Goal-directed perfusion to reduce acute kidney injury: A randomized trial

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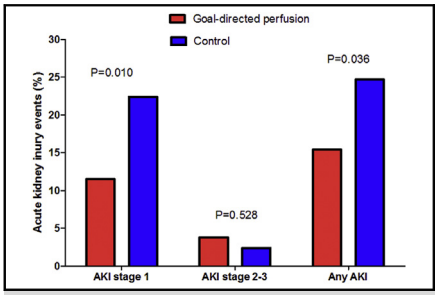
ABSTRACT

Objective: To determine whether a goal-directed perfusion (GDP) strategy aimed at maintaining oxygen delivery (DO_2) at $\geq$280 mL·min^{-1}·m^{-2} reduces the incidence of acute kidney injury (AKI).

Methods: This multicenter randomized trial enrolled a total of 350 patients undergoing cardiac surgery in 9 institutions. Patients were randomized to receive either GDP or conventional perfusion. A total of 326 patients completed the study and were analyzed. Patients in the treatment arm were treated with a GDP strategy during cardiopulmonary bypass (CPB) aimed to maintain DO_2 at $\geq$280 mL·min^{-1}·m^{-2}. The perfusion strategy for patients in the control arm was factored on body surface area and temperature. The primary endpoint was the rate of AKI. Secondary endpoints were intensive care unit length of stay, major morbidity, red blood cell transfusions, and operative mortality.

Results: Acute Kidney Injury Network (AKIN) stage 1 was reduced in patients treated with GDP (relative risk [RR], 0.45; 95% confidence interval [CI], 0.25-0.83; $P = .01$). AKIN stage 2-3 did not differ between the 2 study arms (RR, 1.66; 95% CI, 0.46-6.0; $P = .528$). There were no significant differences in secondary outcomes. In a prespecified analysis of patients with a CPB time between 1 and 3 hours, the differences in favor of the treatment arm were more pronounced, with an RR for AKI of 0.49 (95% CI, 0.27-0.89; $P = .017$).

Conclusions: A GDP strategy is effective in reducing AKIN stage 1 AKI. Further studies are needed to define perfusion interventions that may reduce more severe levels of renal injury (AKIN stage 2 or 3). (J Thorac Cardiovasc Surg 2018;156:1918-27)



Acute kidney injury in the goal-directed perfusion and control groups.

Central Message

A goal-directed perfusion strategy aimed at preserving oxygen delivery during cardiopulmonary bypass is effective in reducing AKIN class 1 postoperative acute kidney injury.

Perspective

Acute kidney injury (AKI) is a major complication of cardiac surgery. This study demonstrates that minor patterns of AKI in medium- to low-risk patients may be limited by a strategy of cardiopulmonary bypass based on a target oxygen delivery. Further studies are needed to define perfusion interventions that may reduce more severe levels of renal injury (AKIN stage 2 or 3).

See Editorial Commentary page 1928.

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Abbreviations and Acronyms

AIC = Akaike information criterion
AKI = acute kidney injury
AKIN = Acute Kidney Injury Network
ARF = acute renal failure
CI = confidence interval
CPB = cardiopulmonary bypass
DO_2 = oxygen delivery
GDP = goal-directed perfusion
GIFT = Goal-Directed Perfusion Trial
HCT = hematocrit
ICU = intensive care unit
IQR = interquartile range
OR = odds ratio
RBC = red blood cell
RCT = randomized controlled trial
RR = relative risk
SvO_2 = venous oxygen saturation

Scanning this QR code will take you to supplemental tables and video for this article.

Acute kidney injury (AKI) is a serious complication of cardiac surgery, affecting a considerable proportion of patients and increasing postoperative morbidity and mortality.[1] Various factors, including age, preoperative renal function, hemodynamic state, and duration and complexity of surgery, have been associated with postoperative AKI.[2] Studies of AKI following coronary artery bypass graft surgery using the Acute Kidney Injury Network (AKIN) classification have shown that small increases in serum creatinine level (AKIN class 1) increase the risk of end-stage renal disease by 3-fold (relative risk [RR], 2.92; 95% confidence interval [CI], 1.87-4.55) and that of mortality by nearly 1.5-fold (RR, 1.34; 95% CI, 1.23-1.45).[3]

An association between the nadir hematocrit (HCT) value during cardiopulmonary bypass (CPB) and postoperative AKI was first reported in 1994.[4] Numerous retrospective studies subsequently confirmed this finding, and some authors have hypothesized that insufficient oxygen delivery (DO_2) may be the mechanism underlying the link between severe hemodilution on CPB and poor renal outcomes.[5-8]

Subsequent retrospective studies[9-11] have confirmed the association between nadir DO_2 on CPB and postoperative AKI, with the identification of a "critical DO_2" in the range of 260 to 272 $mL \cdot min^{-1} \cdot m^{-2}$ for patients undergoing moderately hypothermic (>32°C) CPB. Based on these observations, the concept of goal-directed perfusion (GDP), aimed at maintaining the DO_2 on CPB above the critical value, was introduced.[9] The current guidelines of the American Society of Extracorporeal Technology include measurement of DO_2 within the standard measurements for assessing arterial pump flow rate.[12] Historically, the primary strategy for meeting oxygen and metabolic requirements during adult CPB was based on cardiac index, typically in the range of 1.8 to 2.4 $L \cdot min^{-1} \cdot m^{-2}$. However, the concept that arterial pump flow should be adjusted based on the DO_2 rather than simply on the basis of the body surface area and temperature is still based on retrospective studies on large patient populations.

To date, high-level evidence demonstrating that a GDP strategy intended to avoid a nadir DO_2 below the critical value will reduce the rate of postoperative AKI is lacking. The current study (Goal-Directed Perfusion Trial [GIFT]) sought to test the hypothesis that the GDP approach to avoid a DO_2 nadir <280 $mL \cdot min^{-1} \cdot m^{-2}$ will reduce the rate of postoperative AKI in patients undergoing moderately hypothermic CPB.

METHODS

Study Design and Population

The GIFT multicenter randomized controlled trial (RCT) was conducted at 9 institutions in Europe, Australia, New Zealand, and the United States. The study protocol was approved by the Ethics Committee of the coordinating institution (Istituto Di Ricovero e Cura a Carattere Scientifico, Policlinico San Donato; June 17, 2014; protocol 24/int/2014) and by the Ethics Committee or Institutional Review Board of each participating institution before study commencement, and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice guidelines.

