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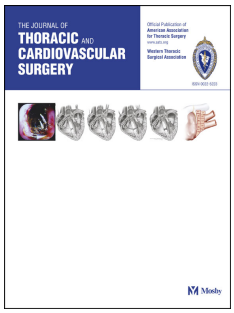

Goal directed perfusion to reduce acute kidney injury: A randomized trial

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GOAL DIRECTED PERFUSION TO REDUCE ACUTE KIDNEY INJURY: A RANDOMIZED TRIAL.

Short title: Goal-directed perfusion and acute kidney injury

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Glossary of abbreviations

AKI: acute kidney injury

AKIN: Acute Kidney Injury Network

ARF: acute renal failure

CPB: cardiopulmonary bypass

DO_2: oxygen delivery

DSWI: deep sternal wound infection

GDP: goal-directed perfusion

GIFT: Goal Directed Perfusion Trial

IRCCS: Istituto Di Ricovero e Cura a Carattere Scientifico

ICU: intensive care unit

NHYA: New York Heart Association

OR: operating room

O_2ER: oxygen extraction rate

PSD: Policlinico San Donato

RBC: red blood cells

RAP: retrograde autologous prime

SvO_2: venous oxygen saturation

Central message

A goal-directed perfusion aiming to preserve oxygen delivery during cardiopulmonary bypass is effective in reducing AKIN class 1 postoperative acute kidney injury.

Perspective statement

Acute kidney injury is a major complication of cardiac surgery. The present study demonstrates that minor patterns of AKI in medium-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)

Abstract

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

Methods. Multicenter randomized trial enrolling 350 patients undergoing cardiac surgery in nine institutions. Patients were randomized to receive either GDP or conventional perfusion. Three hundred and twenty-six patients completed the study and were analyzed. Patients in the treatment arm received a GDP strategy during cardiopulmonary bypass aimed to maintain an oxygen delivery ≥ 280 $mL \cdot min^{-1} \cdot m^{-2}$. The perfusion strategy for patients in the control arm was factored on body surface area and temperature. The primary endpoint was acute kidney injury rate. Secondary endpoints were intensive care unit length of stay; major morbidity; red blood cell transfusions; operative mortality.

Results. Acute Kidney Injury Network (AKIN) stage 1 was reduced in patients treated with GDP (relative risk 0.45, 95% CI 0.25-0.83, P = 0.01). AKIN stage 2-3 did not differ between groups (relative risk 1.66, 95% CI 0.46-6.0, P = 0.528). There were no significant differences in secondary outcomes. In a pre-specified analysis of patients with a cardiopulmonary bypass time between 1 and 3 hours, the differences in favor of the treatment arm were more pronounced, with a relative risk for acute kidney injury of 0.49 (95% CI 0.27-0.89, P = 0.017).

Conclusions. A GDP strategy is effective in reducing AKIN stage 1 acute kidney injury, further studies are needed to define perfusion interventions that may reduce more severe levels of renal injury (AKIN stage 2 or 3).

Introduction

Acute kidney injury (AKI) is a serious complication of cardiac surgery, affecting a considerable proportion of patients and increasing postoperative morbidity and mortality.[1] Different factors, including age, preoperative renal function, hemodynamic state, 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 small increases in serum creatinine, classified as AKIN class 1, to increase the risk of end stage renal disease 3-fold (2.92 (95% CI 1.87-4.55) and mortality nearly 1.5 times (1.34 (1.23-1.45).[3]

In 1994 an association between the nadir hematocrit during cardiopulmonary bypass (CPB) and postoperative AKI was first reported.[4] Numerous retrospective studies subsequently confirmed this finding, and some authors hypothesized that the mechanism underlying the link between severe hemodilution on CPB and poor renal outcomes could be insufficient oxygen delivery (DO_2).[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 260-272 $mL \cdot min^{-1} \cdot m^{-2}$ for patients undergoing moderately (> 32 °C) hypothermic CPB.

Based on these observations, the concept of goal-directed perfusion (GDP), aimed to maintain 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 - 2.4 $L \, min^{-1} m^{-2}$.

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

GDP, to avoid nadir DO2 less than 280 ml min-1m-2, will reduce the rate of postoperative acute kidney injury in patients undergoing moderately hypothermic CPB.

Methods

Study design and study population

This multicenter, randomized controlled trial 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 co-ordinating institution (Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Donato (PSD), 17/07/2014 protocol number 24/int/2014) and of the other participating institutions, and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice guidelines.

Recruitment of patients occurred between October 2014 and January 2017. On August 2016 the protocol was amended with minor changes. All the patients provided written informed consent to participate before entering the study.

Patients were eligible if they were older than 18 years of age and were scheduled for cardiac operations with an expected CPB duration of 90 minutes or longer. Patients were screened at the time of hospital admission or at the first cardiac surgery visit. Specific exclusion criteria were: severe chronic renal failure (dialysis or serum creatinine > 3.0 mg/dL); emergent surgery; moderate-severe anemia (preoperative hematocrit < 32%); expected nadir CPB temperature < 32 °C. The values of hematocrit and serum creatinine considered for inclusion in the study were the last ones 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 unexpected need for deep hypothermic CPB.

Study data were prospectively collected starting on the day prior to surgery or the day of surgery until hospital discharge (or 30 days after surgery for the operative mortality).

Intervention

Patients were randomized 1:1 into the control arm or 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 (i) adjustment of the arterial pump flow according to the hematocrit value to reach and maintain a DO_2 above the pre-specified threshold; (ii) in case of low values of hematocrit and inability to maintain the DO_2 above the threshold by increasing the pump flow, transfusion of one unit of red blood cells (RBC) if the venous oxygen saturation (SvO_2) was below 68% and/or the oxygen extraction rate (O_2ER) was > 40%.

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 RBC during CPB was triggered by the hematocrit value, according to local institutional standards (see eTable1).

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 while SvO_2 was either continuously or intermittently monitored. Details of the perfusion techniques and equipment are provided in eTable 1 and eTable 2 in the Supplement. For patients in the GDP arm the perfusionist had a direct view of the GDP monitor data, to meet 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 was collected at 20-30 second intervals, with the value of DO_2 during CPB reported for the study at 10 minute intervals. For the purposes of the present study, the nadir DO_2 was adjudicated as the lowest value maintained for at least two consecutive measures (10 minute interval), and defined as the mean of the two consecutive measures.

