ANESTHESIOLOGY

Restrictive Transfusion Strategy after Cardiac Surgery

Role of Central Venous Oxygen Saturation Trigger: A Randomized Controlled Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Multiple studies and guidelines on erythrocyte transfusion in cardiac surgery have used hemoglobin values as a target. However, more clinically relevant criteria such as mixed venous oxygen saturation to assess oxygen delivery and consumption may be important.

What This Article Tells Us That Is New

- A restrictive transfusion strategy using a central Svo_2 endpoint also reduces allogeneic erythrocyte transfusion.
- Using a mixed venous physiologic criterion rather than a hemoglobin target for erythrocyte transfusion represents an improved clinically relevant transfusion trigger for future clinical trials.

ABSTRACT

Background: Recent guidelines on transfusion in cardiac surgery suggest that hemoglobin might not be the only criterion to trigger transfusion. Central venous oxygen saturation (Svo_2), which is related to the balance between tissue oxygen delivery and consumption, may help the decision process of transfusion. We designed a randomized study to test whether central Svo_2–guided transfusion could reduce transfusion incidence after cardiac surgery.

Methods: This single center, single-blinded, randomized controlled trial was conducted on adult patients after cardiac surgery in the intensive care unit (ICU) of a tertiary university hospital. Patients were screened preoperatively and were assigned randomly to two study groups (control or Svo_2) if they developed anemia (hemoglobin less than 9 g/dl), without active bleeding, during their ICU stay. Patients were transfused at each anemia episode during their ICU stay except the Svo_2 patients who were transfused only if the pretransfusion central Svo_2 was less than or equal to 65%. The primary outcome was the proportion of patients transfused in the ICU. The main secondary endpoints were (1) number of erythrocyte units transfused in the ICU and at study discharge, and (2) the proportion of patients transfused at study discharge.

Results: Among 484 screened patients, 100 were randomized, with 50 in each group. All control patients were transfused in the ICU with a total of 94 transfused erythrocyte units. In the Svo_2 group, 34 (68%) patients were transfused (odds ratio, 0.031 [95% CI, 0 to 0.153]; $P < 0.001$ *vs.* controls), with a total of 65 erythrocyte units. At study discharge, eight patients of the Svo_2 group remained nontransfused and the cumulative count of erythrocyte units was 96 in the Svo_2 group and 126 in the control group.

Conclusions: A restrictive transfusion strategy adjusted with central Svo_2 may allow a significant reduction in the incidence of transfusion.

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Erythrocyte transfusion is common in cardiac surgery. Cardiac surgery represents only a small fraction of all surgical procedures but consumes a significant proportion of the stored erythrocytes, with almost 50% of patients receiving a perioperative transfusion, though highly variable between centers.[1–4]

Since transfusion is associated with an increased risk of morbidity and mortality, even for 1 or 2 units,[5–8] a patient blood management strategy has been promoted to favor the prevention of anemia, reduction of bleeding, and limitation of transfusion.[2,9–11] In this respect, the transfusion trigger, determined by the concentration of hemoglobin has been questioned during the past two decades. Recent randomized controlled studies have shown that lowering the hemoglobin concentration to trigger transfusion, the so-called restrictive transfusion strategy, is noninferior to liberal strategies in short- and long-term outcomes.[12,13] However, other studies have raised some concerns: the restrictive strategy may sometimes be more deleterious, particularly in older or weak patients.[14–16] Anemia may be associated with worse outcomes, both in terms of morbidity and mortality.[14,16] Moreover, a restrictive transfusion strategy may contribute to prolonging anemia. As an example, in the

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International Transfusion Requirements in Cardiac Surgery (TRICS) trial, the mean hemoglobin remained around 9 g/dl for up to 28 days after surgery.[12] As a matter of fact, current guidelines recommend a hemoglobin threshold as low as 7 g/dl, but still with a wide possible range (7 to 9 g/dl) and a rather vague notion of anemia clinical tolerance.[11]

Taken together, recent studies and guidelines suggest that hemoglobin alone may not be the best criteria for triggering transfusion. As hemoglobin is an oxygen carrier, the fundamental issue of transfusion is not to get the hemoglobin concentration to a predefined range, but rather to ensure that transfusion helps to match the metabolic demand. The rationale for erythrocyte transfusion should be to increase tissue oxygen delivery, thus avoiding the risk of a switch from aerobic metabolism to anaerobic conditions. In a previous observational study, we showed that central venous oxygen saturation (Svo_2), which is related to the balance between tissue oxygen delivery and consumption, might help to assess anemia tolerance after cardiac surgery.[17] In the case of anemia with central Svo_2 greater than 65%, transfusion did not improve central Svo_2. Conversely, transfusion increased central Svo_2 by at least 5%, when anemia was associated with a central Svo_2 less than or equal to 65%, possibly demonstrating the limit of anemia tolerance in these cases.[17]

Assuming that central Svo_2 may help the decision process of erythrocyte transfusion after cardiac surgery, we hypothesized that, to guide transfusion, central Svo_2 used with hemoglobin concentration, may reduce the incidence of transfusion in the intensive care unit (ICU). We designed a prospective randomized controlled study to test whether central Svo_2–guided transfusion could reduce the proportion of patients transfused after surgery.

Materials and Methods

Trial Design

The study was designed as a single-center, single-blinded, randomized controlled trial. It was approved by the institutional review board and the national drug safety agency and registered at ClinicalTrails.gov (NCT 02761564; principal investigator: Norddine Zeroual, M.D.; May 4, 2016). The full trial protocol can be obtained upon request. Eligible patients signed an informed consent before surgery and agreed that they could be included in the study should anemia occur in the ICU.