Patients were recruited between October 2014 and January 2017. In August 2016, the protocol was amended with minor changes. All patients provided written informed consent to participate before enrolling in the study.

All patients who were age >18 years and scheduled for cardiac surgery with an expected CPB duration of ≥90 minutes were eligible for inclusion in the study. Patients were screened at the time of hospital admission or at the first cardiac surgery visit. Specific exclusion criteria were severe chronic renal failure (receipt of dialysis or a serum creatinine level >3.0 mg/dL), emergent surgery; moderate to severe anemia (preoperative HCT <32%), and expected nadir CPB temperature <32°C. The values of HCT and serum creatinine considered for inclusion in the study were the last values recorded before surgery. Withdrawal criteria (after randomization) included the need for allogeneic blood transfusions before CPB (including the use of allogeneic blood to prime the CPB circuit) and an unexpected need for deep hypothermic CPB. Study data were collected prospectively starting on the day before surgery or the day of surgery and extending until hospital discharge (or 30 days after surgery for operative mortality).

Intervention

Patients were randomized 1:1 into the control arm or the GDP arm. Patients in the GDP arm received a specific intervention aimed to maintain a DO_2 value ≥280 $mL \cdot min^{-1} \cdot m^{-2}$ during CPB. This intervention was based on adjustment of the arterial pump flow according to the HCT value

to reach and maintain a DO_2 above the prespecified threshold. In the event of low HCT values and an inability to maintain the DO_2 above the threshold by increasing the pump flow, 1 unit of red blood cells (RBCs) was transfused if the venous oxygen saturation (SvO_2) was <68% and/or the oxygen extraction rate was >40%.

The patients in the control arm received arterial pump flow based on body surface area and temperature, with a target value of 2.4 $L \cdot min^{-1} \cdot m^{-2}$ at normothermia. Transfusion of RBCs during CPB was triggered by the HCT value, according to local institutional standards (Table E1).

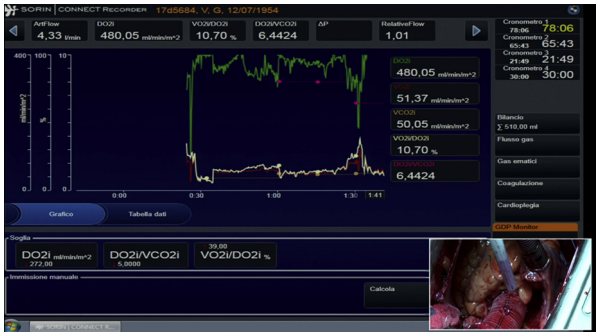
With respect to the other perfusion details, the patients were treated according to the local institutional standards. The DO_2 levels of patients in both study arms were continuously monitored during CPB, and SvO_2 was monitored either continuously or intermittently. Details of the perfusion techniques and equipment are provided in Tables E1 and E2. For patients in the GDP arm, the perfusionist had a direct view of the GDP monitor data to achieve compliance with the GDP protocol. For patients in the control arm, the DO_2 value was excluded from the screen of the GDP monitor to avoid any intervention based on DO_2 values in the group that was intended to be treated with the conventional strategy.

DO_2 data were collected at 20- to 30-second intervals, with the DO_2 value during CPB reported for the study at 10-minute intervals. For the purpose of this study, the nadir DO_2 value was defined as the lowest value maintained for at least 2 consecutive measurements (10-minute intervals) and expressed as the mean of the 2 consecutive measurements. An example of data collection during CPB is provided in Video 1.

Study Outcomes

The primary outcome of the GIFT was the postoperative rate of AKI. For this study, AKI was defined according to the creatinine changes specified in the AKIN classification.[13] AKI stage 1 is defined as an increase in serum creatinine level of 150% to 200% of baseline or an absolute increase of ≥0.3 mg/dL, and AKI stage 2 as an increase in serum creatinine level of >200% of the baseline value, within the first 48 hours postsurgery. Patterns of AKI stage 3 are incorporated in the AKI stage 2 definition. Minor serum creatinine changes were defined as "any serum creatinine increase." The primary outcome was therefore defined in terms of AKI stage 1, stage 2-3, any AKI, and any serum creatinine increase.

Secondary outcomes were intensive care unit (ICU) length of stay; major morbidity (ie, mechanical ventilation for >24 hours, stroke, deep sternal wound infection, acute renal failure [ARF; defined as renal replacement therapy or a serum creatinine level >4.0 mg/dL at any postoperative time point], reoperation, or mortality); rate of receipt of RBC transfusion and number of units transfused; and operative mortality (in-hospital or within 30 days of surgery after discharge). The presence of morbidities was considered for the safety analysis.



VIDEO 1. Monitoring of goal-directed perfusion with a dedicated tool. Video available at: https://www.jtcvs.org/article/S0022-5223(18)31029-8/fulltext.

Randomization

The participants were randomized with a Web-based randomization protocol using a nonstratified fixed-block size of 4. The order of blocks was also randomized. Randomization was performed on the day of surgery in the majority of the cases. The medical team involved in the surgical process (ie, surgeon, perfusionist, and anesthesiologists) was aware of the patients' treatment arm assignment, but staff members involved in the postoperative care in the ICU and ward were not. The patient files did not contain information related to the study arm, to avoid different treatments in the ICU.

Sample Size Calculation

Sample size calculation was based on a previous study[10] retrospectively comparing AKI rates in patients with a nadir DO_2 on CPB of ≥280 $mL \cdot min^{-1} \cdot m^{-2}$ or <280 $mL \cdot min^{-1} \cdot m^{-2}$, by retrieving the original rough dataset. The rate of AKI (stage 1 or 2) was 12% in the former group and 30% in the latter. Based on these figures, and with a power of 80% and a significance level of 0.05, 2 groups of 80 patients each were needed to confirm the difference in AKI rates within the RCT. However, based on the experimental design, it was considered that the control arm could include a rate of patients spontaneously reaching and maintaining the critical DO_2, and that some patients in the GDP arm might not reach and maintain the desired DO_2 value despite our efforts. These rates were prudentially settled at 50% and 5%, respectively. Based on this assumption, the hypothesized AKI rate would be 21% in the control arm and 12.8% in the GDP arm, leading to a sample size of 327 patients per each arm. Considering a plausible rate of patients lost for the final analysis, the sample size was finally settled at 2 groups of 350 patients each.