Study outcomes

The primary outcome of the trial was the postoperative AKI rate. AKI was defined according to the creatinine changes criteria of the AKIN classification[13]: AKI stage 1 is an increase in serum creatinine levels of 150% to 200% of the baseline or an absolute increase ≥ 0.3 mg/dL; AKI stage 2

is a serum creatinine level increase > 200% of the baseline value. The serum creatinine increase was limited to the first 48 hours after surgery. Patterns of AKI stage 3 were incorporated in the AKI stage 2 definition. Additionally, 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 kind of AKI, and any serum creatinine increase.

Secondary outcomes were: intensive care unit (ICU) stay; major morbidity (mechanical ventilation > 24 hours, stroke, deep sternal wound infection, acute renal failure [renal replacement therapy or serum creatinine> 4.0 mg/dL at any postoperative time], surgical re-operation, or mortality); rate of patients receiving RBC and number of units transfused; operative mortality (in-hospital or within 30 days from surgery after discharge). The presence of morbidity outcomes were considered for the safety analysis.

Randomization

The participants were randomized with a web-based randomization protocol using a non-stratified 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 (i.e. surgeon, perfusionist, and anesthesiologists) was aware of the treatment arm. Conversely, staff members involved in the postoperative care in the ICU and ward were unaware of the treatment arm. The patient's files did not contain the information related to the study arm, to avoid different treatments in the ICU.

Sample size calculation

Sample size calculation was based on the existing studies[10] retrospectively comparing AKI rates in patients with a nadir DO_2 on CPB ≥ 280 $mL \cdot min^{-1} \cdot m^{-2}$ or < 280 $mL \cdot min^{-1} \cdot m^{-2}$, by retrieving the original rough dataset. The AKI (stage 1 or 2) rate was 12% in the first group and 30% in the second. Based on these figures, and with a power of 80% and a level of significance of 0.05, two groups of 80 patients each were needed to confirm the difference in AKI rates within a randomized controlled trial (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 control arm and 12.8% in GDP arm, leading to a sample size of 327 patients per each arm. Considering a possible rate of patients lost for the final analysis, the sample size was finally settled at two 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 eProtocol). The protocol was amended in August 2016 following the completion of the first interim analysis (data closed in February 2016). The amendments included the inclusion of a sub group analysis based upon bypass time (see below) and changes to the stopping rule for efficacy being changed from $p<0.005$ at the 50% interim analysis to $p<0.05$.

Data are presented as mean and standard deviation (SD) for continuous, normally distributed variables, median and interquartile range (IQR) for continuous non-normally distributed variables, and as number and percentage for categorical variables. Normality of the distribution was tested with the Kolmogorov-Smirnov test. Missing data for the primary outcome (baseline and peak serum creatinine levels) were assumed missing completely and the 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 a relative risk analysis, producing a relative risk with 95% confidence interval (CI), and the significance level was assessed with a Pearson's chi-square or a Fisher exact test when appropriate. Comparisons of continuous non-normally distributed secondary outcome measurements (ICU stay and number of RBC units transfused) were based on non-parametric tests, while a Student's t-test was used for continuous normally distributed variables.

Two (generalized) mixed effects models were implemented: (i) a regression model for the DO_2 level through time and (ii) a regression model for the probability that DO_2 level falls below 280 $mL \cdot min^{-1} \cdot m^{-2}$ through 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 two different spline representations was performed using Aikake Information Criterion (AIC). The interaction between time and treatment was used to allow different patterns through times of the two investigated quantities according to treatment. The interaction was tested using likelihood ratio tests. Random intercept at patient and center levels were considered for both the generalized linear and linear mixed effects model. For the linear mixed effects model random slopes for time effect were also considered. Simulation-based 95% confidence intervals for predicted marginal probabilities of the generalized mixed models were considered.

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 transfusions, participating institution, and of differences in the baseline renal risk (defined according to the Acute Renal Failure (ARF) score.[14]

A pre-specified subgroup analysis excluding patients with a short or very long CPB duration 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, excessively long CPB times may lead to a difficulty in weaning from CPB (with reduced arterial pump flow during CPB weaning and reduced postoperative cardiac output) and therefore possible postoperative renal dysfunction may be related to these factors rather than the experimental effect. Therefore, patients with a CPB duration > 90^{th} percentile of the CPB time distribution were excluded by the subgroup analysis.

All the analyses were performed using computerized statistical packages (SPPS 13.0, IBM, Chicago, IL, MedCalc, Ostend, Belgium, and STATA 15.0, StataCorp LLC, Lakeway Drive College Station, Texas); a P value < 0.05 was considered significant.

Results

The study was prematurely halted after 26 months, as the efficacy endpoint at the 50% interim analysis had been met, according to the stopping rules.

During the study period 2,346 patients were screened for participation in GIFT (see figure 1). One thousand nine hundred and ninety-six patients were excluded primarily for failure to meet the inclusion criteria. A total of 350 patients were enrolled, but only 344 were randomized, due to unexpected unavailability of the GDP monitor. There were an additional 7 patients (5 in the GDP arm and 2 in the control arm) who received the allocated treatment but with lacking outcome data. Withdrawal criteria were met in seven patients in the GDP arm and none in the control arm. Finally, two patients in both arms died during surgery or immediately after the arrival in the ICU, therefore missing the peak postoperative serum creatinine measure. This left 326 patients (GDP arm: 156; control arm: 170) available for the primary outcome analysis, and 330 patients available for the secondary outcome (mortality) analysis.

Table 1 shows the baseline and intraoperative characteristics of each cohort. The two groups were comparable, with a significantly higher preoperative serum creatinine value in the GDP arm, but no differences in baseline creatinine clearance. The median CPB duration was 116 minutes in the GDP arm and 109 minutes in the control arm. Twenty-two (14.1%) patients in the GDP arm and 47 (27.6%) patients in the control arm did not reach the expected CPB duration of 90 minutes, while 3 (1.9%) patients in the GDP arm and 11 (6.5%) patients in the control arm had CPB duration shorter than 1 hour.

