pressure was < 90 mmHg, cardiac index< 2.2 L/m^2, and pulmonary capillary wedge pressure (PCWP)>15 mmHg; during or after the operation. In cases with inadequate response to inotropes, an IABP was applied in addition.

Statistical Analysis

Data are reported as a percentage or as a mean ± standard deviation. Univariate comparisons were computed using the χ^2 test or Fisher's exact test for categorical variables and *t* tests for continuous variables. Any factor with a p value of less than 0.1 on univariate analysis was entered into multiple logistic regression analysis. Statistical analysis was performed using SPSS statistical software (SPSS version 11.0, SPSS Inc, Chicago, IL). Variables were considered significant at p values less than 0.05.

Results

Overall mean lowest hematocrit level of patients was 27.7±4.4% during CPB; it was 19.7±1.9% (range: 17-21.0%) in the low hematocrit group and 28.5±4.1% (range: 21.1-50.6%) in the high hematocrit group.

The preoperative and perioperative variables were similar in both groups except for the slightly longer CPB and cross-clamp times in the low hematocrit group (Table 1). Univariate analysis revealed the risk factors for developing hematocrit levels ≤21% as: increased age, female sex, body mass index < 25 kg/m^2, preoperative hematocrit ≤ 30%, preoperative use of diuretics, preoperative use of intravenous nitrates and serum creatinine >200 mmol/l (Table 2). The predictors for developing hematocrit levels ≤21% were: preoperative hematocrit ≤30%, body mass index < 25 kg/m^2, female sex and preoperative serum creatinine >200 mmol/l at multivariate regression analysis (Table 3).

Hematocrit levels at the end of the operation were higher in the high hematocrit group when compared to the low hematocrit group (p<0.001). Fluid balance at the end of the operation was higher in the low hematocrit group (p=0.003); however, it equalized in the two groups at the end of postoperative day 1.

Ventilation time, duration of intensive care unit stay, ICU and hospital re-admission, reoperation for bleeding

Table 1. Preoperative and intraoperative variables

	High hematocrit group (n=1680)	Low hematocrit group (n=174)	*p* value
*CCS≥3 (%)	32.3	34.5	NS
*NYHA≥3 (%)	6.9	9.8	NS
Preop. congestive heart failure (%)	1.3	1.2	NS
Hypertension (%)	46	50	NS
Chronic lung disease (%)	12.5	11.5	NS
Preoperative usage of aspirin (%)	57	55	NS
Preoperative usage of clopidogrel (%)	2.9	1.1	NS
Preoperative usage of heparin (%)	4.1	4.0	NS
Ejection fraction < % 50 (%)	39.5	42.4	NS
Nonelective operation (%)	8.9	10.3	NS
Redo operation (%)	3.4	3.5	NS
Preop. atrial fibrillation (%)	2.1	1.1	NS
Diabetes mellitus (%)	22.4	25.3	NS
Renal insufficiency with dialysis (%)	0.7	1.7	NS
Preop. cerebrovascular event (%)	0.5	0	NS
Body mass index (kg/m^2)	28.1±3.9	27.8±4.2	NS
Number of distal anastomosis (n)	3.1±1	3.2±1	NS
Cardiopulmonary bypass time (min.)	57±20	61±20	0.02
Cardiac arrest time (min.)	32±13	35±14	0.02

*CCS, Canadian Cardiovascular Society Score; NYHA, New York Heart Association Score.

Table 2. Risk factors for developing hematocrit levels of 21% or lower during cardiopulmonary bypass (univariate analysis)

	High hematocrit group (n=1680)	Low hematocrit group (n=174)	*p* value
Age (y) (mean±SD)	59±9	61±8	0.001
Female sex (%)	18.5	39.1	<0.001
Preoperative hematocrit (%)	40.9±4.4	34.1±4.7	<0.001
Preoperative hematocrit≤30% (%)	4.2	23.6	<0.001
Preoperative use of diuretics (%)	6.5	11.8	0.05
Preoperative use of intravenous nitrates (%)	6.4	12.9	0.02
Body mass index<25 kg/m^2 (%)	4.5	7.1	0.04
Serum creatinine>200 mmol/l (%)	2.1	7.1	0,014

