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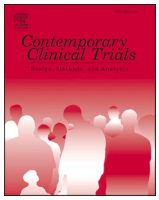

Acute normovolemic hemodilution in cardiac surgery: rationale and design of a multicenter randomized trial

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ABSTRACT

Background: Minimizing the use of blood component can reduce known and unknown blood transfusion risks, preserve blood bank resources, and decrease healthcare costs. Red Blood Cell (RBC) transfusion is common after cardiac surgery and associated with adverse perioperative outcomes, including mortality. Acute normovolemic hemodilution (ANH) may reduce bleeding and the need for blood product transfusion after cardiac surgery. However, its blood-saving effect and impact on major outcomes remain uncertain.
Methods: This is a single-blinded, multinational, pragmatic, randomized controlled trial with a 1:1 allocation ratio conducted in Tertiary and University hospitals. The study is designed to enroll patients scheduled for elective cardiac surgery with planned cardiopulmonary bypass (CPB). Patients are randomized to receive ANH before CPB or the best available treatment without ANH. We identified an ANH volume of at least 650 ml as the critical threshold for clinically relevant benefits. Larger ANH volumes, however, are allowed and tailored to the patient's characteristics and clinical conditions.
Results: The primary outcome is the percentage of patients receiving RBCs transfusion from randomization until hospital discharge, which we hypothesize will be reduced from 35% to 28% with ANH. Secondary outcomes are all-cause 30-day mortality, acute kidney injury, bleeding complications, and ischemic complications.
Conclusion: The trial is designed to determine whether ANH can safely reduce RBC transfusion after elective cardiac surgery with CPB.
Study registration: This trial was registered on ClinicalTrials.gov in April 2019 with the trial identification number NCT03913481.

1. Background

In developed countries, blood transfusion is a common procedure [1]. Every day almost 36,000 units of red blood cells (RBCs) are transfused in the US alone [2]. A significant proportion of blood components is used in cardiac surgery [3–5]. Over one million patients undergo cardiac surgery annually worldwide, and up to 60% of cardiac surgery patients receive at least one unit of RBCs [6]. The nature and invasiveness of cardiac surgery procedures, along with the need for full heparinization and cardiopulmonary bypass (CPB), contribute to such blood loss. Unfortunately, RBC transfusion is not a risk-free treatment, and is a risk factor for adverse perioperative outcomes and mortality [7–9]. Nonetheless, it is uncertain whether blood transfusion contributes directly to adverse outcomes or is simply a marker of surgical complexity and its related complications. Historically, mild fever, chills, and allergic reactions were common complications, impacting approximately 0.5 to 1% of transfusions [10]. However, with heightened awareness and reporting, transfusion-associated circulatory overload (TACO) has emerged as the most frequent side effect, documented in 1 to 5% of transfusion episodes [11].

In patients undergoing cardiac surgery at moderate-to-high risk for death, a restrictive red-cell transfusion strategy was deemed non-inferior to a liberal strategy concerning the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure requiring dialysis, with a reduced volume of blood transfused [12]. However, patients with ongoing myocardial infarction and anemia may have potential benefits from a more liberal transfusion strategy, albeit with an increased risk of heart failure at 30 days and TACO [13].

In recent years, red-cell transfusion rates have significantly decreased, falling from 50 units per 1000 population in 2008 to approximately 40 units per 1000 population in 2013 [14,15]. This reduction is primarily attributed to hospitals worldwide actively adopting patient-centered blood-management programs (PBM) [16]. The goal of these programs is to decrease morbidity, mortality, and healthcare-associated costs. The potential for a blood-saving approach, even in cardiac surgery, has been demonstrated through the successful avoidance of transfusions in specific patient groups, such as those who decline blood transfusions (e.g., Jehovah's Witnesses) and in those with difficult blood compatibility matches. In addition, the need for blood sparing become evident in periods of RBCs shortage [17–19].

Acute normovolemic hemodilution (ANH) may help reduce RBCs transfusions [3]. Several studies and meta-analyses found that ANH may be effective in decreasing the odds of transfusion-related adverse reactions in patients undergoing cardiac surgery with CBP. An ANH strategy allows the reinfusion of the patients' whole blood (not exposed to CPB and heparin), and appears to improve the post-CPB coagulation profile, and reduce both activation of inflammatory pathways and consumption of clotting factors and platelets [20]. In addition, reducing hematocrit levels through hemodilution during CPB (to a value no $<$24%), can decrease blood viscosity and may improve perfusion in capillaries and the microcirculation.