Nadir DO_2 < 280 $mL \cdot min^{-1} \cdot m^{-2}$ occurred in 23/156 (14.5%) patients in the GDP arm, and 52/170 (30%) of patients in the control group (relative risk 2.6, 95% CI 1.5-4.6, p<0.001). The DO_2 values at different points in time during CPB are reported 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 120 minutes of CPB because of the low sample size after that period (40 points in time in GDP arm and 55 in 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 AIC, a restricted cubic spline with 4 knots was used. The model with random slopes for the time effect was always preferred to the model with only random intercepts (independently of the spline representation). The interaction between time and treatment was not significant (P=0.106). 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 two groups was not significant (difference 6.82, P=0.186).

Considering the mixed effects logit regression model for the probability that DO_2 level is below 280 $mL \cdot min^{-1} \cdot m^{-2}$ as a function of time and treatment, according to AIC, a restricted cubic spline with 3 knots was used. The interaction between time and treatment was significant (p=0.012, degrees of freedom=2). The estimated marginal probabilities for patients in GDP and control groups are reported in figure 4. The 95% confidence intervals are overlapping but do not contain the point estimates. The difference in probability of DO2<280 $mL \cdot min^{-1} \cdot m^{-2}$ between the two groups was significant (time 20: odds ratio 0.36, P=0.023; time 50: odds ratio 0.15, P=0.001; time 90: odds ratio 0.17, P=0.001).

Primary and secondary outcomes – overall population

Primary and secondary outcomes are reported in table 2. AKI stage 1 was found in 18 (11.5%) patients in the GDP arm and 38 (22.4%) patients in the control arm, with a relative risk of 0.45 (95% CI 0.25-0.83, P=0.01). AKI stage 2-3 was found in 6 (3.8%) patients in the GDP arm and 4 (2.4%) patients in the control arm, with a relative risk of 1.66 (95% CI 0.46-6.0, P=0.528). AKI stage 1 or stage 2-3 was found in 24 (15.4%) patients in the GDP arm and 42 (24.7%) patients in the control arm, with a relative risk of 0.55 (95% CI 0.32-0.97, P=0.036). A serum creatinine increase

of any level was observed in 84 (53.8%) patients in the GDP arm and 104 (61.2%) patients in the control arm, with a relative risk of 0.74 (95% 0.48-1.15, P=0.181).

Given the fact that 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 transfusions were investigated in a sensitivity analysis. Patients with a nadir $DO_2 \geq 280$ $mL \cdot min^{-1} \cdot m^{-2}$ had a median serum creatinine increase of 0.04 mg/dL (IQR -0.08 to 0.2), significantly (P=0.039) lower than patients with a nadir $DO_2 < 280$ $mL \cdot min^{-1} \cdot m^{-2}$ (0.11 mg/dL, IQR -0.01 to 0.27). They had a significantly (P=0.017) lower rate of any kind of serum creatinine increase (55% vs 71%, odds ratio 1.99, 95% confidence interval 1.13-3.51), but the AKI stage 1 rate (15%) was not significantly different from that (21%) of patients with a nadir $DO_2 < 280$ $mL \cdot min^{-1} \cdot m^{-2}$ (P=0.240). When tested in a multivariable linear regression model, the absolute increase in serum creatinine levels was not significantly associated with the study arm nor the nadir DO_2. A principal component analysis (multivariable logistic regression) for any kind of serum creatinine increase was performed (eTable 3). Within this model, independent predictors of serum creatinine increase were the body surface area, diabetes, recent myocardial infarction, left ventricle ejection fraction, baseline creatinine value, and a nadir $DO_2 < 280$ $mL \cdot min^{1} \cdot m^{-2}$ (odds ratio 2.420, 95% confidence interval 1.326-4.417, P=0.004).

A multivariable model inclusive of the amount of RBC transfused during CPB, in the OR (after CPB) and in the ICU and the study arm and adjusted for the center-effect and for the preoperative ARF score was applied having AKI stage 1 as the outcome variable (eTable 4). Transfusions of RBC in the ICU was independently associated with AKI stage 1 (odds ratio 1.31, 95% confidence interval 1.10-1.56 per unit of RBC). In this model, GDP remained independently associated with a reduction in the AKI stage 1 (odds ratio 0.48, 95% confidence interval 0.25– 0.93). No center-based effect was identified.

The nadir SvO_2 on CPB was 76% (IQR 71%-81%) in the control arm and 77% (IQR 72%-81%) in the GDP arm (P=0.391). 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=0.940).

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

Primary and secondary outcomes – excluding short / long CPB time.

According to the pre-specified subgroup analysis, patients with short (< 60 minutes) and long CPB duration were excluded. The 90th centile of CPB time distribution corresponded to 178 minutes, and the exclusion criterion related 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 one and three hours are reported in table 3. The differences found in the overall population became more pronounced, with a relative risk for AKI stage 1 of 0.39 (95% CI 0.21-0.75, P=0.004) and a relative risk for AKI of any kind of 0.49 (95% CI 0.27-0.89, P=0.017).

Additionally, serum creatinine increase of any level became significant, with a relative risk of 0.56 (95% CI 0.35-0.90, P=0.017).

Discussion

This study found that use of a goal-directed perfusion strategy aiming to avoid a DO_2 on CPB < 280 $mL \cdot min^{-1} \cdot m^{-2}$ is effective in reducing AKIN stage 1 kidney injury after cardiac surgery. The primary endpoint (avoidance of AKI of any kind as per protocol) was reached at a P value of 0.036. These results were more pronounced when excluding patients with a short or very long CPB time. 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 for the first time they provide the 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 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 to maintain 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% vs. 19.3% respectively, with a relative risk of about 0.3. Our results show a lower degree of benefit for the GDP group (relative risk 0.45); however, the effect size of the Magruder's study is considerably higher, with a mean difference in nadir DO_2 that reaches 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] has supported the finding of 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 significant reduction in the release of serum creatinine (AKIN class 1 kidney injury) 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 non-pulsatile flow generated by CPB. Due 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 up to 45%, indicating a renal oxygen supply/demand mismatch. Therefore, the concept of GDP is sustained by sound physiological and pathophysiological concepts.