Patient Population

Adult patients (older than 18 yr) scheduled for elective or urgent (meaning during the index hospitalization of a coronary syndrome or an endocarditis) on-pump cardiac surgery were screened (eligibility assessment) before surgery (inclusion/exclusion criteria reported in table 1). After surgery, whenever a postoperative anemia (hemoglobin less than 9 g/dl) occurred, patients were randomly assigned to the study groups (see below, Transfusion Management: In the ICU) provided they fulfilled three conditions: (1) the central venous catheter inserted in the superior vena cava routinely before surgery (checked by chest x-ray) was functional; (2) no early active bleeding; and (3) no ongoing transfusion. Randomization was postponed if the patient had significant bleeding within the first postoperative hours, as assessed by a blood loss of more than 2 ml · kg^{-1} · h^{-1}, or if the patient was receiving a transfusion decided before ICU admission. When the active bleeding decreased significantly, or after the ongoing transfusion, anemia was re-checked and the patient was eventually randomized. To study anemia in stable condition, besides delaying the randomization of patients with sustained early bleeding, those among them who cumulated more than 1,000 ml or those requiring a transfusion of more than 4 erythrocyte units within the first 12 postoperative hours (severe bleeding class according to the Universal Definition of Perioperative Bleeding)[18] were excluded from the study.

The first occurrence of hemoglobin less than 9 g/dl in the ICU fixed the group assignment according to the randomization. However, the design of the study anticipated including all transfusions in the final count, *i.e.* until postoperative day 28 or hospital discharge. The study was conducted in the cardiac surgery ICU of a tertiary university hospital and in the surgical ward until postoperative 28 or hospital discharge.

Interventions

Perioperative Management. The usual cardiac treatment was maintained until the day before surgery except for antiplatelets or oral anticoagulants, which were stopped as recommended in guidelines. Perioperative management (anesthesia, cardiopulmonary bypass [CPB], and cardioplegia) is standardized for all patients. CPB was set up with a membrane oxygenator primed with 1.5 l of crystalloid

Table 1. Inclusion Criteria

Inclusion Criteria	Exclusion Criteria
	Patient with acute bleeding*
Age > 18 yr	
Elective cardiac surgery	
Coronary artery bypass graft	
Aortic or mitral valve	
Ascending aorta	
Urgent surgery	
Coronary artery bypass graft	
Endocarditis	
Aortic dissection	
On-pump surgery	
Patients admitted to intensive care after cardiac surgery	
Anemic patient (Hb < 9 g/dl)	
Patient with a central venous catheter in the superior vena cava territory	

*Defined as postoperative bleeding greater than 1,000 ml or the transfusion of greater than 4 blood units within the first 12 postoperative hours.

Hb, hemoglobin.

(Isofundin; B.Braun, Germany) and with body temperature maintained at 34° to 36°C. After aortic clamping, a hyperkalemic blood cardioplegic solution was infused into the aortic root of the aorta until myocardial arrest. A nonpulsatile pump flow rate was maintained between 2.2 and 2.6 l · min^{-1} · m^{-2}, provided the mixed Svo_2 monitored on the pump machine exceeded 60%. A crystalloid solution (balanced crystalloid solution) could be added to maintain pump flow, and blood products were used to maintain the hemoglobin concentration at greater than 7 g/dl during CPB and greater than 8 g/dl after CPB. Hypotension (mean arterial pressure [MAP] less than or equal to 60 mmHg) was treated with a continuous intravenous administration of norepinephrine in order to maintain MAP greater than 60 mmHg. After completion of the surgical procedure, patients were weaned from CPB when a rectal temperature of 36°C had been reached.

In the ICU, inotropic support (dobutamine) was used to obtain a cardiac index greater than or equal to 2.2 l · min^{-1} · m^{-2} output as assessed by thermodilution (pulmonary catheter) or echocardiography (aortic flow measured by pulsed Doppler time velocity integral) with normal left ventricular filling pressure. Hypotension (MAP less than or equal to 60 mmHg) without cardiogenic shock features (cardiac index greater than 2.2 l · min^{-1} · m^{-2}) was treated with a continuous intravenous administration of norepinephrine in order to restore MAP to greater than 60 mmHg; repeated boluses of morphine were used to keep patients pain-free. Weaning from the ventilator was started during the emergence of anesthesia and extubation was performed when stable hemodynamics and normothermia had been maintained for greater than or equal to 1 h. Oxygen supply was provided to maintain oxygen saturation measured by pulse oximetry at greater than or equal to 94%.

Transfusion Management. A patient blood management protocol was implemented in our institution in 2016. It specified how to manage anemia, how to optimize erythrocyte mass, and how to minimize blood loss. Besides the routine use of cell savage, perioperative tranexamic acid administration, and anemia medical treatment (iron supplementation, erythropoietin) when appropriate, the patient blood management protocol established hemoglobin thresholds for transfusion, either during CPB (less than or equal to 7 g/dl) or in postoperative care, in the ICU, and in the surgical ward (less than 9 g/dl). Hemoglobin was measured (1) at arrival in the ICU and (2) every 12 h during the first 2 days after surgery, then (3) once daily in the ICU and (4) once a week and at the physician's discretion in the surgery ward, as well as (5) after any transfusion.

In the ICU. Patients assigned to the control group were transfused if hemoglobin was less than 9 g/dl. Transfusion was repeated whenever hemoglobin was less than 9 g/dl.