Although ANH is generally deemed safe, it carries potential side effects and risks. These may encompass hemodynamic instability such as hypotension and atrial fibrillation, especially if intravenous fluid replacement is insufficient, anemia resulting in a temporary reduction in oxygen delivery, increased myocardial oxygen consumption due to elevated cardiac output, dilutional coagulopathy, fluid overload, and electrolyte imbalances such as hyponatremia or hypokalemia, which can be exacerbated in the presence of renal failure [21].

In a meta-analysis of randomized controlled trials (RCTs) performed in cardiac surgery, ANH was shown to be associated with a reduced need for RBC transfusion (356/845 [42%] in the ANH group vs 491/876 [56%] in the control group risk ratio [RR] = 0.74, 95% confidence interval [CI] 0.62 to 0.87; $p < 0.0001$), and with reduced transfusion of allogenic blood products (mean difference [MD] = −0.79; 95% CI = −1.25 to −0.34; $p = 0.001$) [22]. Additionally, such meta-analysis revealed a greater reduction in the requirement for postoperative RBCs transfusion when a larger volume of blood was removed from the

patients. We identified an ANH volume of 650 ml as the critical threshold [23]. Based on this meta-analysis, recent European guidelines on perioperative coagulation management suggested that ANH should be considered to reduce allogeneic blood transfusion. However, there is a lack of high-quality evidence supporting this strategy [3,4], as most of the available trials assessed in the meta-analysis were performed before the introduction of modern PBM strategies.

We designed this RCT to investigate whether ANH can reduce the need for allogeneic blood transfusions in cardiac surgery patients managed according to modern PBM strategies (Fig. 1).

2. Methods

2.1. Study design

This is a phase III, multinational, patient- and assessor-blinded randomized trial aiming to assess the effect of pre-CBP ANH (compared to standard care) on the number of patients receiving RBC transfusions.

Patients scheduled for elective cardiac surgery with CPB will be considered eligible. Consent for enrollment will be obtained by trained study staff members and patients will be randomized to either pre-CPB ANH or standard care (Fig. 2).

The primary outcome is the percentage of patients receiving RBCs during their hospital stay. This will be evaluated by examining patients during surgical procedures, daily after surgery, and at the time of discharge.

Secondary outcomes will be all-cause 30-day mortality, acute kidney injury, bleeding-related and ischemic complications (definitions are reported in Supplemental Table 1).

Patients and outcome assessors will be blinded to patient allocation. The intraoperative physician performing ANH will be aware while clinicians responsible for patient care during the post-operative period and in charge for transfusions, will be kept blind. Patient allocation will be easily accessible for safety reason, and blind break will be recorded. Data collection and telephone follow-up will be performed by trained personnel unaware of treatment allocation. All statistical analyses will be independently performed by a statistician not involved in the patient allocation process.

2.2. Study registration

This trial will be approved by local Ethics Committees of all participating centers and conducted in compliance with the principles of the Declaration of Helsinki. The trial was registered on ClinicalTrials.gov in April 2019 with trial identification number NCT03913481.

2.3. Inclusion and exclusion criteria

All patients older than 18 years and scheduled for elective cardiac surgery with planned CPB will be enrolled in the study after signing of informed consent.

The exclusion criteria will be evaluated at two different times: A) bedside before surgery (patients with these exclusion criteria will not be approached); and B) in the operating theatre by the attending anesthesiologist (patients with exclusion criteria at this time point will not be randomized).

For example, bedside assessment will allow exclusion of patients with unstable coronary disease, critical preoperative status, those taking drugs that could impair hemostasis (e.g., antiplatelet drugs except aspirin, heparin, bivalirudin, dual antiplatelet therapy, and direct oral anticoagulant). The full list of exclusion criteria is reported in Table 1 (Table 1).

After entering the operating theatre, patients will be evaluated for ANH feasibility: exclusion criteria at this time point include pre-CPB anemia (defined as hematocrit <30%) or an anticipated low hematocrit during CPB or expected hemodynamic instability resulting from the withdrawal of ≥650 ml of blood. (Table 1; Supplemental table 2).