Table 3. Risk factors for developing hematocrit levels of 21% or lower during cardiopulmonary bypass (multivariate analysis)

	Odds ratio	95 % CI	*p* value
Preoperative hematocrit ≤ 30%	28.5	13–62.2	<0.001
Female sex	5.2	3.1–8.8	<0.001
Body mass index < 25 kg/m^2	2	1.2–3.4	0.006
Serum creatinine > 200 mmol/l	4.4	1.5–12.5	0.01

or tamponade, low cardiac output, postoperative new atrial fibrillation, stroke, creatinine level at hospital discharge, new onset renal failure, mediastinitis, postoperative pulmonary complication and mortality rates were similar in both groups (Table 5). However, the mean postoperative drainage was higher in the high hematocrit group (518 ± 213ml vs.473±191ml; p=0.004) and the hospital stay time was slightly higher in the low hematocrit group (5.0 ±2.5 days vs. 5.4 ± 2.5 days; p=0.04).

Discussion

The study has two main findings. First, we observed that hematocrit levels between 17% and 21% during isolated coronary artery bypass surgery with moderate hypothermic CPB are well tolerated and have no adverse impact on outcome. These hematocrit levels may be encountered in an uncomplicated routine practice of CPB due to hemodilution and can be managed without transfusion. However, a decision process depending on a choice of the physician more than the physiologic needs of the patient may lead to unnecessary transfusions.

Second, preoperative hematocrit ≤ 30%, female sex, body mass index < 25 kg/m^2, and preoperative serum creatinine >200 mmol/l were defined as independent risk factors for the development of a hematocrit level ≤21% during CPB.

Table 4. Operative variables including hematocrit levels and fluid balance

	High hematocrit group	Low hematocrit group	*p* value
Hematocrit level before the induction of anesthesia (%) (mean±SD)	41.9±5.4	35.9±4.7	<0.001
Lowest hematocrit during CPB (%) (mean±SD)	28.5±4.1	19.7±1.2	<0.001
Hematocrit at the end of CPB (%) (mean±SD)	33.0±4.3	26.0±3.3	<0.001
Hematocrit at hospital discharge (%) (mean±SD)	27.9±4.4	27.0±4.0	NS
Fluid balance at the end of the operation (ml) (mean±SD)	139±551	330±554	0.003
Fluid balance at the end of day 1 (ml) (mean±SD)	923±633	880±556	NS

Table 5. Outcome parameters

	High hematocrit group	Low hematocrit group	*p* value
Mean drainage (ml)	518±213	473±191	0.004
Ventilation time (h)	3.9±3.2	4.1±2.0	NS
Duration of intensive care unit stay (h)	21.8±34.6	20.9±6.4	NS
Duration of hospital stay (d)	5.0±2.5	5.4±2.5	0.04
ICU readmission (%)	1.0	1.7	NS
Hospital readmission (%)	2.2	3.4	NS
Reoperation for bleeding or tamponade (%)	0.2	0.6	NS
Low cardiac output (%)	3.9	6.9	NS
New onset atrial fibrillation (%)	10.4	6.9	NS
Stroke (%)	0.1	0.6	NS
Creatinine level at hospital discharge (mg/dl)	0.8±0.2	0.8±0.3	NS
New onset renal failure (%)	0.1	–	NS
Mediastinitis (%)	0.4	0.6	NS
Postoperative lung complication (%)	0.2	0.1	NS
Mortality (%)	1.0	–	NS