Of notice, 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 of time, reducing the need for post-CPB transfusion and the associated AKIN stage 1 risk.

There are limitations in our study. Cardiac surgery-associated AKI is certainly a multifactorial event, and we could not include all of the possible determinants in our analyses. Other factors which could be linked to the incidence of AKI (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 as the efficacy endpoint was reached in at 50% of the enrollment rate. The efficacy stopping rule change was recommended in August 2016 by the statisticians at the IRCCS PSD 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 alpha value (0.05) was considered at that time. The original planned sample size of 700 patients was overestimated due to an effect size larger than expected, and due to the lack of preliminary data on the rate of patients fulfilling the goal in the GDP and control arms. Trial recruitment was directed toward a low risk patient population and our rate of AKIN 2 and 3 highlights that the study was not powered adequately for this outcome. A study focusing on high-risk patients, to gain enough 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 study 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 frequently patients in the control group spontaneously reached the goal of a $DO_2 \geq 280$ mL·min^{-1}·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·min^{-1}·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 hematocrit 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 variation exists between centers in how they perform CPB and the protocols they utilize for various aspects of CPB. We have reported in etable 1 and 2 detail on equipment and protocols to help increase the generalizability of these results.

Conclusions

A GDP strategy during CPB is effective in reducing the risk of minor patterns of AKI (any kind of serum creatinine increase and AKIN stage 1) following cardiac surgery in adult patients. However, given the efficacy of GDP only in preventing 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)

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Figure legends

Central picture: Acute kidney injury (AKI) in goal-directed perfusion (GDP) and control groups.

Figure 1: Diagram showing the flow of participants through each stage of the trial.

Figure 2: Oxygen delivery (DO_2) values in the goal-directed perfusion (GDP, Panel A, blue color) and control (Panel B, red color) arms during CPB. Boxes represent interquartile range, line in the boxes is the median, whiskers are 95% confidence interval, dots are outliers. Green line represents the critical DO_2 value of 280 $mL \cdot min^{-1} \cdot m^{-2}$. Data restricted to the first 120 minutes of cardiopulmonary bypass.

Figure 3: Mixed model for oxygen delivery (DO_2) differences as a function of time, study arm, and center-effect. The solid circles are estimated marginal means, the dotted line the fitted average, and the solid lines the 95% confidence interval (GDP blue; Control red). The difference in average DO_2 levels between the two groups was not significant. Data analysis restricted to the first 120 minutes of cardiopulmonary bypass.

GDP: goal-directed perfusion.

Figure 4: Mixed effects logit regression model for the probability that the oxygen delivery (DO_2) level is below 280 $mL \cdot min^{-1} \cdot m^{-2}$. The solid circles are the observed proportions, the dotted line the fitted probabilities, and the solid lines are 95% confidence interval (GDP blue; Control red). GDP group has a significantly lower rate of patients below 280 $mL \cdot min^{-1} \cdot m^{-2}$ at 20 (P=0.023), 50 (P=0.001), and 90 (P=0.001) minutes. Data analysis restricted to the first 120 minutes of cardiopulmonary bypass.

GDP: goal-directed perfusion.

VIDEO LEGEND: monitoring of goal-directed perfusion with a dedicated tool.

Table 1. Demographics, preoperative profile and operative details of the patient population.

Variable	GDP arm (N=156)	Control arm (N=170)
Age (years)	68 (59-75)	67 (59-74)
Gender male	108 (69.2)	125 (73.5)
Body surface area (m^2)	2.04 (0.24)	2.01 (0.24)
NYHA class	2 (2-3)	2 (2-3)
Extracardiac arteropathy	11 (7.1)	15 (8.8)
Poor mobility	3 (1.9)	4 (2.4)
Previous cardiac surgery	7 (4.5)	11 (6.5)
Chronic lung disease	12 (7.7)	13 (7.6)
Previous cerebrovascular accident	10 (6.4)	9 (5.3)
Active endocarditis	0 (0)	2 (1.2)
Diabetes (insulin dependent)	13 (8.3)	10 (5.9)
Angina class 4	1 (0.6)	2 (1.2)
Recent myocardial infarction	18 (11.5)	10 (5.9)
Pulmonary hypertension	12 (7.7)	18 (10.6)
EuroSCORE II	2.6 (3.8)	2.5 (2.9)
Hematocrit (%)	39 (36-42)	39 (36-43)
Left ventricular ejection fraction (%)	55 (50-60)	55 (50-60)
Serum creatinine (mg/dL)*	1.03 (0.26)	0.97 (0.23)
Creatinine clearance (mL/min)	80 (63-103)	82 (65-101)
Acute renal failure score	0 (1-2)	0 (0-1)
CPB duration (min)	116 (95-144)	109 (86-144)
Aortic cross clamp time duration (min)	84 (65-108)	82 (65-113)
Lowest temperature on CPB (°C)	33 (32-34)	33 (32-34)
Nadir oxygen delivery ($mL \cdot min^{-1} \cdot m^{-2}$)°	315 (290-350)	301 (270-345)
Delta creatinine (mg/dL)	-0.04 (-0.08 – 0.19)	0.07 (-0.08 -0.30)
Priming volume (mL)	930 (800-1,262)	930 (653-1,260)
Priming nature		
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		
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)

Data are number (%) or median (interquartile range) or mean (standard deviation). CPB: cardiopulmonary bypass; GDP: goal directed perfusion; NYHA: New York Heart Association.
*Only significant differences *P=0.036 and °P=0.013