There are challenges to implementing ANH. For example, ANH requires a relatively high preoperative hematocrit. Platelet plasmapheresis provides a partial solution to this issue by enabling the separation of autologous blood into various components, including a concentrated platelet-rich plasma (PRP) fraction, a concentrated RBCs fraction, and a portion of platelet-poor plasma. Therefore, the packed RBCs can be stored or immediately returned to the patient if the hematocrit drops below a critical threshold or if there is a need to improve oxygen delivery. Meanwhile, the concentrated platelet-rich plasma and the platelet-poor plasma can be preserved and given following the weaning from CPB to mitigate the consumption coagulopathy, often observed in cardiac surgery [24]. The American Society of Thoracic Surgeons and the Society of Cardiac Anesthesiologists guidelines on perioperative coagulation management recently has endorsed platelet-rich plasma as an effective strategy to reduce allogeneic blood transfusion [5,25]. The ANH study protocol, therefore, allows enrolling anemic patients in the setting where the above logistic options are available, and a subgroup analysis will be performed. We expect, however, that such procedures will affect <10% of study patients.

2.4. Randomization and study intervention

Patients who are consented and are deemed eligible will be randomized in equal proportions (1:1) via a password-protected web-based

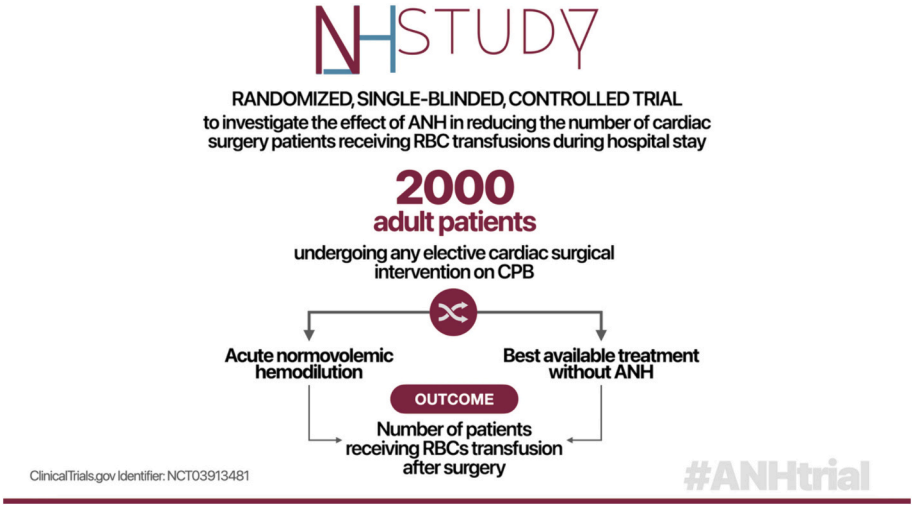

Fig. 1. Graphical abstract.

Inclusion criteria	Exclusion criteria
- ≥18 years old - Signed informed consent - Any cardiac surgical intervention on CPB - Elective surgery (planned)	- Medical decision - Unstable coronary artery disease: Recent (< 6 weeks) myocardial infarction Unstable angina Severe (>70 %) left main coronary artery stenosis - Critical preoperative state Ventricular tachycardia Ventricular fibrillation, aborted sudden cardiac death, preoperative cardiac massage Preoperative ventilation Hemodynamic instability Preoperative inotropes Preoperative IABP Preoperative LVAD Preoperative ECMO Preoperative severe acute renal failure - Emergency surgery - Pregnancy - Therapy with one of the following at the time of surgical intervention: DAPT Antiplatelet drugs (except ASA) Heparin < 6 h Tirofiban < 8 h Bivalirudin < 12 h