Findings in Context of the Literature

The minimum safe level of hematocrit necessary to maintain oxygen delivery during CPB is controversial. In an animal study to determine the minimum hematocrit supporting cerebral oxygenation during normothermic normovolemic progressive hemodilution, Cook and colleagues[12] found a near trebling (2.7-fold) of cerebral blood flow when the hematocrit reached 9% during CPB. They also added that the curve describing the relationship between hematocrit and cerebral oxygen balance has a broad plateau, indicating cerebral tolerance for a wide range of hematocrits, and the cerebral metabolism becomes delivery-dependent below a hematocrit value of 15%. In their further study concerning minimum hematocrit at differing CPB temperatures, they demonstrated that the minimum hematocrit that supports cerebral oxygenation is shifted leftward as temperature is reduced, and cerebral oxygen demand was maintained at hematocrit values of 14%, 11%, and ≤ 10% in 38°C, 28°C, and 18°C CPB temperatures, respectively[16]. The same group also showed that, in humans, cerebral oxygen delivery is more than twice the cerebral oxygen demand with hemoglobin values less than 6 g/dL (~ 18% hematocrit), and suggested to be more conservative in transfusion decisions under hypothermic conditions, with a prerequisite of excluding the presence of cerebral vascular disease[17].

In a prospective, randomized and controlled trial, von Heymann and colleagues demonstrated that hemodilution to a hematocrit of 20% during 'normothermic CPB' did not induce a 'critical' imbalance between oxygen delivery and consumption that would have resulted in a worse clinical outcome[14]. We also transfused patients when the hematocrit value was below 20% just before rewarming.

There are several reports defining increased adverse outcome due to low hematocrit levels during CPB. However, nearly all of them failed to include the intraoperative management of low hematocrit and, thus, the effect of transfusion as a confounding effect to their reports. It is clear that disregarding the effect of transfusions in a study that focuses on intraoperative anemia can produce uncertain results. As an example, Habib and colleagues, in a series of 5,000 consecutive cardiac operations, found the severity of hemodilution on CPB as a predictor of operative mortality, prolonged intensive care unit and hospital stay, and worse 0- to 6-year survival[1].

In this study, the incidence of each complication was compared among lowest hematocrit quintile groups. The patients were allocated to 5 subgroups, with the lowest hematocrit levels (%) of 15.9±1.4, 18.9±0.7, 21.3±0.7, 23.6±0.8, and 27.5±2.1. The mortality rate was 7.5% in the first quintile compared to 1.6% in the fifth. The confounding issue in this study was the liberal use of transfusion. The intraoperative transfusion rate was 66.6% in the first quintile compared to only 3.6% in the fifth and this tendency continued in the postoperative period. Fang and associates, in a series of 2,738 patients, found a more than doubling (2.7-fold) of mortality when the lowest nadir hematocrit reached 14% during CPB, but they also did not investigate transfusion as a covariant or a confounder[4]. Finally, analyzing 6,980 patients, the Northern New England Cardiovascular Disease Study Group demonstrated that the lowest hematocrit on CPB was correlated with increased mortality and postoperative heart failure[18]. The category variable for lowest hematocrit had the following cut points in this study: less than 19%, 19% to 20%, 21% to 22%, 23% to 24%, equal to or greater than 25. However, when transfusion was added as a cofactor to the subsequent analysis of the same cohort, it was suggested that the tendency for anemic patients to be transfused explains much of this correlation[7]. It was also concluded that the management of hemodilutional anemia during surgery with red blood cell transfusion was associated with an increased risk of low cardiac output, irrespective of the extent of anemia.

As Spiess stated in his review, studies that show an adverse outcome associated with low hematocrit are not definitive, because they fail to distinguish between the impact of low hematocrit per se and the possible adverse effects of transfusion, for which the low hematocrit may simply be a surrogate. Moreover, the observation that a low hematocrit is associated with an adverse outcome does not necessarily prove that 'treatment' of the anemia with a red cell transfusion will improve outcome[19].