Statistical Analysis

Interim analyses were planned at 25%, 50%, and 75% of patient recruitment, with stopping rules for safety, futility, and efficacy (see Online Data Supplement). The protocol was amended in August 2016 following completion of the first interim analysis (data closed in February 2016). The amendments included the inclusion of a subgroup analysis based on bypass time (see below) and a change to the stopping rule for efficacy from $P < .005$ at the 50% interim analysis to $P < .05$. Data are presented as mean ± standard deviation for continuous normally distributed variables, median and interquartile range (IQR) for continuous non–normally distributed variables, and number and percentage for categorical variables. The normality of distribution was tested with the Kolmogorov–Smirnov test. Missing data for the primary outcome (baseline and peak serum creatinine levels) were assumed to be missing completely, and these patients were excluded from the efficacy analysis.

The analysis was based on an intention to treat. Differences in the primary and secondary dichotomous outcome measures between the GDP arm and the control arm were tested using an RR analysis, producing an RR with 95% CI, and the significance level was assessed with the Pearson χ^2 or Fisher exact test as appropriate.

Comparisons of continuous non–normally distributed secondary outcome measurements (ICU stay and number of RBC units transfused) were based on nonparametric tests. The Student t test was used for continuous normally distributed variables.

Two (generalized) mixed-effects models were implemented: a regression model for DO_2 level over time and a regression model for the probability of DO_2 level dropping below 280 $mL \cdot min^{-1} \cdot m^{-2}$ over time. The effect of time was modeled considering restricted cubic splines with 3 or 4 knots. The choice among a simple linear effect and the 2 different spline representations was performed using the Akaike information criterion (AIC). The interaction between time and treatment was used to allow for different patterns of the 2 investigated quantities over time according to treatment. The interaction was tested using likelihood ratio tests. Random intercepts at patient and center levels were considered for

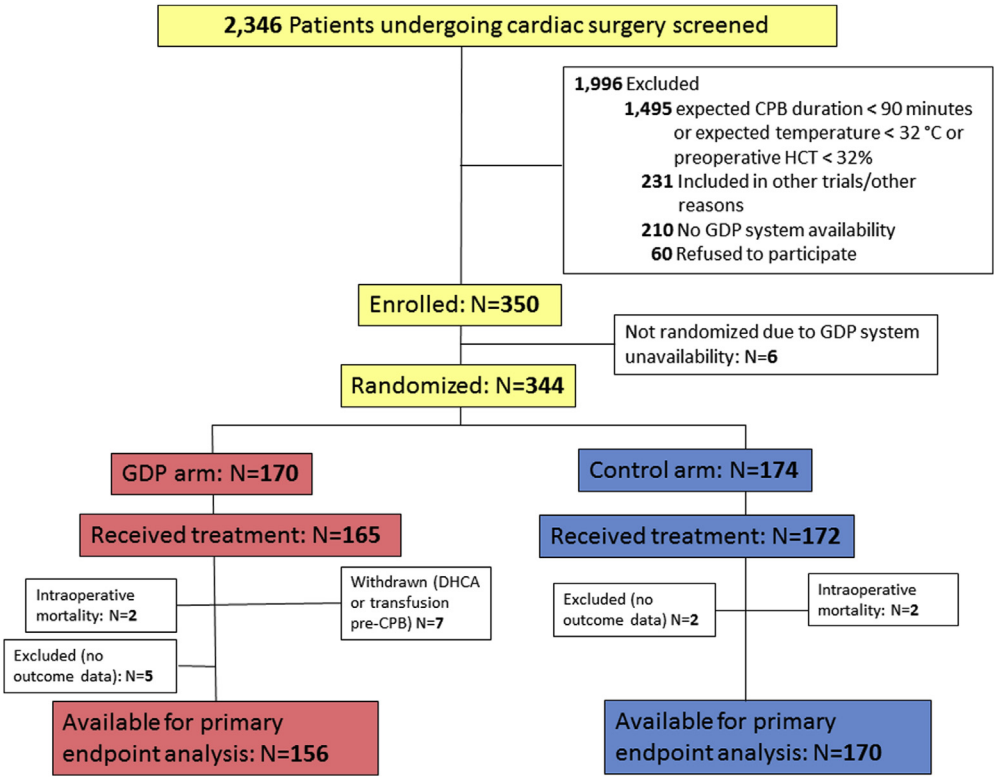


FIGURE 1. Diagram showing the flow of participants through each stage of the trial. *CPB*, Cardiopulmonary bypass; *HCT*, hematocrit; *GDP*, goal-directed perfusion; *DHCA*, deep hypothermic circulatory arrest.

both the generalized linear and linear mixed-effects models. For the linear mixed-effects model, random slopes for time effect were considered as well. Simulation-based 95% CIs for predicted marginal probabilities of the generalized mixed models were calculated.

A multivariable logistic regression model was applied to the outcome variable AKIN stage 1 to adjust the effect of the experimental variable (GDP) for the potential effects of RBC transfusion, participating institution, and differences in the baseline renal risk, defined according to the acute renal failure (ARF) score.[14]

A prespecified subgroup analysis excluding patients with a short or very long duration of CPB was performed. This subgroup analysis was justified by the fact that the entry criterion was an expected CPB duration >90 minutes. To avoid a negligible experimental effect (short exposure to a low nadir DO_2), the subgroup analysis excluded all patients with a CPB duration <1 hour. At the same time, an excessively long CPB time may lead to difficulty in weaning from CPB (with reduced arterial pump flow during CPB weaning and reduced postoperative cardiac output), and thus possible postoperative renal dysfunction may be related to these factors rather than to the experimental effect. Therefore, patients with a CPB duration >90th percentile of the CPB time distribution were excluded by the subgroup analysis.

The statistical analyses were performed using SPSS 13.0 (SPSS, Chicago, Ill), MedCalc (Ostend, Belgium), or Stata 15.0 (StataCorp, College Station, Tex). A P value <.05 was considered to indicate statistical significance.

RESULTS

The study was halted prematurely after 26 months because the efficacy endpoint at the 50% interim analysis had been met, according to the stopping rules. During the study period, 2346 patients were screened for participation in the GIFT (Figure 1), of whom 1996 were excluded primarily for failure to meet the inclusion criteria. A total of 350 patients were enrolled but only 344 were randomized, due to an unexpected unavailability of the GDP monitor. An additional 7 patients (5 in the GDP arm and 2 in the control arm) received the allocated treatment but lacked outcome data. The withdrawal criteria were met by 7 patients in the GDP arm but by no patients in the control arm. Finally, 2 patients in each arm died during surgery or immediately after arrival in the ICU, thus missing the peak postoperative serum creatinine measurement. This left 326 patients (GDP arm, n = 156; control arm, n = 170) available for the primary outcome analysis and 330 patients available for the secondary outcome (mortality) analysis.