Patients assigned to the Svo_2 group were transfused if hemoglobin was less than 9 g/dl and central Svo_2 less than or equal to 65%. When hemoglobin was less than 9 g/dl and central Svo_2 greater than 65%, no transfusion was administered. Transfusion was repeated whenever hemoglobin concentration was less than 9 g/dl and central Svo_2 less than or equal to 65%. The central Svo_2 less than or equal to 65% threshold was chosen based on a previous observational study, which showed that 85% of anemic patients with central Svo_2 less than or equal to 65% responded to transfusion by an increase in central Svo_2 of at least 5%.[17] Central Svo_2 was measured on a blood sample obtained from the distal lumen of the central venous catheter. Oximetry was used for measurement with a point-of-care of gas analysis located in the ICU (Gem 4000; Instrumentation Laboratory, USA).

Physicians were permitted to deviate from the hemoglobin/Svo_2 criterion when deciding whether to transfuse in the case of critical clinical conditions including: (1) severe sepsis; (2) septic shock; (3) hemodynamic instability (defined either by the introduction of inotropic or vasopressor treatment, or by a significant change in the dosage [increase or decrease of more than 20%]); or (4) an episode of severe pulmonary failure (defined by partial pressure of oxygen in the arterial blood on the fraction of the inspired oxygen ratio as less than 200). If physicians decided to transfuse Svo_2 patients when central Svo_2 was greater than 65%, they had to specifically document their reason.

Other blood components, fresh frozen plasma, platelets, fibrinogen, or prothrombin complex concentrates were also administered according to our institutional patient blood management protocol. In brief, they were administered in order to maintain the prothrombin time ratio at greater than 50 to 70%, the platelets at above 50 to 100 gigas, and the fibrinogen plasma concentration at greater than 1.5 to 2 g/l, (the lower range limits without active bleeding, and the upper range limits in the case of active bleeding).

After ICU Discharge. Until hospital discharge or postoperative 28 (study discharge), transfusion was managed according to the patient blood management protocol in both groups, meaning that transfusion was considered when hemoglobin was less than 9 g/dl with no further central Svo_2 measurements in the Svo_2 group.

Endpoints

The primary endpoint was the proportion of patients transfused during the ICU stay. Secondary endpoints consisted of transfusion and postoperative outcomes. For transfusion, we collected the total number of erythrocyte units transfused in the ICU, the proportion of patients transfused, and the total number of units transfused at study discharge. Postoperative outcomes included the incidence of mortality and postoperative complications at study discharge, along with the length of the ICU and hospital stays.

Postoperative complications were defined as infection (respiratory, septicemia), ischemic events (myocardial infarction, stroke, mesenteric ischemia), organ failure (renal dysfunction according to Kidney Disease: Improving Global Outcomes classification), or liver dysfunction (if plasma hepatic enzymes or bilirubin exceeded twofold the standard value).

A composite outcome included mortality and/or any of the aforementioned postoperative complications. The Simplified Acute Physiology Score was collected within the first 24 h in the ICU to assess disease severity on ICU admission. The bleeding volume was quantified by the amount of blood collected by surgical drains at postoperative day 1.

Sample Size

According to a previous study,[16] we could expect a reduction of at least 20% in the transfusion incidence of the Svo_2 group, compared to 100% in the control group. A sample size of 100, with 50 patients in each group, would be sufficient for a superiority hypothesis to have 90% power to detect the 20% difference with a two-sided test at a 5% significance level. We used the StudySize 2.0 tool that gives N = 45.25 for each group and 50 patients per group after an increase of 8%.

Randomization and Blinding

Before surgery, the research assistant evaluated the patients' eligibility, and the investigators obtained their informed consent. The participants were then enrolled only if they fulfilled the inclusion criteria in the ICU. Patients screened before surgery underwent balanced randomization 1:1 and blocks of random size to either the control group or the Svo_2 group using a central internet-based randomization system (Cs Random online software; Ennov Clinical, France). The data manager of the study set up the central internet-based randomization system according to the protocol. The patient was blinded from his/her randomization arm. Care providers were aware of the group assignment.

Statistical Analysis

The primary and secondary outcomes of all randomized patients were analyzed on an intention-to-treat basis. Baseline characteristics were reported using the mean and SD for normally distributed data (Kolmogorov–Smirnov test), and median with interquartile range [25 to 75] for other cases. Numbers and percentage were reported for qualitative cases.

The main endpoint (proportion of patients transfused during the ICU stay) was compared between the two groups using a chi-square test. The effect size was estimated with the odds ratio and its 95% CI.

For the secondary endpoints, the total number of erythrocyte units transfused in the ICU and at study discharge, and the ICU length of stays were compared between the two strategies. The Student *t* or Mann–Whitney tests were used according to the distribution of continuous data. The proportion of patients transfused, the incidence of mortality, and the postoperative complications at study discharge were all compared using Fisher exact test or expansion of Fisher test by A.W. Ghent.[19] Firth logistic regression[20] was used to avoid any problems of convergence and to mitigate the bias of maximum likelihood estimates. When the model did not converge, exact logistic regression[21] was applied.

All tests were two-sided. A probability value of less than 0.05 was considered to be significant for all statistical tests. Statistical analysis was performed using SAS Enterprise Guide, version 7.3 (SAS Institute, USA).

Results

Participants

Between November 2016 and August 2018, 484 patients were screened. One hundred and thirty-seven (28.3%) had anemia (hemoglobin less than 9 g/dl) in the ICU, of whom 37 (7.6%) met exclusion criterion. The remaining 100 patients were included in the study, randomized (50 in each group) and were analyzed (fig. 1). During follow-up, four patients died: two from each group. There were no missing data (except those of the deceased patients), nor adverse events related to the protocol.

All the patients were analyzed and followed up to study discharge. The trial was conducted in accordance with the original protocol and was stopped when the target enrollment was obtained.