Table 2. Primary and secondary outcomes – overall population

Outcome	GDP arm (N=156)	Control arm (N=170)	RR or difference (95% CI)	P
Primary outcome				
AKI stage 1	18 (11.5)	38 (22.4)	0.45 (0.25-0.83)	0.010
AKI stage 2-3	6 (3.8)	4 (2.4)	1.66 (0.46-6.0)	0.528
AKI of any kind	24 (15.4)	42 (24.7)	0.55 (0.32-0.97)	0.036
Any creatinine increase	84 (53.8)	104 (61.2)	0.74 (0.48-1.15)	0.181
Secondary outcomes				
Mortality	6 (3.8)	4 (2.3)	1.65 (0.46-5.95)	0.529
Major morbidity	21 (13.3)	25 (14.6)	0.89 (0.48-1.67)	0.728
Prolonged MV	13 (8.2)	20 (11.8)	0.67 (0.2-1.40)	0.279
Stroke	2 (1.3)	2 (1.2)	1.07 (0.15-7.7)	0.942
Renal failure	2 (1.3)	4 (2.3)	0.53 (0.09-3.0)	0.686
Re-operation	5 (3.2)	3 (1.8)	1.81 (0.42-7.7)	0.490
DSWI	0 (0)	1 (0.6)	Not applicable	0.333
ICU stay (days)	2.0 (1.0-3.0)	2.0 (1.0-3.0) 0.13	(-0.94-0.55)	0.663
Transfusion rate				
Overall	55 (35)	55 (32)	1.15 (0.72-1.81)	0.557
On CPB	11 (7)	6 (3.5)	2.1 (0.75-5.7)	0.213
After CPB (OR)	10 (6.4)	18 (10.5)	0.58 (0.26-1.29)	0.235
In the ICU or ward	43 (27.4)	43 (25.1)	1.12 (0.69-1.84)	0.645
Number of units	0 (0-1)	0 (0-1)	0.16 (-0.61-3.0)	0.617

Data are number (%) or median (interquartile range). CI: confidence interval; CPB: cardiopulmonary bypass; GDP: goal-directed perfusion; DSWI: deep sternal wound infection; ICU: intensive care unit; MV: mechanical ventilation; OR: operating room.

Table 3. Primary and secondary outcomes – CPB time between one and three hours.

Outcome	GDP arm (N=142)	Control arm (N=144)	RR or difference (95% CI)	P
Primary outcome				
AKI stage 1	16 (11.3)	35 (24.3)	0.39 (0.21-0.75)	0.004
AKI stage 2-3	6 (4.2)	4 (2.8)	1.54 (0.43-5.6)	0.539
AKI of any kind	22 (15.5)	39 (27.1)	0.49 (0.27-0.89)	0.017
Any creatinine increase	74 (52.1)	95 (66.0)	0.56 (0.35-0.90)	0.017
Secondary outcomes				
Mortality	4 (2.8)	1 (0.7)	4.1 (0.45-37)	0.371
Major morbidity	16 (11.1)	17 (11.9)	0.93 (0.45-1.91)	0.873
Prolonged MV	9 (6.3)	14 (9.8)	0.61 (0.26-1.47)	0.269
Stroke	1 (0.7)	2 (1.4)	0.49 (0.04-5.5)	0.622
Renal failure	1 (0.7)	3 (2.1)	0.33 (0.03-3.2)	0.371
Re-operation	4 (2.8)	3 (2.1)	1.33 (0.29-6.1)	0.707
DSWI	0 (0)	1 (0.6)	Not applicable	0.498
ICU stay (days)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.13 (-0.47-0.74)	0.782
Transfusion rate				
Overall	47 (32.9)	47 (29.2)	1.19 (0.72-1.96)	0.770
On CPB	7 (4.9)	5 (3.5)	2.1 (0.75-5.7)	0.213
After CPB (OR)	7 (4.9)	14 (9.8)	0.47 (0.18-1.21)	0.173
In the ICU or ward	37 (25.9)	32 (22.4)	1.21 (0.70-2.1)	0.770
Number of units	0 (0-1)	0 (0-1)	0.14 (-0.44-0.41)	0.948

Data are number (%) or median (interquartile range). AKI: acute kidney injury; CI: confidence interval; CPB: cardiopulmonary bypass; GDP: goal-directed perfusion; DSWI: deep sternal wound infection; ICU: intensive care unit; MV: mechanical ventilation; OR: operating room; RR: relative risk.

eTable 1 (online version only) . 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[a]	Exhaust CO_2 measurement	Patients enrolled
1	RX25	PHISIO	Non pulsatile	US flow distal to all shunts	M4	CONNECT[b] M4	M4 / VAMOS	33
2	Inspire6 Inspire8	SMART	Non pulsatile	US flow distal to all shunts	M4	M4	M4	54
3	Inspire8	PHISIO	Non pulsatile	Roller pump	CDI 500	CONNECT[b]	VAMOS	70
4	Inspire6 Inspire8	PHISIO	Non pulsatile	US flow distal to all shunts	BCare 5	CONNECT[b]	PRIMUS	69
5	Inspire6	PHISIO	Non pulsatile	Roller pump	SATCRIT	MANUALLY	GENERAL ELECTRIC	13
6	Inspire 8 Quadrox	PHISIO SOFTLINE	Non pulsatile	Roller pump	CDI 500	CONNECT[b]	IntelliVue G5-M1019A	26
7	Inspire 6	PHISIO	Non pulsatile	US distal to all shunts	BCare 5	CONNECT[b]	Ohmeda	22
8	Inspire 8	PHISIO	Non pulsatile	US flow distal to all shunts	CDI 500	CONNECT[b]	N/A	33
9	Inspire6	PHISIO	Non pulsatile	Roller pump	DATAMASTER	CONNECT[b]	PRIMUS	6

CO_2: carbon dioxide; GDP: goal directed perfusion; Hb: haemoglobin; HCT: haematocrit; US: ultrasound. RX25, CDI-500, Terumo Corporation, Tokyo, Japan; Inspire6 , Inspire8, Phisio, B-care 5,CONNECT, DATAMASTER LivaNova, London, UK; Softline Maquet, Rastatt, Germany; M4, Spectrum Medical Gloucester, England; Vamos, Primus, Dräger Medical GmbH. Lübeck, Germany; Satcrit,Siemens, Solona, Sweden; Ohmeda, General Electric Healthcare, Chicago, USA; IntelliVue G5-M1019A, Koninklijke Philips, Amsterdam, Netherlands.

[a]GDP calculated as oxygen content (mL/dL) x pump flow (dL/min/m^2), and oxygen content as haemoglobin (g/dL) x arterial saturation 1.34 + 0.03xPaO_2 (mmHg).