Table 1 presents patient baseline and intraoperative characteristics. The 2 arms were comparable, with a significantly higher preoperative serum creatinine value in the GDP arm but no difference in baseline creatinine clearance. The median CPB duration was 116 minutes in the GDP arm and 109 minutes in the control arm. Twenty-two patients (14.1%) in the GDP arm and 47 (27.6%) in the control arm did not reach the expected

TABLE 1. Demographic data, preoperative profile, and operative details of the patient population

Variable	GDP arm (n = 156)	Control arm (n = 170)
Age, y, median (IQR)	68 (59-75)	67 (59-74)
Male sex, n (%)	108 (69.2)	125 (73.5)
Body surface area, m^2, mean (SD)	2.04 (0.24)	2.01 (0.24)
NYHA class, median (IQR)	2 (2-3)	2 (2-3)
Extracardiac arteriopathy, n (%)	11 (7.1)	15 (8.8)
Poor mobility, n (%)	3 (1.9)	4 (2.4)
Previous cardiac surgery, n (%)	7 (4.5)	11 (6.5)
Chronic lung disease, n (%)	12 (7.7)	13 (7.6)
Previous cerebrovascular accident, n (%)	10 (6.4)	9 (5.3)
Active endocarditis, n (%)	0 (0)	2 (1.2)
Diabetes (insulin-dependent), n (%)	13 (8.3)	10 (5.9)
Angina class 4, n (%)	1 (0.6)	2 (1.2)
Recent myocardial infarction, n (%)	18 (11.5)	10 (5.9)
Pulmonary hypertension, n (%)	12 (7.7)	18 (10.6)
EuroSCORE II, mean (SD)	2.6 (3.8)	2.5 (2.9)
Hematocrit, %, median (IQR)	39 (36-42)	39 (36-43)
Left ventricular ejection fraction, %, median (IQR)	55 (50-60)	55 (50-60)
Serum creatinine, mg/dL,* mean (SD)	1.03 (0.26)	0.97 (0.23)
Creatinine clearance, mL/min, median (IQR)	80 (63-103)	82 (65-101)
Acute renal failure score, median (IQR)	0 (1-2)	0 (0-1)
CPB duration, min, median (IQR)	116 (95-144)	109 (86-144)
Aortic cross clamp-time duration, min, median (IQR)	84 (65-108)	82 (65-113)
Lowest temperature on CPB, °C, median (IQR)	33 (32-34)	33 (32-34)
Nadir oxygen delivery, $mL \cdot min^{-1} \cdot m^{-2}$, median (IQR)†	315 (290-350)	301 (270-345)
Delta creatinine, mg/dL, median (IQR)	−0.04 (−0.08 to 0.19)	0.07 (−0.08 to 0.30)
Priming volume, mL, median (IQR)	930 (800-1262)	930 (653-1260)
Priming nature, n (%)		
Crystalloids	86 (55.1)	92 (54.1)
Artificial colloids	38 (24.4)	46 (27.1)
Crystalloids and colloids	18 (11.5)	16 (9.4)
20% albumin	14 (9.0)	16 (9.4)
Type of surgery, n (%)		
Isolated coronary surgery	44 (28.2)	42 (24.7)
Other isolated procedure	40 (25.6)	65 (38.2)
Double procedure	63 (40.4)	54 (31.8)
Triple procedure	9 (5.8)	9 (5.3)
Ascending aorta	20 (13.0)	25 (14.7)

GDP, Goal-directed perfusion; *IQR*, interquartile range; *SD*, standard deviation; *NYHA*, New York Heart Association; *CPB*, cardiopulmonary bypass. Only significant differences: *$P = .036$ †$P = .013$.

CPB duration of 90 minutes, and 3 patients (1.9%) in the GDP arm and 11 (6.5%) in the control arm had a CPB duration of <1 hour.

A nadir DO_2 <280 $mL \cdot min^{-1} \cdot m^{-2}$ occurred in 23 of 156 patients (14.5%) in the GDP arm and in 52 of 170 (30%) in the control arm (RR, 2.6; 95% CI, 1.5-4.6; $P < .001$). The DO_2 values at various time points during CPB are shown in Figure 2.

A mixed model for DO_2 differences as a function of time, study arm, and center effect was applied to investigate the efficacy of GDP implementation in achieving a higher DO_2 level. Data analysis was restricted to the first

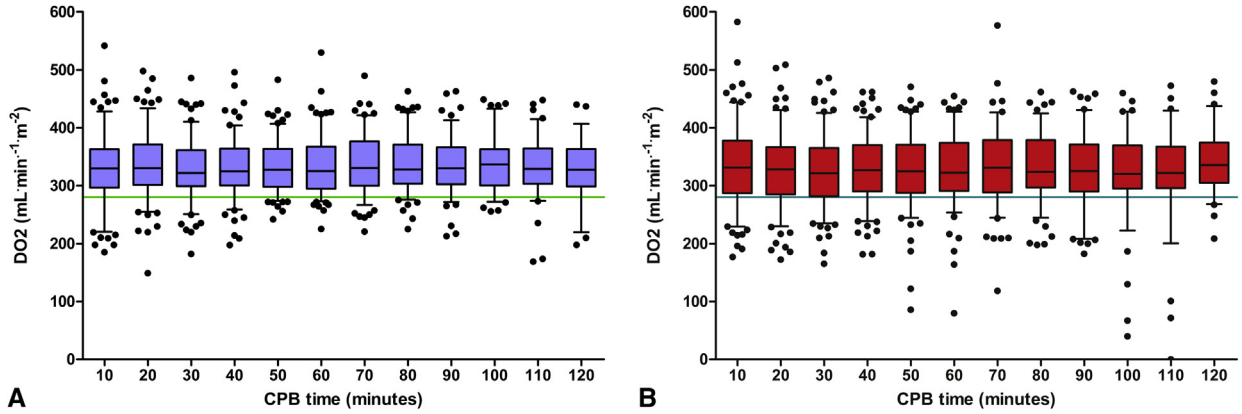


FIGURE 2. Oxygen delivery (DO_2) values in the goal-directed perfusion (*blue*; A) and control (*red*; B) arms during cardiopulmonary bypass (*CPB*). *Boxes* represent interquartile range, lines in the *boxes* represent the median, whiskers are 95% confidence intervals, and *dots* are outliers. The *green line* represents the critical DO_2 value of 280 mL·min^{-1}·m^{-2}. Data are restricted to the first 120 minutes of CPB.