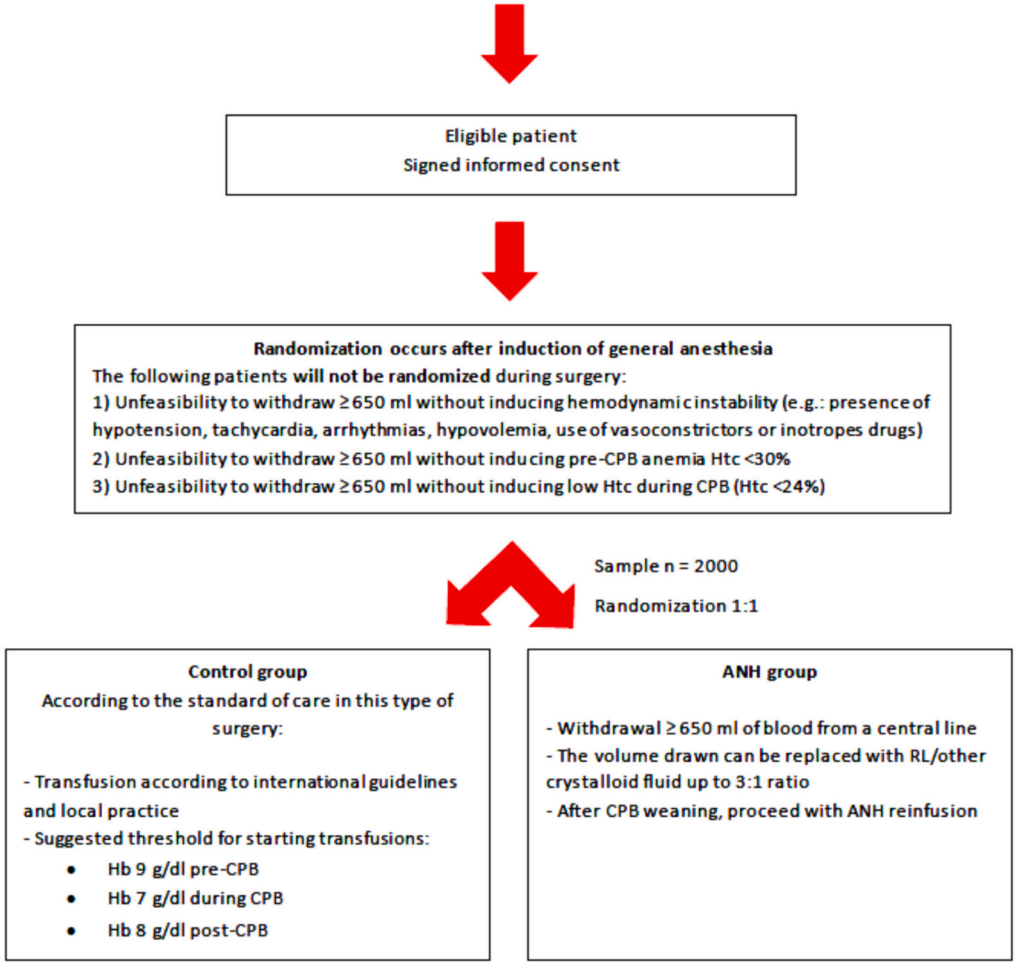

Fig. 2. Study flow chart.

Table 1
Exclusion criteria are evaluated at two different timepoint: before surgery; and in the operating theatre.

Exclusion criteria before surgery	Exclusion criteria in operating theatre
Medical Decision	Medical Decision:
Unstable coronary artery disease	
- Recent (<6 weeks) myocardial infarction;	- Unfeasibility to withdraw ≥650 ml without inducing hemodynamic instability;
- Unstable angina;	- Unfeasibility to withdraw ≥650 ml without inducing pre-CPB anemia (Htc <30%);
- Severe (>70%) left main coronary artery stenosis.	- Unfeasibility to withdraw ≥650 ml without inducing low Htc during CPB (Htc <24%).
Critical preoperative state	When plasmapheresis is available, anemia will not be exclusion criteria.
- Ventricular Tachycardia;	
- Ventricular fibrillation, aborted sudden cardiac death, preoperative cardiac massage;	
- Preoperative MV;	
- Hemodynamic instability;	
- Preoperative inotropes;	
- Preoperative IABP;	
- Preoperative LVAD;	
- Preoperative ECMO;	
- Preoperative severe acute renal failure.	
Emergency surgery	
Pregnancy	
Therapy with one of the following at time of surgery:	
- DAPT[a];	
- Antiplatelet drugs (except ASA);	
- Heparin <6 h;	
- Tirofiban <8 h;	
- Bivalirudin <12 h.	

Abbreviations: MV = mechanical ventilation; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; ECMO = extracorporeal membrane oxygenation; ASA = acetylsalicylic acid; Htc = hematocrit.

[a] Stop clopidogrel and ticagrelor 5 days prior to surgery and prasugrel 7 days before surgery, while continuing ASA.

interface to the best available treatment plus ANH or the best available treatment without ANH. Treatment allocation will be block randomized with permuted size and stratified by center. To reduce the risk of bias, the randomization will be performed at the last available moment, after general anesthesia induction and after the attending anesthesiologist considers the ANH procedure feasible. The implementation of a web-based, password-protected randomization interface will enable a rapid patient allocation (3 to 5 min). Following randomization, each patient will receive a unique study number.