[b]GDP formula CONNECT software: DO2 = Flow(Hct/2:94 x 1:36 x SaO2 + PaO2 _ 0:003)10

[c]GDP formula M4 formula : ecDO2 = 10.Qblood _x Hb x 1:34(SaO2/100)

eTable 2 (online version only). Perfusion practices

Site	Static prime volume	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	1,300-1,500 mL	20% albumin + crystalloid	42%	0 %	0 %	Alpha-stat	64%	Hb 7 g/dL	34°C NP	36°C NP
2	1,100-1,250 mL	Crystalloid	0%	7%	0%	Alpha-stat	21%	Hb 7.3 g/dL	32-33°C NP	36-37°C NP
3	1,300 mL	Crystalloid	100%	3%	31%	Alpha-Stat	0%	Hb 7.0 g/dL	32-34°C NP	36.5°C NP
4	600 mL	Colloid (gelatins)	0%	0%	100%	Alpha-stat	45%	Hb 7 g/dL	32°C NP	36°C Rectal
5	800-1,200 mL	Colloid (gelatins)	0%	0%	0%	Alpha-stat	100%	Hb 7 g/dL	32°C NP	36°C Rectal
6	900-1,300 mL	Crystalloid	0%	0%	100%	Alpha-stat	0%	Hb 7.5 g/dL	37°C NP with active warming	36°C Bladder
7	935 mL	Crystalloid	20%	100%	100%	Alpha-stat	100%	Hb 7 g/dL	32°C Bladder	36°C Bladder
8	1,200	Crystalloid+ starches	0%	0%	0%	Alpha-stat	100%	Hb 7.3 g/dL	34°C Rectal	36°C Rectal
9	605 mL	Crystalloid	100%	0%	100%	Alpha Stat	100%	Hb 8 g/dl	34°C NP	36.5°C NP

CPB: cardiopulmonary bypass; NP: nasopharyngeal; RAP: retrograde autologous prime.

723 eTable 3 (online version only). Component analysis for factors associated with any kind of serum creatinine increase.

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Factor	Regression coefficient	P value	Odds ratio	Lower limit 95% CI	Upper limit 95% CI
Body surface area (m^2)	1.479	0.004	4.390	1.598	12.062
Diabetes	1.640	0.007	5.154	1.578	16.083
Recent myocardial infarction	-0.956	0.035	0.384	0.158	0.935
LVEF (%)	-0.028	0.013	0.972	0.951	0.994
Baseline creatinine (mg/dL)	-1.183	0.023	0.306	0.111	0.847
Nadir DO_2 < 280 $mL \cdot min^{-1} \cdot m^{-2}$	0.884	0.004	2.420	1.326	4.417
Constant	-0.182				

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726 DO_2: oxygen delivery; LVEF: left ventricle ejection fraction

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737 eTable 4 (online version only). Effects of red blood cell transfusions and study arm in determining acute kidney injury stage 1.

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Factor	Regression coefficient	P value	Odds ratio	Lower limit 95% CI	Upper limit 95% CI
RBC units_OR	0.169	0.685	1.184	0.523	2.677
RBC units_CPB	-0.490	0.447	0.612	0.173	2.167
RBC units_ICU	0.273	0.002	1.314	1.103	1.565
GDP arm	-0.741	0.029	0.477	0.245	0.928
Center	N/A	0.726	N/A	N/A	N/A
ARF score	-0.036	0.828	0.965	0.700	1.331
Constant	-1.697				

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740 ARF: acute renal failure; CI: confidence interval; CPB: cardiopulmonary bypass; GDP: goal-directed perfusion; ICU: intensive care

741 unit; OR: operating room; RBC: red blood cells.