120 minutes of CPB because of the small sample size after that period (at 40 time points in the GDP arm and 55 in the control arm). The first model considered the absolute DO_2 value. Considering the mixed-effects linear regression model for DO_2 level as a function of time and treatment, according to the AIC, a restricted cubic spline with 4 knots was used. The model with random slopes for the time effect was always preferred over the model with only random intercepts (independent of the spline representation). The interaction between time and treatment was not significant ($P = .106$). The estimated marginal levels for patients in GDP group and control are reported in Figure 3. The difference in average DO_2 levels between the 2 groups was not significant (difference, 6.82; $P = .186$).

Considering the mixed-effects logit regression model for the probability that DO_2 level is <280 mL·min^{-1}·m^{-2} as a function of time and treatment, according to the AIC, a restricted cubic spline with 3 knots was used. The interaction between time and treatment was significant ($P = .012$, 2 degrees of freedom). The estimated marginal probabilities for patients in the GDP and control arms are reported in Figure 4. The 95% CIs overlap but do not contain the point estimates. The difference in probability of a DO_2 <280 mL·min^{-1}·m^{-2} between the 2 groups was significant (time 20: odds ratio [OR], 0.36; $P = .023$; time 50: OR, 0.15; $P = .001$; time 90: OR, 0.17; $P = .001$).

Primary and Secondary Outcomes, Overall Population

Primary and secondary outcomes are reported in Table 2. AKI stage 1 was found in 18 patients (11.5%) in the GDP arm and in 38 patients (22.4%) in the control arm (RR,

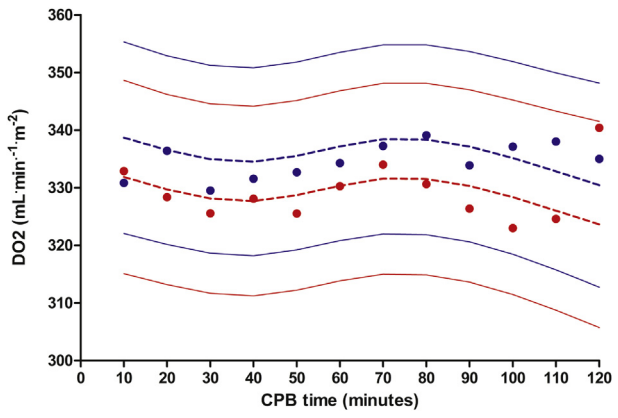


FIGURE 3. Mixed model for oxygen delivery (DO_2) differences as a function of time, study arm, and center effects. The *solid circles* represent estimated marginal means, the *dotted line* is the fitted average, and the *solid lines* are the 95% confidence interval (goal-directed perfusion, *blue*; control, *red*). The difference in average DO_2 levels between the 2 groups was not significant. Data analysis restricted to the first 120 minutes of cardiopulmonary bypass (*CPB*).

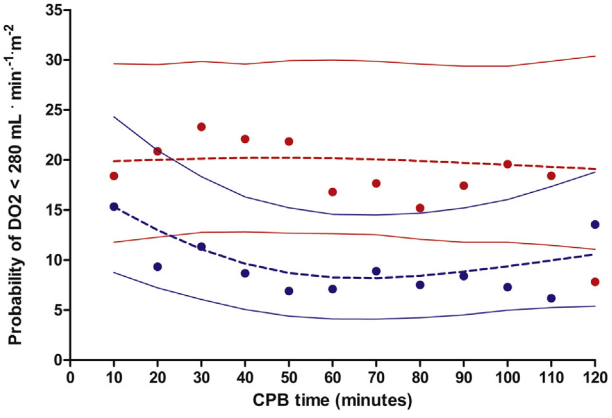


FIGURE 4. Mixed-effects logit regression model for the probability of an oxygen delivery (DO_2) level <280 mL·min^{-1}·m^{-2}. The *solid circles* are the observed proportions, the *dotted line* represents the fitted probabilities, and the *solid lines* delineate the 95% confidence interval (goal-directed perfusion, *blue*; control, *red*). The goal-directed perfusion group has a significantly lower rate of patients with DO_2 <280 mL·min^{-1}·m^{-2} at 20 ($P = .023$), 50 ($P = .001$), and 90 ($P = .001$) minutes. Data analysis was restricted to the first 120 minutes of cardiopulmonary bypass (*CPB*).

TABLE 2. Primary and secondary outcomes, overall population

Outcome	GDP arm (n = 156)	Control arm (n = 170)	RR or difference (95% CI)	*P* value
Primary outcome				
AKI stage 1	18 (11.5)	38 (22.4)	0.45 (0.25-0.83)	.010
AKI stage 2-3	6 (3.8)	4 (2.4)	1.66 (0.46-6.0)	.528
AKI of any kind	24 (15.4)	42 (24.7)	0.55 (0.32-0.97)	.036
Any creatinine increase	84 (53.8)	104 (61.2)	0.74 (0.48-1.15)	.181
Secondary outcomes				
Mortality	6 (3.8)	4 (2.3)	1.65 (0.46-5.95)	.529
Major morbidity	21 (13.3)	25 (14.6)	0.89 (0.48-1.67)	.728
Prolonged MV	13 (8.2)	20 (11.8)	0.67 (0.2-1.40)	.279
Stroke	2 (1.3)	2 (1.2)	1.07 (0.15-7.7)	.942
Renal failure	2 (1.3)	4 (2.3)	0.53 (0.09-3.0)	.686
Reoperation	5 (3.2)	3 (1.8)	1.81 (0.42-7.7)	.490
DSWI	0 (0)	1 (0.6)	Not applicable	.333
ICU LOS, d, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.13 (−0.94 to 0.55)	.663
Transfusion rate				
Overall	55 (35)	55 (32)	1.15 (0.72-1.81)	.557
On CPB	11 (7)	6 (3.5)	2.1 (0.75-5.7)	.213
After CPB (operating room)	10 (6.4)	18 (10.5)	0.58 (0.26-1.29)	.235
In the ICU or ward	43 (27.4)	43 (25.1)	1.12 (0.69-1.84)	.645
Number of units, median (IQR)	0 (0-1)	0 (0-1)	0.16 (−0.61 to 3.0)	.617

GDP, Goal-directed perfusion; *RR*, relative risk; *CI*, confidence interval; *AKI*, acute kidney injury; *MV*, mechanical ventilation; *DSWI*, deep sternal wound infection; *ICU*, intensive care unit; *LOS*, length of stay; *CPB*, cardiopulmonary bypass.