In the study arm, after induction of general anesthesia, a total volume of at least 650 ml of blood will be drawn [23] and replaced with crystalloids in up to a 3:1 ratio, according to clinical judgment and local protocols.

In some anemic patients, ANH can be performed together with plasmapheresis to store the platelet-rich plasma fraction while returning the RBCs (see above).

Collected blood will be stored at a controlled temperature in standard citrate-phosphate-dextrose collection bags labeled with the patient's name for a maximum of six hours.

After CPB weaning and heparin reversal with protamine, collected blood will be reinfused at a rate decided by the attending anesthesiologist. The timing and sequence of reinfusion of autologous blood, platelet-rich plasma fraction, blood from cardiotomy suction or any cell-saver will be decided by the attending anesthesiologist. Patients enrolled in the control arm will be treated according to standard local procedures. Hemostasis will be optimized using blood products and hemostatic drugs according to clinical routine and coagulation tests, in both allocation groups.

2.5. Study outcomes and their measures

2.5.1. Primary endpoint

The primary outcome of the study is the percentage of patients transfused with RBCs during hospital stay. RBC transfusion will be evaluated daily during ICU and hospital stay until discharge.

Prespecified subgroup analyses for the primary endpoint will be according to type of surgery, CPB time, CPB strategy (hypothermic vs normothermic CPB), patient sex and age (group defined as ≤65 years old vs >65 years old), transfusion strategies driven by viscoelastic tests or not, preoperative chronic kidney disease, re-do surgery, preoperative hemoglobin concentration (Hb <12 g/dl vs >14 g/dl), use of preoperative antithrombotic drugs, and use of intraoperative plasmapheresis technique. Post-hoc subgroup analyses will be conducted to investigate differences between centers who did and did not administer preoperative iron or erythropoietin supplements.

2.5.2. Secondary endpoints

Secondary outcomes will include 30-day mortality, defined according to the Society of Thoracic Surgeons definition for operative mortality as the death occurred within 30 days from surgery or during the same hospitalization [26,27]; acute kidney injury defined by the KDIGO (Kidney Disease: Improving Global Outcomes) criteria [28]; bleeding complications (assessed by postoperative blood loss, the need for surgical revision, and the blood components administered) and ischemic complications (myocardial infarction, stroke and thromboembolic events, defined according to the latest international guidelines) [29–32] (see Supplemental Table 1). Blood components are defined as: packed RBC, FFP, PLT and any other hemostatic agent (e.g. fibrinogen, PCC, cryoprecipitate).

Other collected postoperative clinical variables include pulmonary complications (including duration of mechanical ventilation, incidence of acute respiratory distress syndrome and pneumonia), clinical evidence of infection (mediastinitis, pneumonia, sepsis/septic shock), cardiogenic shock [33], worst hematocrit value during ICU stay, ICU and hospital length of stay, as well as hospital readmission rate at 30 days and 1 year after surgery.

Postoperative complications will be defined according to standard European Society of Anesthesiology (ESA) and European Society of Intensive Care Medicine (ESICM) definitions [34]. (Supplemental section "Other variables definitions").

2.6. Data collection

All data (Supplemental table 3 to 5) will be prospectively collected by trained research team members at each center, not otherwise involved in patients' management. All data will be stored electronically in a database using appropriate software. Security measures and restricted access will be applied to all data in the electronic case report forms to protect data integrity and patient privacy. All centers will fill out a screening log to track all patients who are eligible but not randomized.

2.6.1. Baseline data

Baseline data will be collected during the preoperative stay and will include: demographic characteristics, date of hospital admission, medical history, concurrent medical conditions and comorbidities (with particular reference to cardiovascular diseases), history of previous transfusions, New York Heart Association (NYHA) class, preoperative medications (in particular preoperative antithrombotic medications and when they were discontinued), recent laboratory values, and preoperative echocardiographic data (if available).