Baseline Data

The baseline characteristics are reported in table 2. Most patients were men (63%), the mean age was 68.8 ± 8.8 yr, 27% underwent urgent surgery, and 40% received erythrocyte transfusion during surgery.

In the ICU, we observed 77 anemia episodes in the control group and 82 in the Svo_2 group. Sixty-two (62%) patients had only one episode of anemia and 38 (38%) had repeated occurrences with no significant difference between the control group (n = 17) and the Svo_2 group (n = 21; odds ratio, 1.39 [95% CI, 0.62 to 3.14]; $P = 0.411$; fig. 2). Among the 21 Svo_2 patients who had repeated episodes of anemia: (1) six (29%) had only anemia episodes with central Svo_2 greater than 65% each time and were not transfused; (2) five (24%) had only anemia episodes with central Svo_2 less than or equal to 65% each time and were transfused at each episode; and (3) 10 (48%) had both—anemia episodes with central Svo_2 less than or equal to 65% and anemia episodes with Svo_2 greater than 65%—and were transfused only when central Svo_2 was less than or equal to 65% (fig. 3).

In the ICU, there was no significant difference between the two groups in mean hemoglobin concentration (table 3). Similarly, in the Svo_2 group, hemoglobin concentration was not significantly different between patients with central Svo_2 less than or equal to 65% and patients with central Svo_2 greater than 65% (7.9 ± 0.9 g/dl *vs.* 8.1 ± 1.2, respectively; $P = 0.370$). However, central Svo_2 was significantly different (58.7 ± 7.0% *vs.* 72.0 ± 8.5%, respectively; $P < 0.001$).

Endpoints

Primary Endpoint. The restrictive central Svo_2–guided protocol resulted in a 32% reduction of the proportion of patients transfused in the ICU. Thirty-four (68%) patients

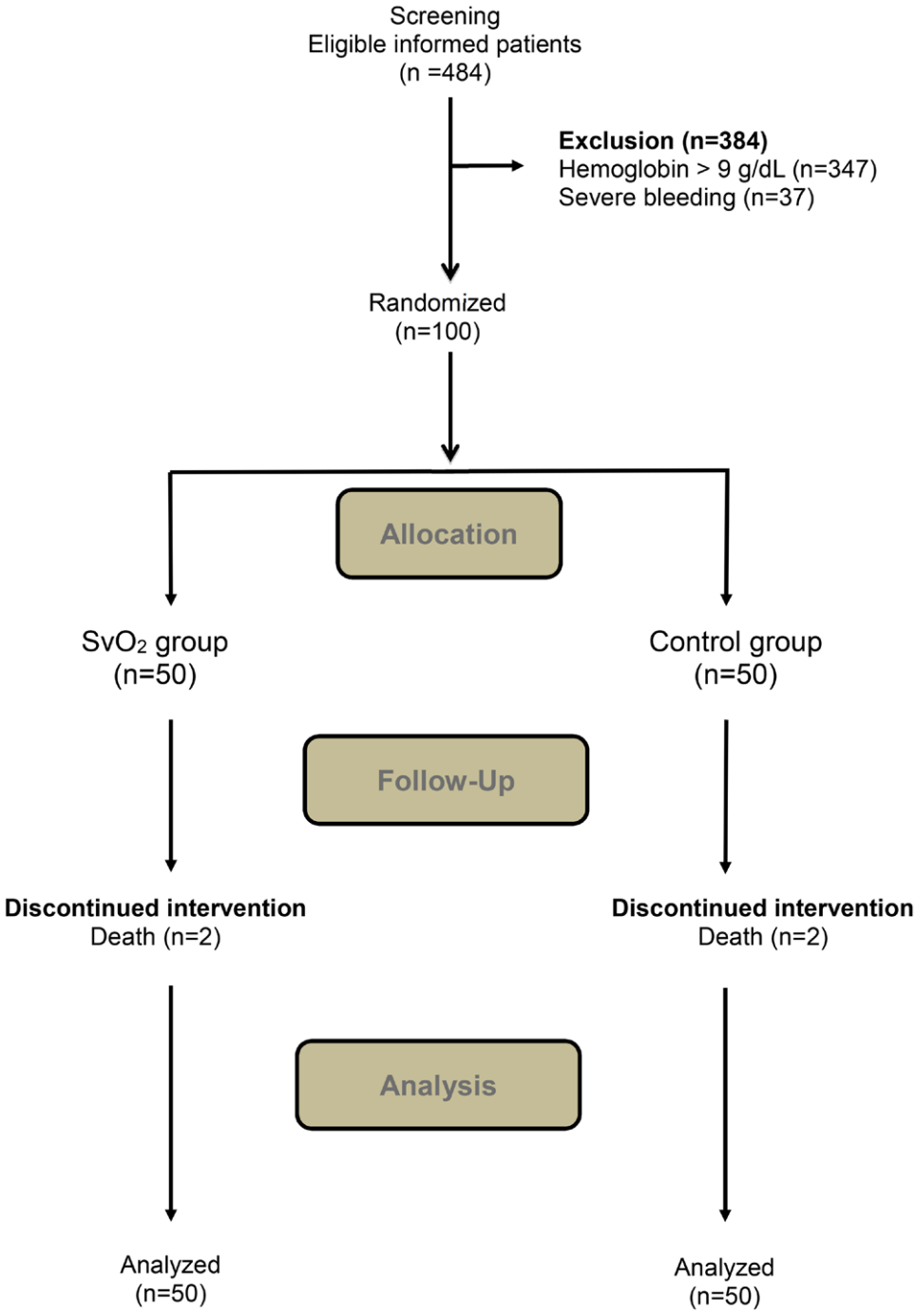

Fig. 1. Flowchart. Patients were randomly assigned to control or Svo_2 groups. In the Svo_2 group, patients were supposed to receive transfusion provided their pre-transfusion central Svo_2 was less than or equal to 65%. Severe bleeding was defined by a postoperative bleeding of more than 1,000 ml or those requiring a transfusion of more than 4 erythrocyte units within the first 12 postoperative hours.[17] ICU, intensive care unit; Svo_2, mixed venous oxygen saturation.

in the Svo_2 group were transfused in the ICU, compared to all patients (n = 50) in the control group in agreement with our standard protocol (odds ratio, 0.03 [95% CI, 0 to 0.15]; $P < 0.001$).