0.45; 95% CI, 0.25-0.83; $P = .01$). AKI stage 2-3 was found in 6 patients (3.8%) in the GDP arm and in 4 patients (2.4%) in the control arm (RR, 1.66; 95% CI, 0.46-6.0; $P = .528$). AKI stage 1 or stage 2-3 was found in 24 patients (15.4%) in the GDP arm and in 42 patients (24.7%) in the control arm (RR, 0.55; 95% CI, 0.32-0.97; $P = .036$). A serum creatinine increase of any level was observed in 84 patients (53.8%) in the GDP arm and in 104 patients (61.2%) in the control arm (RR, 0.74; 95% CI, 0.48-1.15; $P = .181$).

Because the GDP strategy was based on a DO_2-targeted strategy and a specific trigger for RBC transfusions, the effects of nadir DO_2 and RBC transfusion were investigated in a sensitivity analysis. Patients with a nadir DO_2 $\geq$280 mL·min^{-1}·m^{-2} had a median serum creatinine increase of 0.04 mg/dL (IQR, −0.08 to 0.2 mg/dL), which was significantly lower ($P = .039$) than that in patients with a nadir DO_2 <280 mL·min^{-1}·m^{-2} (0.11 mg/dL; IQR, −0.01 to 0.27). They had a significantly lower ($P = .017$) rate of any kind of serum creatinine increase (55% vs 71%; OR, 1.99; 95% CI, 1.13-3.51), but the AKI stage 1 rate was not significantly different from that of patients with a nadir DO_2 <280 mL·min^{-1}·m^{-2} (15% vs 21%; $P = .240$). When tested in a multivariable linear regression model, the absolute increase in serum creatinine levels was not significantly associated with the study arm or the nadir DO_2. In a principal component analysis (multivariable logistic regression) for any kind of serum creatinine increase, independent predictors of serum creatinine increase were body surface area, diabetes, recent myocardial infarction, left ventricle ejection fraction, baseline creatinine value, and a nadir DO_2 <280 mL·min^{1}·m^{-2} (OR, 2.420; 95% CI, 1.326-4.417; $P = .004$) (Table E3).

A multivariable model inclusive of the amount of RBCs transfused during CPB in the operating room (after CPB) and in the ICU and the study arm and adjusted for the center effect and for the preoperative ARF score was applied, with AKI stage 1 as the outcome variable (Table E4). Transfusions of RBC in the ICU was independently associated with AKI stage 1 (OR, 1.31; 95% CI, 1.10-1.56 per RBC unit). In this model, GDP remained independently associated with a reduction in the AKI stage 1 (OR, 0.48; 95% CI, 0.25-0.93). No center-based effect was identified.

The median nadir SvO_2 on CPB was 76% (IQR, 71%-81%) in the control arm and 77% (IQR, 72%-81%) in the GDP arm ($P = .391$). The nadir SvO_2 was 76% (IQR, 72%-81%) in patients without AKI stage 1 and 77% (IQR, 71%-81%) in patients with AKI stage 1 ($P = .940$).

There were no significant differences in secondary outcomes between the 2 arms, and the mortality rate reflected the preoperative risk stratification in both arms.

Primary and Secondary Outcomes, Excluding Short and Long CPB Time

According to the prespecified subgroup analysis, patients with short (<60 minutes) and long duration of CPB were excluded. The 90th percentile of CPB time distribution corresponded to 178 minutes, and the exclusion criterion related

TABLE 3. Primary and secondary outcomes, CPB time 1 to 3 hours

Outcome	GDP arm (n = 142)	Control arm (n = 144)	RR or difference (95% CI)	*P* value
Primary outcome, n (%)				
AKI stage 1	16 (11.3)	35 (24.3)	0.39 (0.21-0.75)	.004
AKI stage 2-3	6 (4.2)	4 (2.8)	1.54 (0.43-5.6)	.539
AKI of any kind	22 (15.5)	39 (27.1)	0.49 (0.27-0.89)	.017
Any creatinine increase	74 (52.1)	95 (66.0)	0.56 (0.35-0.90)	.017
Secondary outcomes				
Mortality, n (%)	4 (2.8)	1 (0.7)	4.1 (0.45-37)	.371
Major morbidity, n (%)	16 (11.1)	17 (11.9)	0.93 (0.45-1.91)	.873
Prolonged MV, n (%)	9 (6.3)	14 (9.8)	0.61 (0.26-1.47)	.269
Stroke, n (%)	1 (0.7)	2 (1.4)	0.49 (0.04-5.5)	.622
Renal failure, n (%)	1 (0.7)	3 (2.1)	0.33 (0.03-3.2)	.371
Reoperation, n (%)	4 (2.8)	3 (2.1)	1.33 (0.29-6.1)	.707
DSWI, n (%)	0 (0)	1 (0.6)	Not applicable	.498
ICU LOS, d, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.13 (−0.47 to 0.74)	.782
Transfusion rate, n (%)				
Overall	47 (32.9)	47 (29.2)	1.19 (0.72-1.96)	.770
On CPB	7 (4.9)	5 (3.5)	2.1 (0.75-5.7)	.213
After CPB (OR)	7 (4.9)	14 (9.8)	0.47 (0.18-1.21)	.173
In the ICU or ward	37 (25.9)	32 (22.4)	1.21 (0.70-2.1)	.770
Number of units, median (IQR)	0 (0-1)	0 (0-1)	0.14 (−0.44 to 0.41)	.948

GDP, Goal-directed perfusion; *RR*, relative risk; *CI*, confidence interval; *AKI*, acute kidney injury; *MV*, mechanical ventilation; *DSWI*, deep sternal wound infection; *ICU*, intensive care unit; *LOS*, length of stay; *CPB*, cardiopulmonary bypass; *OR*, operating room.

to excessively long CPB duration was settled at 3 hours, with 142 patients in the GDP arm and 144 in the control arm.