2.6.2. Intraoperative data

The following data will be collected during surgery: date of surgery, duration and type of anesthesia (balanced vs. total intravenous

anesthesia), type of surgical procedure, duration of surgery, use of CPB and aortic cross-clamp, use of cell-saver, deep hypothermic circulatory arrest and ultrafiltration, anti-coagulation strategy (ACT values, heparin and protamine doses), temperature (lowest, at CPB weaning and at operating room exit), arterial blood gas analyses (baseline, post-heparin, post-protamine, and at the end of surgery), hemodynamic parameters, use of inotropic support and inotropic score [35], use of mechanical circulatory support, blood products and coagulation factors administered, diuresis, ANH data (volume of autologous blood withdrawal and crystalloids replacement) and any methodological issues (e.g. patients who were later discovered to have exclusion criteria, those who experienced major and minor protocol deviations, crossover, patients in whom the surgical plan no longer requires CPB as originally planned, premature interruption of the intervention). The most common side effects associated with the ANH such as hypotension, atrial fibrillation, and anemia, will also be collected [20].

2.6.3. Postoperative data (collected both during ICU and hospital stay)

The following data will be collected at ICU admission: arterial blood gases parameters, hemodynamic data, inotropic and vasoactive agents, mechanical circulatory support and laboratory tests.

During ICU stay, the data collected will be arterial blood gases parameters, inotropic and vasoactive agents, mechanical circulatory supports, fluid management, diuresis, blood loss via chest drains, laboratory tests, RBC transfusion episodes, and transfusion of blood products (e.g., platelets, fresh frozen plasma, and cryoprecipitate).

The complications recorded will include death, acute kidney injury, bleeding complications, and ischemic complications (myocardial infarction, stroke, and thromboembolic events). Moreover, we will collect the rate of respiratory complications, infections, mediastinitis and septic shock, cardiogenic shock, arrhythmias, neurological damage, and transfusion-related adverse reaction.

Phone call follow-up will be performed at 30 days and 1 year after randomization to investigate episodes of hospital readmission and mortality.

2.6.4. Safety monitoring

During the entire study period, clinical staff and study staff will work together to guarantee protocol adherence and patient safety. The feasibility of ANH will be evaluated both at the bedside on the day before surgery and by the attending anesthesiologist at the beginning of the surgical procedure. Any clinical concern about the feasibility of ANH will be considered as an exclusion criterion. The study team will constantly evaluate for adverse events and protocol compliance. If any serious suspected trial treatment-related adverse events occur, clinical staff can immediately stop study treatment.

However, ANH is a commonly performed procedure and no serious adverse events have been reported in available scientific literature and previous trials [20,21].

An independent data safety and monitoring committee will perform interim analyses three times during the study period (when reaching 25%, 50% and 75% of planned patients) and decide whether the trial should continue or be stopped for efficacy, futility, or harm. Data evaluation at each interim analysis will be based on the alpha spending function concept, according to Lan and De Mets' [36] and will use O'Brien-Fleming *Z*-test boundaries [37].

2.6.5. Sample size calculation

The sample size is based on previous large international trials, which identified the rates of post-surgical blood transfusion of 38% (ATACAS) and 52% (TRICS II) [12,38] and on a meta-analysis of RCTs [20] which investigated the effect of ANH and which found a transfusion rate of 56% in the control group and 42% in the ANH group. (RR = 0.74; 95% CI, 0.62 to 0.87; $P < 0.0001$; I2 = 72.5%) [21].

Considering the improvements in perioperative blood management, for the sample size calculation we conservatively assumed an incidence of transfusions of 35% in the control group and 28% in the treatment group which corresponds to a 20% expected relative risk reduction of the primary endpoint. Applying a 90% power and 5% alpha error, with a two-tailed test and continuity correction, we calculated that it would be necessary to randomize 952 subjects per group for a total of 1904 patients, which was rounded to 2000 to account for possible dropouts.

2.6.6. Data analysis

Data will be analyzed according to the intention-to-treat principle. Per-protocol analyses will also be performed. Data will be presented stratified by country and by center.

Web-based electronic case report form will be completed and electronically stored. Data will be analyzed using STATA (Stata Statistical Software: version 18, College Station, TX, USA).

Demographic information and baseline data will be summarized using descriptive statistics. Categorical variable will be expressed as number and percentage. To compare the two groups, the univariate analyses will be performed, based on Chi-square or Fisher's exact test as appropriate. Relative risk and 95% confidence interval will be obtained employing the two-by-two table method, using log-normal approximation.

Continuous variables will be expressed as median and interquartile range or, if appropriate, as mean and standard deviation. The normal distribution will be plotted in visual histogram evaluation and a Q-Q plot. To analyze the differences between treatment groups, for data that do not or do follow normality of distribution, a non-parametric test or *t*-test will be performed.