In the Svo_2 group, 16 patients were not transfused because central Svo_2 was always greater than 65% during their anemia episodes in the ICU. Their mean Hb was at 8.2 ± 0.8 g/dl (*vs.* 8.9 ± 0.8 g/dl in control; $P = 0.023$) at

Table 2. Preoperative and Intraoperative Characteristics

	Central Svo_2 (n = 50)	Control (n = 50)
Preoperative		
Age, yr*	68.3 ±8.9	69.3 ± 8.7
Male sex†	36 (72)	27 (54)
Body mass index, kg/m²*	26.4 ± 4.9	26.5 ± 4.6
Euroscore II‡	5.7 [2.5–11.7]	5.2 [3.3–10.9]
TRUST score‡	4 [3–5]	4 [3–5]
Hemoglobin, g/dl*	12.2 ± 2.0	12.3 ± 1.8
Medical history		
Left ventricle ejection fraction < 30%†	3 (6)	4 (8)
Coronary artery disease†	30 (60)	29 (58)
Chronic renal failure†	14 (28)	17 (34)
Hemodialysis†	5 (10)	6 (12)
Stroke†	4 (8)	8 (16)
Liver cirrhosis†	1 (2)	2 (4)
COPD†	9 (18)	15 (30)
Intraoperative surgery		
Urgent surgery†	14 (28)	13 (26)
Endocarditis†	6 (12)	4 (8)
Redo surgery†	11 (22)	8 (16)
Cardiac procedure		
CABG†	22 (44)	18 (36)
Valve†	35 (70)	36 (72)
Ascending aorta†	11 (22)	10 (20)
Cardiopulmonary bypass		
Cardiopulmonary bypass duration, min‡	152 [102–194]	150 [107–195]
Aortic clamp time, min‡	99 [71–157]	107 [81–138]
Circulatory arrest†	6 (12)	5 (10)
Intraoperative transfusion†	22 (44)	27 (54)
Erythrocytes†	17 (34)	23 (46)
Fresh frozen plasma†	11 (22)	14 (28)
Platelets†	9 (18)	7 (14)
Fibrinogen†	12 (24)	12 (24)
Prothrombin complex†	1 (2)	0

*Mean ± SD. †n (%). ‡Median [interquartile range, 25–75].

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; Svo_2, mixed venous oxygen saturation.

ICU discharge. Among the 34 transfused patients, 31 had central Svo_2 less than or equal to 65% and 3 had central Svo_2 greater than 65%. These three study protocol violations, which resulted in transfusion despite central Svo_2 greater than 65%, were motivated by the weaning of vasopressor support in a context of low Hb concentration (6.5, 6.8, and 7.1 g/dl, respectively).

Secondary Endpoints.

Transfusion. In the ICU, 94 erythrocyte units (per patient median, 1 [interquartile range, 1 to 2]) were transfused in the control group and 65 (per patient median, 1 [interquartile range, 1 to 2]) in the Svo_2 group (table 3; 31% reduction compared to the control group). Between ICU discharge and study discharge, 14 patients were transfused in the Svo_2 group, including six who had already been transfused in the ICU, while 10 control patients were retransfused ($P = 0.315$; table 3).

At study discharge, eight patients of the Svo_2 group remained nontransfused (table 3). The cumulative count of erythrocyte units at study discharge was 126 in the control group and 96 in the Svo_2 group (a 24% reduction compared to the control group; table 3).

The hemoglobin concentration at study discharge was not significantly different between the two groups (table 2). For the eight Svo_2 nontransfused patients, hemoglobin was 9.1 ± 0.8 g/dl (*vs.* 10.0 ± 1.0 g/dl in control; $P = 0.035$) at study discharge.

Outcomes. At ICU admission, the Simplified Acute Physiology Score was 45 (interquartile range, 37 to 52) for the control group *versus* 46 (interquartile range, 39 to 56) for the Svo_2 group ($P = 0.370$). The bleeding volume at postoperative day 1 reached 665 ± 395 ml in the control group and 658 ± 362 ml in the Svo_2 group ($P = 0.920$).

Postoperative complications and mortality incidences are reported in table 4. Incidence of mortality, ischemic and septic complications, organ dysfunction, or composite outcome were not statistically different between the two groups.

Four patients in each group needed early reoperation for bleeding (8%). Intravenous iron supplementation (ferric hydroxide) was administered in 29 (60%) control *versus* 35 (74%) Svo_2 patients (odds ratio, 1.88; 95% CI, 0.79 to 4.5; $P = 0.144$). Erythropoietin (Epoetin beta) was administered in eight (17%) control *versus* four (8.5%) Svo_2 patients (odds ratio, 0.48; 95% CI, 0.14 to 1.65; $P = 0.216$).

Discussion

This prospective randomized study shows that in anemic patients having undergone cardiac surgery, restrictive transfusion according to central Svo_2 less than or equal to 65% allowed a significant reduction in transfusion incidence in the ICU. The benefit of the central Svo_2–guided restrictive strategy was partially maintained (about half) after the ICU stay.