Outcomes in patients with a CPB time between 1 and 3 hours are reported in Table 3. The differences found in the overall population were more pronounced, with an RR for AKI stage 1 of 0.39 (95% CI, 0.21-0.75; $P = .004$) and an RR for AKI of any kind of 0.49 (95% CI, 0.27-0.89; $P = .017$). In addition, a serum creatinine increase of any level became significant, with an RR of 0.56 (95% CI, 0.35-0.90; $P = .017$).

DISCUSSION

This study found that use of a GDP strategy aimed at avoiding a DO_2 <280 $mL \cdot min^{-1} \cdot m^{-2}$ on CPB is effective in reducing the risk of AKIN stage 1 AKI after cardiac surgery. The primary endpoint (avoidance of any AKI as per protocol) was reached at a *P* value of .036. These results were more pronounced when patients with a short or very long CPB time were excluded from the analysis. A statistical reduction in the combined endpoint was demonstrated; however, given the low rate of AKI stage 2-3, no meaningful interpretation of that result can be discussed. The main effect refers to AKI stage 1, which is the focus of this discussion.

Our results largely confirm previous retrospective studies,[9-11] but also provide the first prospective evidence that changing perfusion practice reduces the rate of postoperative AKI. Current perfusion guidelines[12] advocate limiting hemodilution and consideration of DO_2 as a parameter to guide arterial pump flow; no previous RCT has compared patients based on the nadir DO_2 or nadir HCT on CPB. A recent study from Magruder and associates[15] using propensity-score matching compared patients treated with a GDP strategy (aimed at maintaining a DO_2 >300 $mL \cdot min^{-1} \cdot m^{-2}$) with a standard perfusion technique. The authors found that patients treated with a GDP strategy had an AKI stage 1 rate of 5.7%, compared with 19.3% in those not treated with GDP (RR, 0.3). Our results show a lower degree of benefit for the GDP group (RR, 0.45); however, the effect size of the Magruder study is considerably higher, with a mean difference in nadir DO_2 reaching 60 $mL \cdot min^{-1} \cdot m^{-2}$.

Cardiac surgery–associated AKI is a serious morbidity, and even minor increases in serum creatinine may lead to permanent damage in renal function. Data from the SWEDEHEART Registry[16] support the serious impact of small serum creatinine increases by demonstrating both a 3-fold increase in end-stage kidney disease and increased mortality. Therefore, our finding of a significantly reduced release of serum creatinine (AKIN class 1 AKI) should be considered a strong signal of the efficacy of a GDP strategy leading to a preservation of renal function after cardiac surgery.

Kidney function is highly dependent on oxygen delivery, especially under the conditions of nonpulsatile flow generated by CPB. Owing to its unique blood supply, the kidney medulla enters a hypoxic state under conditions of progressive acute anemia much earlier than the intestine or the heart.[17] In a recent elegant study, Lannemyr and associates[18] demonstrated that during CPB, renal DO_2 is

decreased by 20% due to hemodilution and vasoconstriction, the glomerular filtration rate and renal oxygen consumption remain unchanged, and there is an increase in renal oxygen extraction of up to 45%, indicating a renal oxygen supply/demand mismatch. Therefore, the concept of GDP is sustained by sound physiological and pathophysiological concepts.

Of note, RBC transfusions in the ICU were independently associated with AKI stage 1. Patients in the GDP arm were less likely to receive RBC transfusions after CPB and more likely to be transfused during CPB (although the difference was not statistically significant). This raises the hypothesis that anticipating inevitable RBC transfusions during CPB may better preserve the DO_2 during a critical period, reducing the need for post-CPB transfusion and decreasing the associated AKIN stage 1 risk.

This study has some limitations. Cardiac surgery–associated AKI is certainly a multifactorial event, and we could not include all of the possible determinants in our analyses. Other factors that could be linked to the incidence of AKI (eg, perfusion pressure, preoperative use of angiotensin-converting enzyme inhibitors, postoperative use of inotropes or vasoconstrictors) were not collected and could not be analyzed. The study was terminated early because the efficacy endpoint was reached at 50% of the enrollment rate. The efficacy stopping rule change was recommended in August 2016 by the statisticians at the sponsoring institution following the first interim analysis. At that time no safety concerns were raised however the efficacy endpoint was changed in response to the slow recruitment rate. No change in the original α value (0.05) was considered at that time. The original planned sample size of 700 patients was an overestimate, owing to a larger-than-expected effect size and the lack of preliminary data on the rate of patients fulfilling the goal in the GDP and control arms. Trial recruitment was directed at a low-risk patient population, and our rate of AKIN 2-3 highlights that the study was not powered adequately for this outcome. A study focusing on high-risk patients, to gain sufficient power to address major AKI-associated morbidity and mortality, is under consideration.

A second limitation may have been that the majority of the institutions involved in the GIFT were already familiar with the use of GDP monitors and with the concept of GDP. The standard practice in many of the institutions is to limit severe hemodilution, so patients in the control group frequently spontaneously reached the goal of DO_2 $\geq$280 $mL \cdot min^{-1} \cdot m^{-2}$. This resulted in a limited, albeit significant, DO_2 difference between groups; however, the evidence of a significantly lower rate of patients with DO_2 below 280 $mL \cdot min^{-1} \cdot m^{-2}$ in the GDP group demonstrates an acceptable effect size. The problem faced in the present study may be ascribed to a "dilutional" effect. This suggests that future trials should probably include a more carefully prescribed "baseline" protocol, with patients randomized to receive augmented treatment (GDP) over baseline when the target (DO_2) is not reached.

It would be interesting to assess the efficacy of GDP in centers that accept lower HCT levels on CPB. The DO_2 on CPB reflects oxygen supply to all the organs; it would be an interesting subject for future studies to focus on kidney-related markers of DO_2 adequacy, including urinary biomarkers or regional oxygen saturation.[19] In this study design, double-blinding was not possible, and this may be considered an additional limitation. Finally, CPB protocols vary among centers. Tables E1 and E2 list the equipment and protocols for CPB to help increase the generalizability of our results.

CONCLUSIONS

A GDP strategy during CPB is effective in reducing the risk of minor patterns of AKI (any serum creatinine increase and AKIN stage 1) following cardiac surgery in adult patients. However, given the efficacy of GDP in preventing only minor degrees of AKI in low-risk patients, our results do not definitely suggest a change in clinical practice. Further studies are needed to define perfusion interventions that may reduce more severe levels of renal injury (AKIN stage 2 or 3).