Treatment efficacy and the predictors of the primary endpoint will be analyzed using a logistic regression model with stepwise selection. Clinical data will be entered into the model if their univariate *p*-value is <0.1. We will use collinearity analysis to determine associations between variables. The variables without any collinearity will be incorporated into a logistic regression. In the multivariate model, variables will be expressed as odds ratios with 95% CI.

Time to mortality will be compared between ANH patients and controls with the log-rank test and it will be plotted as a Kaplan-Meier survival curve.

For the hypothesis tested, statistical significance will be set at the two-tailed 0.05 level.

An interim analysis will be performed three times by an independent safety committee. Data will be analyzed after the recruitment of 25% ($n = 500$), 50% ($n = 1000$) and 75% ($n = 1500$) of patients. According to Lan and De Mets' [36], data analyzed early in the trial, at each interim analysis, will be based on the alpha spending function concept, and will employ O'Brien-Fleming *Z*-test boundaries [37]. Thus, for interim analyses, the efficacy-stopping rule requires extremely low *p*-values (<0.000015, 0.003 and 0.02 respectively in the first, second, and third analyses). Investigators will not be informed of the results of the interim analysis, unless interim analyses lead to study interruption.

The Data Safety and Monitoring Committee will also perform conditional power analyses to evaluate interruption for futility. Conditional power will be assumed based on the proportion of outcomes that follow the observed trend. All data analyses will be carried out according to the pre-established analysis plan. Any additional data review will be reviewed the independent Data and Safety Monitoring Committee.

3. Discussion

3.1. Significance

Red blood cell transfusions are used worldwide to treat bleeding and improve oxygen delivery to vital organs and tissues. When using blood products, various issues must be considered including ethical, cost-related, logistic, and infectious aspects. Nevertheless, blood transfusion can be a lifesaving treatment in patients with active bleeding or severe anemia [39]. In cardiac surgery, bleeding depends on intrinsic

procedural risks, need for full heparinization, acquired hemodilution and consumptive coagulopathy.

Postoperative complications are associated with prolonged hospital stay, increased costs, and increased morbidity and mortality.

Patients who do not receive transfusion may have a better outcome than those who are exposed to transfusion [8]. However, this may reflect illness severity for which transfusion is an epiphenomenon without a direct harmful effect. Nonetheless, current literature shows that, while the risk of infection is low, transfusions are associated with non-infectious harmful complications such as transfusion-associated circulatory overload, transfusion-related acute lung injury, transfusion-related immune modulation, and postoperative thromboembolism (Fig. 3). For all the above-mentioned reasons, blood sparing strategies may positively affect patient outcomes. Among possible blood sparing strategies, ANH appears cheap, safe, and largely available around the world. Several studies have addressed the effect of ANH on blood transfusion and outcomes, with conflicting results. However, the overall quality of these studies is relatively low, and the sample size is limited [10,16–22]. Accordingly, we designed a large, randomized, blinded, multi-center trial to assess whether providing ANH before elective-CPB initiation will result in a reduction of the number of patients receiving RBC transfusion during hospital stay after elective cardiac surgery. Long term morbidity and mortality will also be investigated at 30 days and later at 1 year through follow-up calls. The trial has a pragmatic design that reflects routine clinical practice and maximizes protocol adherence and external validity.

A positive trial may help reduce the use of blood products worldwide, a precious resource. In addition, it may help improve the healthcare of millions of patients in low-income countries and meet the expectation of specific communities (e.g., Jehovah's Witnesses).

3.2. Strengths and limitations

We expect to enroll 2000 patients. Any possible loss to follow-up (including withdrawal of consent) may affect secondary outcomes. To reduce this effect, the calculated sample size is relatively large.

All efforts will be made to ensure a complete follow-up and reduce the risk of bias. These efforts will include follow-up phone calls on more than one telephone number, checking for hospital electronic readmissions, checking with general practitioners, checking follow-up with surgeons, checking with local authorities, and sending letters to the home addresses of patients recruited as in our previous experiences [40–42].

Employing widely accepted standard definitions from the scientific committee may help mitigate subjectivity in adjudicating clinical events, thus overcoming this limitation. A blinded adjudication committee is supporting secondary endpoints definition whenever deemed necessary.

The primary outcome is to assess whether implementing ANH can reduce the number of patients requiring RBC transfusions while preserving positive clinical outcomes at a reasonable cost therefore there is a possibility that the study design may lack adequate power to detect noteworthy changes in clinical events (e.g. mortality).