Our findings, with respect to developing an hematocrit value of <21% during CPB, were consistent with previous research[1,18,20]. Increased age, preoperative use of diuretics and preoperative use of intravenous nitrates, which were significant risk factors at univariate analysis, lost their significance at multiple regression analysis. In order to avoid transfusion due to low hematocrit during CPB, it is essential to identify these patients beforehand, so that blood conservation methods and strategies to minimize bleeding may be implemented and enforced. Our strategies to minimize transfusion are in three steps. Before CPB is initiated, we administer furosemide in a routine manner. We restrict the priming volume to ~ 1100 ml. During CPB, if the reservoir level is pretty low (<200ml), the Trendelenburg position is given to the patient and, if this maneuver fails, vacuum assist (-15mmHg) is initiated. After CPB, all the blood within the tubing sets, reservoir, and filters is collected in a sterile bag and transfused back to the patient, either in the operating theater or in the intensive care unit. Despite an increase in high-risk patients undergoing open heart surgery, the rate of transfusion decreased substantially throughout the years in our department, dropping from 30% to 15% between 1999 and 2007. This shows that avoiding transfusion is a skill that can be acquired.

In our institution, the decision for postoperative transfusion is made by the approval of at least 2 physicians (surgeon or anesthesist). Basically, the clinical status of the patient (motor function, cognitive function, urine output, heart rate etc.), apart from the level of hematocrit, guides the physicians. In the postoperative period, besides the evaluation of fluid intake and output, the weight change is controlled daily and the managementof fluid balance is primarily determined according tothe base preoperative weight. One other major policy we acquired in the postoperative management is to re-explore a bleeding patient earlier to avoid transfusion.

There is an increasing amount of evidence that correlates adverse outcome and transfusion during cardiac surgery[19-22]. The possible mechanisms are the alteration in the recipient's immune system that may lead to infections, systemic inflammatory response of the recipient, changes in the shape and skeletal integrity of stored red blood cells leading to capillary sludging and obstruction, and tissue hypoxia resulting from the decreased oxygen delivery capacity of the transfused red blood cells[7,23].

Transfusion is also reported to increase the resource utilization[21]. Murphy and colleagues have speculated that avoiding transfusion would have prevented well over 50% of all infections and ischemic events, leading to a reduction in non-operative costs of an admission by ~40%[8]. Our study confirms these reports by demomstrating very short intensive care unit and hospital stay times, and low mortality, morbidity, and re-admission rates.

The main limitation of our study is that it is not randomized. However, a randomized setting may not be suitable in clinical practice for such studies. The effects of other blood products (fresh frozen plasma, platelets etc.) were not investigated in comparison with the outcome; a total of 1.6% of patients received fresh frozen plasma and 0.8% received platelets in this group. However, the rate of use of these products was similar in both groups. The transfused patients were excluded and the outcomes of transfused patients were not included in the study. Although the comparison between the transfused and non-transfused patients revealed an increased adverse outcome in transfused patients, transfusion was not a standardized factor for each patient in the excluded group (time point for transfusion, gap between repetitive transfusions, gap between the transfusion and observation of outcome), thus, it may not be suitable for making such a comparison.

Several strengths of the study offset these potential limitations. The study includes a large homogeneous cohort of patients, an extensive prospectively collected list of preoperative, laboratory, and operative variables. The transfusion data were double-checked, both from the database and from the blood bank records.

As a consequence, we may suggest that hematocrit levels of ≤21% during CPB may have no impact on outcome with an attentive CPB and fluid balance management. However, this observation was performed in non-transfused patients. Possible link for a 'so called' relationship between low hematocrit and adverse outcome reported in the literature may be through the transfusion factor, which is a confounding factor in many studies. There will, of course, be an adverse effect of critically low hematocrit values at which oxygen consumption becomes delivery-dependent during CPB where transfusion is inevitable; however, this level is probably lower than 21%. Also, as Spiess stated in his review, the observation that a low hematocrit is associated with an adverse outcome does not necessarily prove that 'treatment' of the anemia with a red cell transfusion will improve outcome[19].

Whatever type of blood conservation technique is used, the transfusion rates after cardiac operations may not be decreased below a precise degree in case of not establishing appropriate rules of indications for transfusion. For this reason, the physiological changes during CPB and safe limits of hematocrit levels for maintaining tissue perfusion at this period should be clearly studied to schedule a guideline with a high quality of evidence for managing the most appropriate hematocrit levels during CPB. This study may have an impact on limiting unnecessary transfusions during coronary artery bypass surgery.