The main objective was to evaluate the impact of the central Svo_2–guided strategy on the incidence of transfusion. The originality of the study design was to compare a control group with a transfusion incidence of 100% to the study group, for which we expected a transfusion incidence less than or equal to 80%. Considering the whole cohort (484 screened patients), 137 (28.3%) were candidates for transfusion according to our standard of care. This proportion is in quite a low range compared to previous studies, possibly because of the implementation of the patient blood management protocol in our routine practice.[2,3] Nevertheless, the study demonstrated that 45% of the anemia episodes in the ICU were associated with central Svo_2 greater than 65%; the central Svo_2–guided restrictive strategy therefore resulted in a 32% reduction of transfused patients.

The study provides new information on the restrictive transfusion strategy. First, central Svo_2 appears to be a good complementary parameter to hemoglobin for helping in the transfusion decision. The hemoglobin concentration at

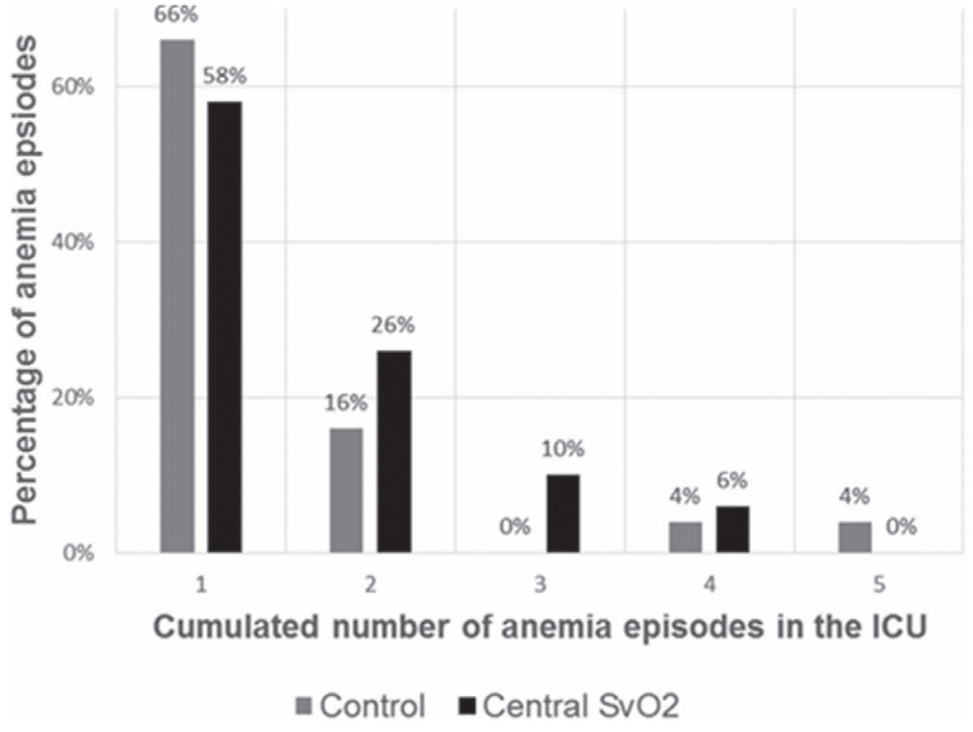

Fig. 2. Percentage of anemia episodes occurring in the ICU for control and Svo_2 groups. The percentage of anemia episodes are reported in *grey bars* for the control group and in *black bars* for the Svo_2 group, according to the cumulated number from 1 to 5 ($P = 0.105$, Fisher exact test). ICU, intensive care unit; Svo_2, mixed venous oxygen saturation.

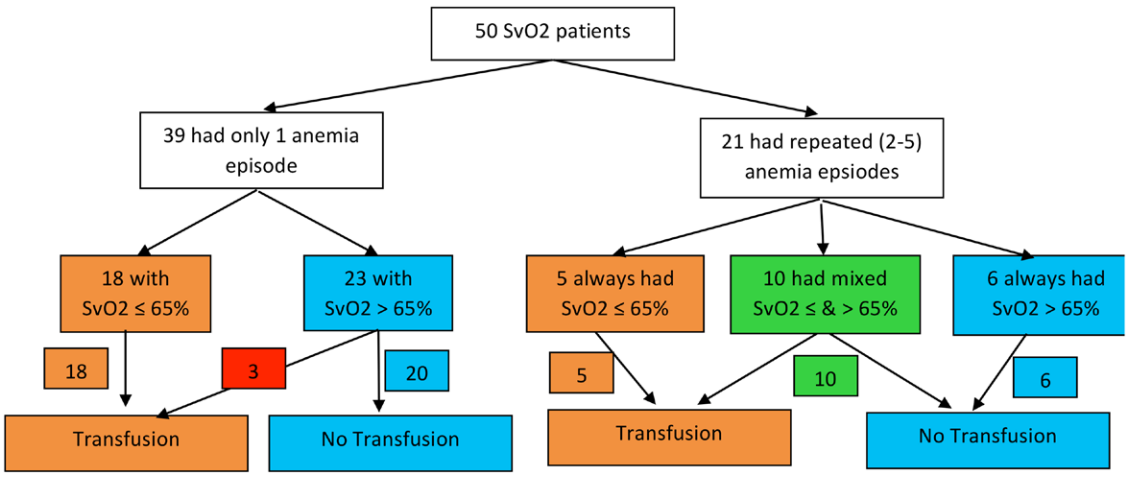

Fig. 3. Distribution of anemia episodes occurring in the ICU in the Svo_2 group. Only three patients who had anemia and Svo_2 greater than 65% were transfused in the Svo_2 group (*red box*). All other anemia episodes were managed according to the protocol, even for 10 patients who had various levels of Svo_2 during anemia episodes (*green box*). ICU, intensive care unit; Svo_2, mixed venous oxygen saturation.