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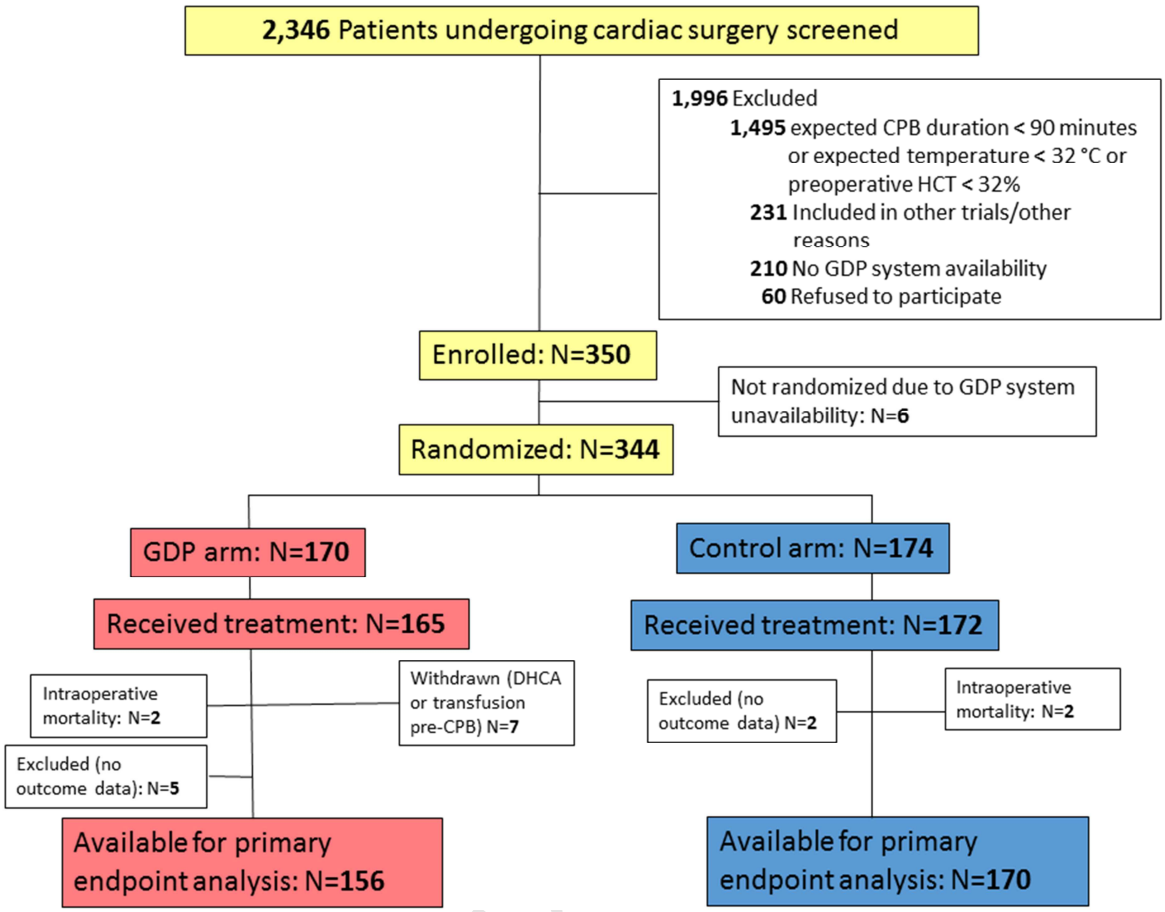
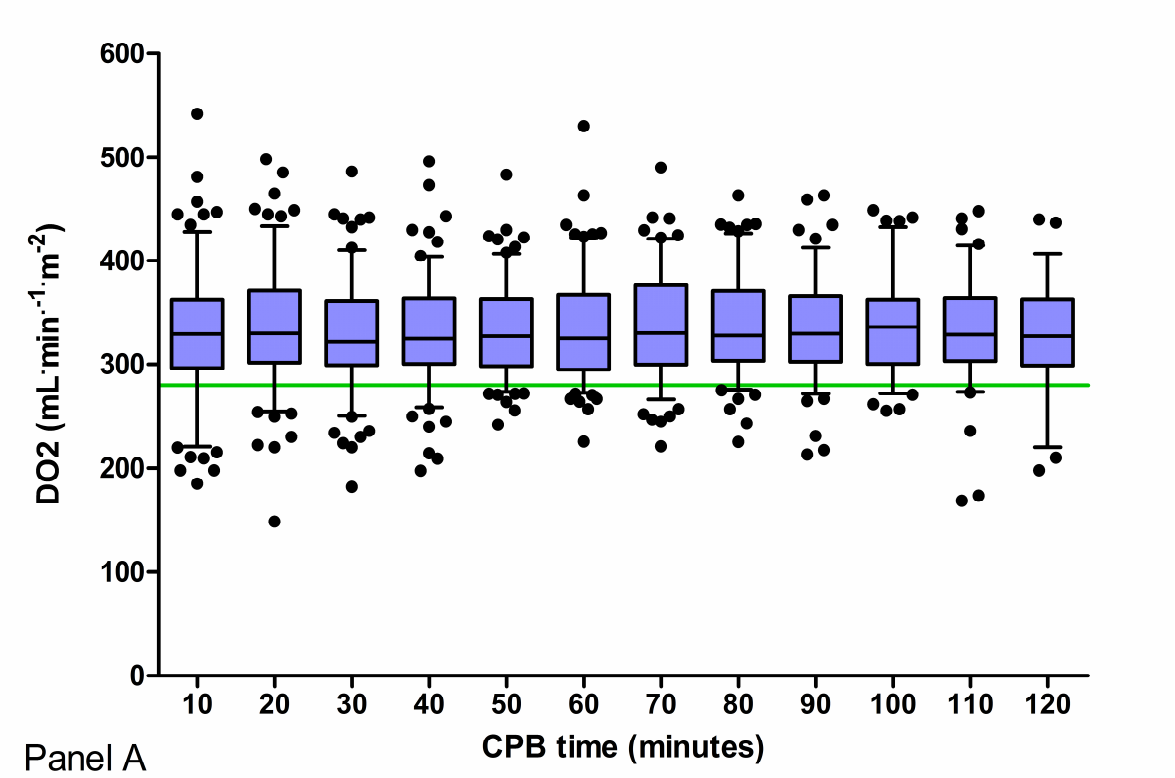
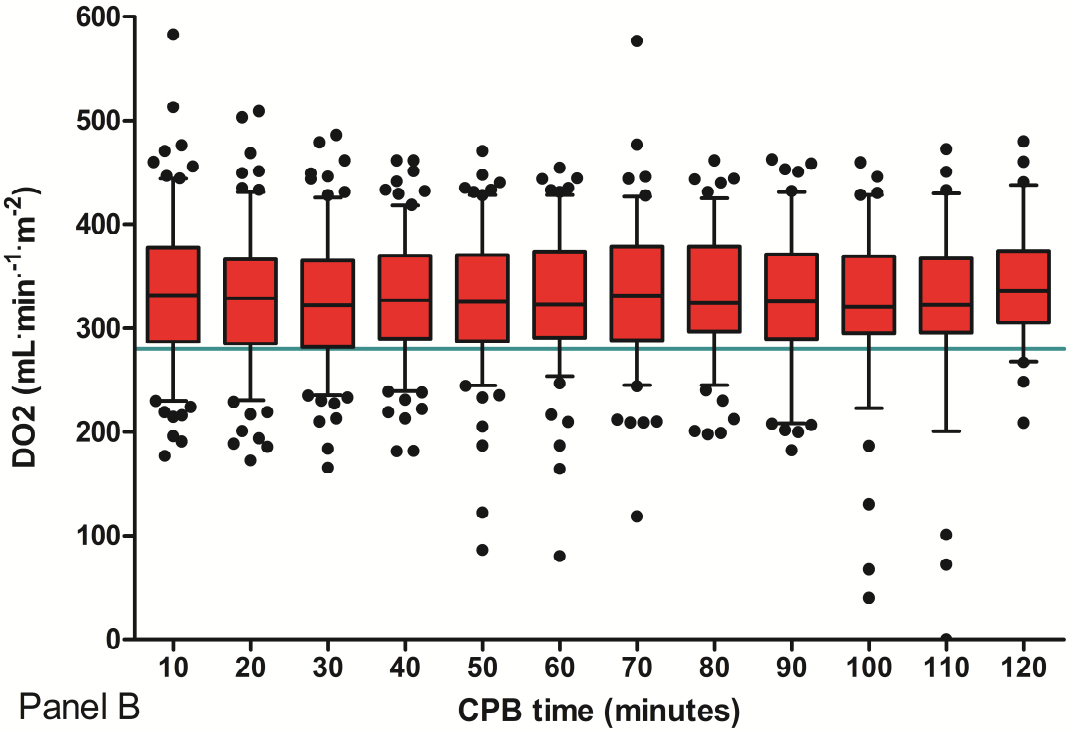