Conflict of Interest Statement

Dr Ranucci has developed and patented an algorithm for monitoring DO_2 and VCO_2 during CPB, which is presently manufactured by LivaNova. Baker and Newland were provided with Vamos Capnographs by LivaNova. Parke received a research grant from Green Lane Research and Education Board for this study. All other authors have nothing to disclose with regard to commercial support.

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Key Words: cardiac surgery, cardiopulmonary bypass, oxygen delivery, acute kidney injury

TABLE E1. Factors affecting calculation of goal-directed perfusion parameters

Site	Oxygenator	Tubing coating	Flow type	Blood flow for GDP calculation	HCT/Hb measurement for GDP calculation	GDP calculation*	Exhaust CO_2 measurement	Patients enrolled, n
1	RX25	Phisio	Nonpulsatile	US flow distal to all shunts	M4	CONNECT,† M4‡	M4/Vamos	33
2	Inspire6 Inspire8	Smart	Nonpulsatile	US flow distal to all shunts	M4	M4‡	M4	54
3	Inspire8	Phisio	Nonpulsatile	Roller pump	CDI 500	CONNECT†	Vamos	70
4	Inspire6 Inspire8	Phisio	Nonpulsatile	US flow distal to all shunts	BCare 5	CONNECT†	Primus	69
5	Inspire6	Phisio	Nonpulsatile	Roller pump	SATCRIT	Manually	GE	13
6	Inspire 8 Quadrox	Phisio Softline	Nonpulsatile	Roller pump	CDI 500	CONNECT†	IntelliVue G5-M1019A	26
7	Inspire 6	Phisio	Nonpulsatile	US distal to all shunts	BCare 5	CONNECT†	Ohmeda	22
8	Inspire 8	Phisio	Nonpulsatile	US flow distal to all shunts	CDI 500	CONNECT†	N/A	33
9	Inspire6	Phisio	Nonpulsatile	Roller pump	Data Master	CONNECT†	Primus	6

RX25, CDI-500, Terumo Corporation, Tokyo, Japan; Inspire6, Inspire8, Phisio, BCare 5, CONNECT, Data Master, LivaNova, London, United Kingdom; Softline, Maquet, Rastatt, Germany; M4, Spectrum Medical, Gloucester, United Kingdom; Vamos, Primus, Dräger Medical, Lübeck, Germany; SAT/CRIT, Livanova, London, United Kingdom; Ohmeda, General Electric Healthcare, Chicago, Ill; IntelliVue G5-M1019A, Koninklijke Philips, Amsterdam, The Netherlands. *GDP*, Goal-directed perfusion; *HCT*, hematocrit; *Hb*, hemoglobin; CO_2, carbon dioxide; *US*, ultrasound. *GDP calculated as oxygen content (mL/dL) × pump flow (dL/min/m^2), and oxygen content as hemoglobin (g/dL) × arterial saturation 1.34 + 0.03 × PaO_2 (mmHg). †GDP for CONNECT software: DO_2 = Flow × (Hct/2:94 × 1:36 × SaO_2 + PaO_2 × 0.03) × 10. ‡GDP for M4: $ecDO_2$ = 10 × Qblood × Hb × 1.34(SaO_2/100).

TABLE E2. Perfusion practices

Site	Static prime volume, mL	Prime nature	RAP, %	Hemofiltration, %	Vacuum-assisted venous return, %	Blood gas management	Cell saver, %	Transfusion trigger (control arm) on CPB	Target temperature on CPB	Target temperature for CPB weaning
1	1300-1500	20% albumin + crystalloid	42	0	0	Alpha-stat	64	Hb 7 g/dL	34°C NP	36°C NP
2	1100-1250	Crystalloid	0	7	0	Alpha-stat	21	Hb 7.3 g/dL	32°C-33°C NP	36°C-37°C NP
3	1300	Crystalloid	100	3	31	Alpha-stat	0	Hb 7.0 g/dL	32°C-34°C NP	36.5°C NP
4	600	Colloid (gelatins)	0	0	100	Alpha-stat	45	Hb 7 g/dL	32°C NP	36°C rectal
5	800-1200	Colloid (gelatins)	0	0	0	Alpha-stat	100	Hb 7 g/dL	32°C NP	36°C rectal
6	900-1300	Crystalloid	0	0	100	Alpha-stat	0	Hb 7.5 g/dL	37°C NP with active warming	36°C bladder
7	935	Crystalloid	20	100	100	Alpha-stat	100	Hb 7 g/dL	32°C bladder	36°C bladder
8	1200	Crystalloid + starches	0	0	0	Alpha-stat	100	Hb 7.3 g/dL	34°C rectal	36°C rectal
9	605	Crystalloid	100	0	100	Alpha-stat	100	Hb 8 g/dL	34°C NP	36.5°C NP

RAP, Retrograde autologous prime; *CPB*, cardiopulmonary bypass; *Hb*, hemoglobin; *NP*, nasopharyngeal.

TABLE E3. Component analysis for factors associated with any serum creatinine increase

Factor	Regression coefficient	*P* value	Odds ratio (95% CI)
Body surface area, m^2	1.479	.004	4.390 (1.598-12.062)
Diabetes	1.640	.007	5.154 (1.578-16.083)
Recent myocardial infarction	−0.956	.035	0.384 (0.158-0.935)
LVEF (%)	−0.028	.013	0.972 (0.951-0.994)
Baseline creatinine (mg/dL)	−1.183	.023	0.306 (0.111-0.847)
DO_2 nadir <280 $mL \cdot min^{-1} \cdot m^{-2}$	0.884	.004	2.420 (1.326-4.417)
Constant	−0.182		

CI, Confidence interval; *LVEF*, left ventricular ejection fraction; *DO_2*, oxygen delivery.

TABLE E4. Effects of red blood cell transfusions and study arm in determining acute kidney injury stage 1

Factor	Regression coefficient	*P* value	Odds ratio (95% CI)
RBC units_OR	0.169	.685	1.184 (0.523-2.677)
RBC units_CPB	−0.490	.447	0.612 (0.173-2.167)
RBC units_ICU	0.273	.002	1.314 (1.103-1.565)
GDP arm	−0.741	.029	0.477 (0.245-0.928)
Center	N/A	.726	N/A
ARF score	−0.036	.828	0.965 (0.700-1.331)
Constant	−1.697		

CI, Confidence interval; *RBC*, red blood cell; *OR*, operating room; *CPB*, cardiopulmonary bypass; *ICU*, intensive care unit; *GDP*, goal-directed perfusion; *N/A*, not applicable; *ARF*, acute renal failure.