the time of evaluating the need for transfusion was rather low (8.0 g/dl) and did not differ between groups, not even between patients in the Svo_2 group, whether central Svo_2 was greater than or less than or equal to 65%. Thus, central Svo_2 was actually the parameter that determined the decision to transfuse or not. Central Svo_2, like the mixed Svo_2, reflects the balance between the amount of oxygen delivered to the organs (*i.e.*, oxygen delivery) and the amount of

Table 3. Hemoglobin Evolution and Erythrocyte Transfusions

	Central Svo_2 (n = 50)	Control (n = 50)	*P* Value
Hemoglobin course (g/dl)*			
Preoperative	12.2 ± 2.0	12.6 ± 1.8	0.407
ICU admission	10.1 ± 1.3	10.2 ± 1.4	0.708
Before transfusion in ICU	8.0 ± 0.7	8.0 ± 0.7	0.865
After transfusion in ICU	8.9 ± 0.1†	9.0 ± 0.1‡	0.409
ICU discharge	8.6 ± 1.0	8.9 ± 0.8	0.254
Hospital discharge or postoperative day 28	9.8 ± 0.9	10.0 ± 1.0	0.512
Erythrocyte transfusion			
In ICU			
Patients transfused§	34 (68)	50 (100)	< 0.001
Units total	65	94	
Median‖	1 [1–2]	1 [1–2]	0.887
Distribution§			
0	16 (32)	0 (0)	
1	21 (42)	31 (62)	
2	8 (16)	14 (28)	
3	2 (4)	1 (2)	
4	2 (4)	1 (2)	
≥ 5	1 (2)	3 (6)	
In the surgical ward			
Patients transfused§	14 (30)	10 (20)	0.315
Patients retransfused§	6 (12)	10 (20)	
Units total	31	32	
Median‖	2 [1–3]	1.5 [1–3]	0.602
Distribution§			
0	34 (68)	40 (80)	
1	1 (2)	3 (6)	
2	10 (20)	4 (8)	
3	2 (4)	0	
4	1 (2)	0	
≥ 5	2 (4)	3 (6)	
At hospital discharge or postoperative day 28§			
Patients transfused	42 (84)	50 (100)	0.006#

*Mean ± SD. †n = 34. ‡n = 50. §n (%). ‖Median [interquartile range, 25–75]. #Fisher exact test *P* value.

ICU, intensive care unit; Svo_2, mixed venous oxygen saturation.

oxygen that the body takes up and utilizes (*i.e.*, tissue oxygen consumption). To measure mixed Svo_2, a pulmonary artery catheter is required to get mixed blood from the whole body. Central Svo_2 requires only a blood sample collected from the central venous line and reflects the venous oxygen saturation of the superior vena cava territory. The measurement of central Svo_2 is therefore less influenced by the oxygen saturation of the inferior vena cava compartment and coronary sinus than that of mixed Svo_2. Nevertheless, there is a satisfactory correlation between central and mixed Svo_2, despite a lack of exact numerical equivalence.[22,23] For a given tissue oxygen consumption, central Svo_2 varies with the arterial oxygen content of blood, which depends on arterial oxygen saturation (Sao_2) and hemoglobin, and with cardiac output. In the conditions of the study, we can assume that Sao_2 and tissue oxygen consumption were stable, and that a low central Svo_2 meant that cardiac output did not compensate the low hemoglobin. Hemodynamic data were similar in both groups, but no measurement of cardiac output was available. Nevertheless, transfusion seems to be the most appropriate treatment in these cases for the following reasons: (1) increasing cardiac output with inotrope would have increased heart rate and myocardial oxygen consumption, whereas arterial oxygen content was low; therefore, patients would have been exposed to a risk of myocardial ischemia; and (2) even though increasing cardiac output by increasing ventricle preload is the best option, fluid loading without red cells would have worsened anemia, and transfusion would have been mandatory anyway. Incidentally, we cannot exclude that transfusion may have also optimized preload. Conversely, central Svo_2 greater than 65% suggested a good adaptation of cardiac output to match oxygen delivery with tissue oxygen consumption, despite the low hemoglobin. Therefore, central Svo_2 can help to identify, beyond "macrohemodynamic" parameters, anemic patients who may not need urgent transfusion, and who can instead receive medical treatment for anemia. As a consequence of this strategy, more than 30% of the patients avoided transfusion in the ICU.

Second, the study results go beyond the incidence of transfusion after cardiac surgery. The analysis of the repeated anemia episodes for each patient shows that patients can alternate anemia episodes with low or high central Svo_2 during the ICU stay. Indeed, patients had up to five anemia episodes, of which a small majority (55%) were associated with central Svo_2 less than or equal to 65%. Among the 21 (42%) Svo_2 patients who had several anemia episodes, almost half (n = 10) had a variable alternation of central Svo_2 less than or equal to 65% and greater than 65%. Moreover, there were similar numbers of repeated anemia episodes in both groups, suggesting that the 32% reduction of transfusion incidence in the Svo_2 group induced only a modest increase in anemia episodes (+6.5%). This result suggests that central Svo_2 may allow for adjustment of transfusion at each anemia episode, favoring individualization of transfusion.

Third, despite the change of transfusion strategy in the Svo_2 group in the surgical ward, we still observed a 16% reduction in the proportion of patients exposed to transfusion, and a 24% reduction in the erythrocyte units transfused at study discharge. In the surgical ward, the loss-of-central-Svo_2 trigger for guiding transfusion brings patient blood management back to the standard of care. However, the effect of the central Svo_2–guided restrictive strategy in the ICU, which spared 29 erythrocyte units, was still preserved in the surgical ward. Of the nontransfused patients in the ICU, 50% remained not transfused with a total of 30 erythrocyte units economized at discharge. Adding to the fact that the hemoglobin concentration at study discharge was not statistically different to that of the control group, these observations suggest that the alternative treatment of anemia was effective enough to obtain an hemoglobin of around 10 g/dl in the Svo_2 group.