2,346 Patients undergoing cardiac surgery screened
1,996 Excluded
1,495 expected CPB duration < 90 minutes or expected temperature < 32 °C or preoperative HCT < 32%
231 Included in other trials/other reasons
210 No GDP system availability
60 Refused to participate
Enrolled: N=350
Not randomized due to GDP system unavailability: N=6
Randomized: N=344
GDP arm: N=170
Control arm: N=174
Received treatment: N=165
Received treatment: N=172
Intraoperative mortality: N=2
Withdrawn (DHCA or transfusion pre-CPB) N=7
Excluded (no outcome data): N=5
Excluded (no outcome data) N=2
Intraoperative mortality: N=2
Available for primary endpoint analysis: N=156
Available for primary endpoint analysis: N=170



Panel A



Panel B

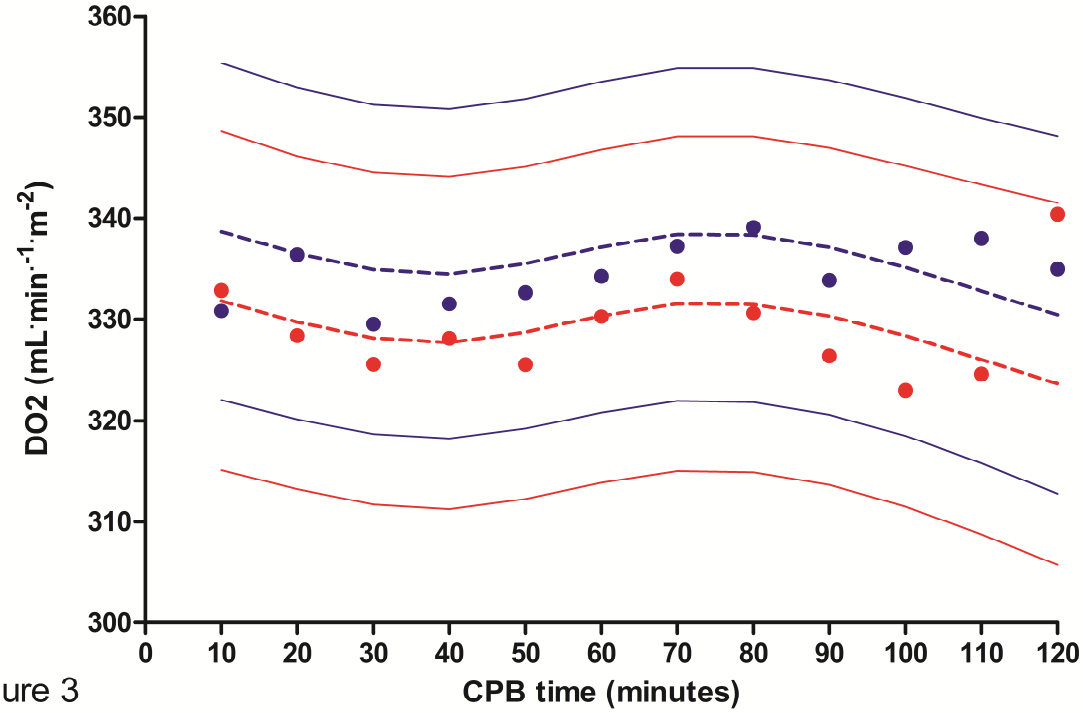


Figure 3

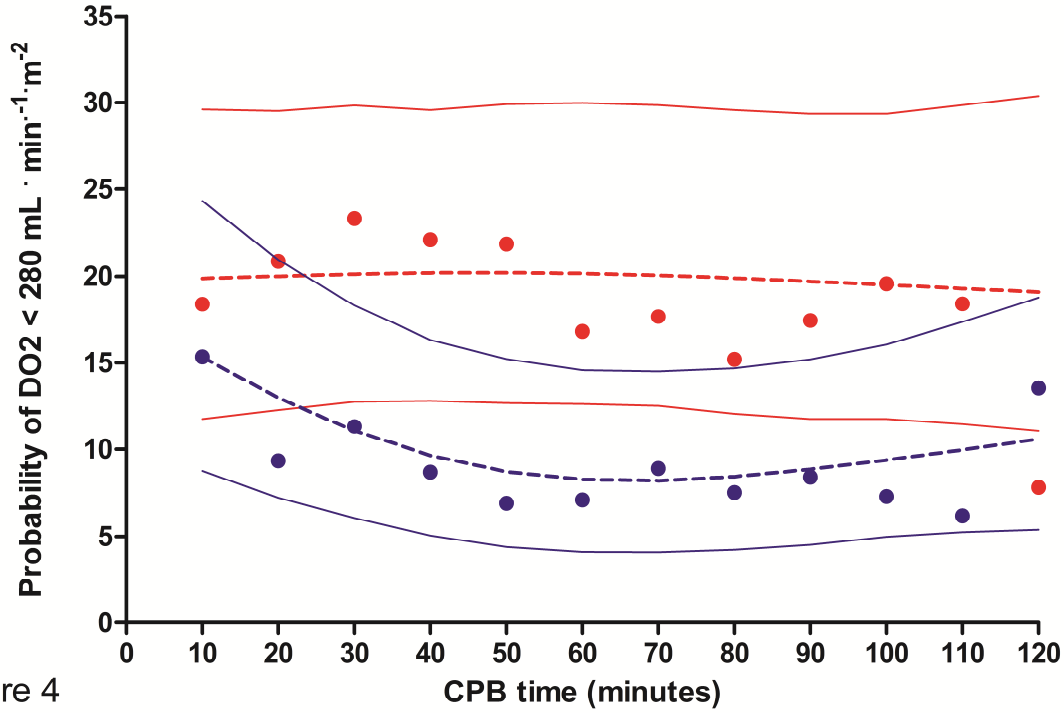


Figure 4