We did not plan to collect data on preoperative iron and erythropoietin supplementation being anemic patients excluded from the study, but we will conduct a post-hoc subgroup analysis investigating the local protocols on preoperative management of anemia.

Although clinicians responsible for post-operative transfusions remain unaware of the assigned group, this becomes unfeasible intraoperatively and may introduce bias. However, in the intraoperative period, the primary factor influencing the need for transfusion is surgical bleeding, which is not influenced by ANH (known for its effectiveness on microvascular bleeding).

If the study results will favor the ANH group. Future studies will be needed to assess the cost effectiveness of ANH as this study could not implement a comprehensive cost analysis given both the notable variation in the cost associated with packed RBC transfusions and standard citrate-phosphate-dextrose collection bags used for ANH and the difficulties in accounting for indirect costs such as time expenditure, workload and eventual management of adverse reactions.

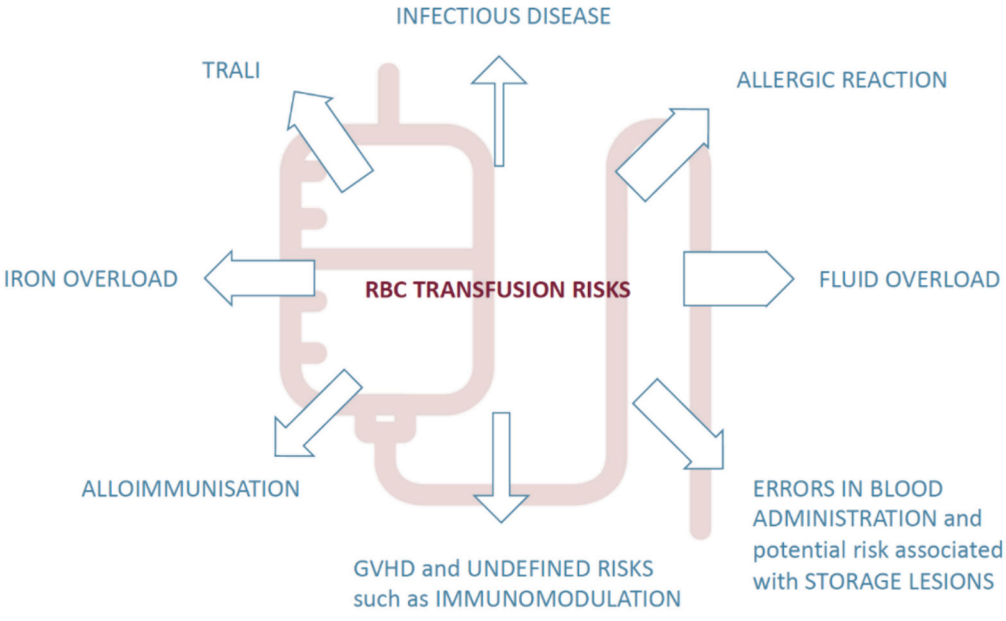

Fig. 3. Infectious and non-infectious risks of transfusions.
Abbreviations; RBC = red blood cells; GVHD = graft versus host disease; TRALI = transfusion related lung injury. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Trial status

The trial is now ongoing with 1380 patients randomized in 21 centers in 11 countries (Italy, China, Russia, US, Singapore, Brazil, Thailand, Saudi Arabia, Kingdom of Bahrain, Serbia, and Turkey) as per April 23, 2024. We expect to complete the recruitment by December 2024.

We regularly provide updates about the trial via the department account: @SRAnesthesiaICU.

Consent to participate and ethics approval

This study has been approved by the Human Research Ethics Committee at IRCCS San Raffaele Scientific Institute, Milan, Italy (127/INT/2018 on September 13, 2018) and each participating center.

All eligible patients will be informed about the rationale of the study and any practical aspects including ANH intervention, data collection and storage, and follow-up strategies. Written informed consent will be obtained from all recruited patients by trained study staff.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Three authors specified the following financial interests even if not related to this paper:

Dr Ranucci declares the following financial interests: CSL Behring, Haemonetics, LFB, Werfen, Grifols.

Dr Guarracino declares the following financial interests: Abbott, AOP Orphan, Edwards, Masimo, Orion, Viatris

Dr Mazzeffi declares the following financial interests: consulting fees from Octapharma, Hemosonics, NovoNordisk

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2024.107605.

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