In conclusion, this study demonstrates that it is the physician, not the patient, who cannot tolerate low hematocrit levels during cardiopulmonary bypass.

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References

1. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: should current practice be changed? J Thorac Cardiovasc Surg 2003; 125: 1438-1450.
2. Swaminathan M, Phillips-Bute BG, Conlon PJ, Smith PK, Newman MF, Stafford-Smith M. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. Ann Thorac Surg 2003; 76: 784-791.
3. Karkouti K, Djaiani G, Borger MA, et al. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. Ann Thorac Surg 2005; 80: 1381–1387.
4. Fang WC, Helm RE, Krieger KH, et al. Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. Circulation 1997; 96: 194-199.
5. Rawn JD. Blood transfusion in cardiac surgery: a silent epidemic revisited. Circulation 2007; 116: 2523-2524.
6. Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006; 34: 1608-1616.
7. Surgenor SD, DeFoe GR, Fillinger MP, et al. Intraoperative red blood cell transfusion during coronary artery bypass graft surgery increases the risk of postoperative low-output heart failure. Circulation 2006; 114: I43-I48.
8. Murphy GJ, Reeves BC, Rogers CA, Sizvi SIA, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007; 116: 2544-2552.
9. Koch CG, Li L, Duncan AI, et al. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg 2006; 81: 1650–1657.
10. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg 2002; 74: 1180–1186.
11. American Society of Anesthesiologists, Practice guidelines for blood component therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. Anesthesiology 1996; 84: 732–747.
12. The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline. Ann Thorac Surg 2007; 83: S27– 86.
13. Habib RH, Zacharias A, Schwann TA, et al. Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: implications on operative outcome Crit Care Med 2005; 33: 1749-1756.
14. von Heymann C, Sander M, Foer A, et al. The impact of a hematocrit of 20% during normothermic cardiopulmonary bypass for elective low risk coronary artery bypass graft surgery on oxygen delivery and clinical outcome – a randomized controlled study [ISRCTN35655335]. Critical Care 2006; 10(2): R58 (doi:10.1186/cc4891)
15. Cook DJ, Orszulak TA, Daly RC, MacVeigh I. Minimum hematocrit for normothermic cardiopulmonary bypass in dogs. Circulation. 1997; 96: 200-204.
16. Cook DJ, Orszulak TA, Daly RC. Minimum hematocrit at differing cardiopulmonary bypass temperatures in dogs. Circulation. 1998; 98: 170-174.
17. Sungurtekin H, Cook DJ, Orszulak TA, Daly RC, Mullany CJ. Cerebral response to hemodilution during

hypothermic cardiopulmonary bypass in adults. Anesth Analg 1999; 89: 1078-1083.
18. DeFoe GR, Ross CS, Olmstead EA, et al. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. Ann Thorac Surg 2001; 71: 769–776.
19. Spiess BD. Transfusion of blood products affects outcome in cardiac surgery. Semin Cardiothorac Vasc Anesth 2004; 8: 267-281.
20. Ranucci M, Pazzaglia A, Bianchini C, Bozzetti G, Isgrò G. Body size, gender, and transfusions as determinants of outcome after coronary operations. Ann Thorac Surg 2008; 85: 481-487.
21. Scott BH, Seifert FC, Grimson R. Blood transfusion is associated with increased resource utilisation, morbidity and mortality in cardiac surgery. Ann Card Anaesth 2008; 11: 15-19.
22. Utley JR, Wilde EF, Leyland SA, Morgan MS, Johnson HD. Intra-operative blood transfusion is a major risk factor for coronary artery bypass grafting. Ann Thorac Surg 1995; 60: 570-575.
23. Senay S, Toraman F, Gunaydin S, Kilercik M, Karabulut H, Alhan C. The impact of allogenic red cell transfusion and coated bypass circuit on the inflammatory response during cardiopulmonary bypass: a randomized study. Interact Cardiovasc Thorac Surg 2009; 8(1): 93-99.