Table 4. Outcomes

	Central Svo_2 (n = 50)*	Control (n = 50)*	Odds Ratio (95% CI)	*P* Value
Postoperative complications				
Infectious event	9 (18)	7 (14)	1.33 (0.46–3.83)	0.585
Sepsis	4 (8)	3 (6)	1.36 (0.22–9.8)†	> 0.999‡
Septic shock	3 (6)	3 (6)	1 (0.13–7.8)†	> 0.999‡
Pneumonia	7 (14)	6 (12)	1.18 (0.38–3.70)†	0.766
Ischemic event	4 (8)	1 (2)	4.2 (0.4–214.0)†	0.362‡
Myocardial infarction	0	0		
Stroke	4 (8)	1 (2)	4.2 (0.4–214.0)†	0.362‡
Mesenteric ischemia	1 (2)	0 (0)	3.06 (0.12–79.5)	0.500‡
Organ dysfunction	30 (60)	35 (70)	0.65 (0.28–1.48)	0.306
Liver dysfunction	4 (8)	3 (6)	1.36 (0.22–9.8)†	> 0.999‡
Acute kidney injury§	30 (60)	35 (70)	0.64 (0.28–1.48)	0.296
Stage 1	10 (33)	13 (37)	1	0.158
Stage 2	6 (20)	13 (37)	0.61 (0.18–2.19)	
Stage 3	14 (47)	9 (26)	1.96 (0.61–6.4)	
Outcomes				
Mortality at study discharge	2 (4)	2 (4)	1 (0.07–14.3)†	> 0.999‡
Composite outcome	31 (62)	36 (72)	0.64 (0.28–1.48)	0.295
ICU length of stay (days)‖	3.5 [2–5]	3 [3–5]		0.927
Hospital length of stay (days)‖	15 [11–22]	15 [11–19]		0.858

Composite outcome: mortality and/or postoperative complications; study discharge: hospital discharge or postoperative day 28.

*n (%). †Exact logistic regression. ‡Fisher exact test *P* value. §Kidney Disease: Improving Global Outcomes classification. ‖Median [interquartile range, 25–75].

ICU, intensive care unit; Svo_2, mixed venous oxygen saturation.

Owing to these observations, we believe that central Svo_2 may be a valuable parameter for adjusting the hemoglobin trigger for transfusion, and that it could be incorporated into the patient blood management strategy. However, further studies are needed to assess whether these treatments can be used more extensively after cardiac surgery, in the aim to reduce transfusion without long-term deleterious effects.

Patient inclusion based on postoperative anemia resulted in selecting the transfused population of our center, a subgroup of patients known to be at higher risk of postoperative complication.[5,7,8] The study was underpowered for safety considerations, but we certainly observed a high incidence of kidney injury (65%) and long ICU stays, which was similar in both groups. The outcome, defined as a composite of ischemic or infection complications and/or mortality, was also similar in both groups, and was close to the results of a previous study with a larger cohort.[15] However, the exact role of restrictive transfusion or other postoperative complications like heart failure, acute kidney injury, or sepsis in a worsening outcome is difficult to establish as mechanisms may be entangled. Restrictive transfusion is noninferior to liberal strategies in short- and long-term outcomes,[12,13] but avoiding transfusion may delay anemia correction.[12,15] If transfusion is to be avoided when unnecessary, keeping patients anemic may expose them to complications.[24,25] A more aggressive treatment of anemia with iron supplementation and erythropoietin in per operative care has already been proposed and has shown encouraging perspectives even with short-term treatment.[26–28] We can assume that the extensive use of iron supplementation (60% of patients in the control group and 74% in the Svo_2 group) had contributed to restoring hemoglobin concentration within a few days.[27,28] However, studies are needed to assess whether these treatments can be used more intensively after cardiac surgery to reduce further transfusion and postoperative complications.

This study has several limits: it is a single-center study. Given that we used the patient blood management protocol as recommended by scientific societies, the results may be extended to centers with a similar practice. However, we cannot exclude bias in relation to the lack of blinding despite the fact that transfusion management was guided by predefined rules, and that very few protocol deviations were observed. Central Svo_2 was used as an adjustment variable to hemoglobin concentration in the transfusion decision. This may appear as a good indication of metabolic equilibrium, but depends on several factors beyond hemoglobin, such as cardiac output, Sao_2, and arterial oxygen content, which should be stable to allow correct interpretation during anemia. Moreover, circumstances where oxygen extraction is impaired, such as during sepsis or systemic inflammation, may render Svo_2 unreliable.

Though the number of included patients is rather small, it is noteworthy that there were no missing data. We deplored only two deaths in each group and there were no adverse events in relation to the protocol, which contributes to the strength of the study, beyond the randomization.

The study was not designed to assess long-term outcome, as it was not powered for this consideration. Therefore, although the complication incidence was in the range observed previously in a larger study on restrictive transfusion strategy,[15] further studies are needed to confirm these preliminary results.

In conclusion, in this randomized controlled study, a restrictive transfusion strategy adjusted with central Svo_2 in complement to the hemoglobin concentration may allow a significant reduction in the proportion of patients with erythrocyte transfusion in comparison to a standard restrictive transfusion.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: p-colson@chu-montpellier.fr. Raw data available at: p-colson@chu-montpellier.fr.

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