G.I.F.T.
The Goal directed perFusion Trial

A multi-center, prospective, randomized, controlled study

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1. Background

Previous studies (1-5) have demonstrated that oxygen delivery (DO2) and carbon dioxide production (VCO2) during cardiopulmonary bypass (CPB) are associated with renal outcome in cardiac surgery. The critical value for DO2 is around 262 – 272 mL/min/m2, and the correspondent critical value of DO2/VCO2 ratio is around 5.0. Patients with nadir DO2 and DO2/VCO2 ratio below these critical levels have an increased incidence of acute kidney injury (AKI) after cardiac operations. These observations offer an interpretation for the well-known deleterious effects of excessive hemodilution during CPB, supported by many studies where an association between nadir hematocrit (HCT) on CPB and bad outcomes (especially renal) was found (6-8). It is reasonable to hypothesize that a low oxygen delivery may determine an ischemic damage to the kidney, that due to its peculiar circulation is particularly susceptible to a decrease in the oxygen supply. However, there is no evidence that a strategy directed towards the specific goal of avoiding critical values of DO2 during CPB may actually decrease the postoperative AKI rate.

The present study is designed to verify the hypothesis that a strategy based on a goal-directed perfusion, aimed to avoid a nadir DO2 below the critical threshold, is effective in limiting the postoperative AKI rate.

2. Study design

Multicenter, international, prospective, randomized and controlled study.

Patient population

a. Inclusion criteria: Adult (> 18 years) patients undergoing cardiac operations with CPB. Expected CPB duration > 90 minutes.

b. Exclusion criteria: severe chronic renal failure (dialysis or serum creatinine > 3.0 mg/dL); emergent (must be operated immediately) procedure; moderate-severe anemia (preoperative HCT < 32%); expected nadir CPB temperature < 32 °C.

c. Withdrawal criteria (after randomization): Need for allogeneic blood transfusions before CPB. Need for allogeneic blood to prime the CPB circuit. CPB duration below 90 minutes will not be withdrawal criterion.

Primary outcomes

Incidence of AKI, defined according to the AKIN criteria (9) as:
AKI stage 1: peak postoperative serum creatinine > 1.5 x baseline or absolute increase ≥ 0.3 mg/dL, within the first 48 hours after surgery.

AKI stage 2: peak postoperative serum creatinine > 2.0 x baseline, within the first 48 hours after surgery (AKI stage 3 will be incorporated in the AKI stage 2 group).

Any AKI: stage 1 or higher

Peak serum creatinine: within the first 48 postoperative hours.

Diagnosis of AKI must be reached within the first 48 hours after surgery, but staging may require a longer time (up to 7 days after surgery).

Secondary outcomes

Length of ICU stay (days)
Transfusion (PRCs) rate and amount of PRCs units transfused
Major morbidity (according to STS): mechanical ventilation > 24 hours, AKI stage 2, surgical revision, mediastinitis, stroke.
Operative (in-hospital) mortality or at 30 days after discharge

3. Sample size

The power analysis is based on the primary outcome “any AKI”.

Data from the previous study (1) provide the following figures for the total patient population:

Any AKI rate: 21.2%
AKI stage 1: 8.8%
AKI stage 2-3: 12.4%

With the following distribution according to a cut-off value settled at a nadir DO2 of 280 mL/min/m2.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All cases N=354</th>
<th>DO2 &lt; 280 mL/min/m2 N= 181</th>
<th>DO2 ≥ 280 mL/min/m2 N= 173</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AKI</td>
<td>75 (21.2%)</td>
<td>54 (29.8%)</td>
<td>21 (12.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>AKI stage 1</td>
<td>31 (8.8%)</td>
<td>23 (12.7%)</td>
<td>8 (4.6%)</td>
<td>0.007</td>
</tr>
<tr>
<td>AKI stage 2-3</td>
<td>44 (12.4%)</td>
<td>31 (17.1%)</td>
<td>13 (7.5%)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Based on the above table, we know that the Control Group will spontaneously meet the goal in 50% of the cases, and that will have an any AKI rate of 21%.

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We hypothesize that the Goal-Directed Perfusion (GDP) group will meet the goal in 95% of the cases. When the goal is met, the AKIN rate will be 12%; when it is not, it will be 29%. This will lead to an expected AKI rate in GDP group of 12.8%.

Therefore, the effect size will be a 40% reduction in the AKI rate (12.8% in GDP group, 21% in Control group).

Based on this effect size, an alpha value of 0.05 and a beta value of 0.20, the number of patients in each group is 350, for a total patient population of 700.

4. Interventions

Patients will be randomly allocated to the Control or the GDP group. Randomization will be performed locally at each participating Institution, using computer-generated schemes. The patients in control Group will be treated according to the local standards. The patients in GDP group will be treated according to the GDP (see table below).

<table>
<thead>
<tr>
<th>CONTROL (N=350)</th>
<th>TREATMENT (N=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP monitor</td>
<td>GDP monitor</td>
</tr>
<tr>
<td>NO Blood prime (withdrawal)</td>
<td>NO Blood prime (withdrawal)</td>
</tr>
<tr>
<td>Priming volume and nature according to local standards</td>
<td>Priming volume and nature according to local standards</td>
</tr>
<tr>
<td>Perfusion targeted on BSA and °C</td>
<td>Perfusion targeted on DO2 ≥ 280 mL/min/m2</td>
</tr>
<tr>
<td>Perfusion pressure according to local standards</td>
<td>Perfusion pressure according to local standards</td>
</tr>
<tr>
<td>Transfusion triggered by HCT according to local standards</td>
<td>Transfusion triggered by SVO2 &lt; 68% and/or O2ER &gt; 40%</td>
</tr>
<tr>
<td>Postoperative care according to local standards</td>
<td>Postoperative care according to local standards</td>
</tr>
</tbody>
</table>

Details of the GDP protocol:

The main intervention to achieve the target value of DO2 is increasing the pump flow.

Additional interventions include hemofiltration to increase the HCT.

Transfusion protocol
a. During CPB: Transfusions are mandatory below a HCT of 18%. Transfusions are generally prohibited for an HCT > 21%. However, based on the individual judgement that the patient is actually in need for packed red cells, transfusions are allowed between an HCT of 22% and 24%. In this case, this will be considered as a protocol violation, but the patient will not be withdrawn. Transfusions are always prohibited for an HCT > 24%.

b. After CPB: HCT < 18%: packed red cells are mandatory
   HCT between 19% and 23%: packed red cells are allowed
   HCT between 24% and 30%: packed red cells generally prohibited, but admitted based on physician’s judgement. This represents a protocol violation. In this case, this will be considered as a protocol violation, but the patient will not be withdrawn.
   HCT > 30%: packed red cells are prohibited.

5. Data collection
The following data will be recorded for each patient:

Preoperative
- Demographics
- Comorbidities
- Serum creatinine (mg/dL)
- Risk stratification (EuroSCORE II)
- Type of operation (CABG+valve; double/triple valve; ascending aorta…)

Operative
- CPB duration
- Pump flow, HCT, DO2, VCO2 (optional), DO2/VCO2 ratio (optional), temperature (°C), recorded every 10 minutes on CPB
- PRCs transfusions

Postoperative
- ICU stay
- Serum creatinine value (daily until postoperative day 2, and in case of AKI, until day 7 or discharge)
- PRCs transfusions
- Mortality
- Severe morbidity (according to STS criteria)
Data collection during CPB will be performed using a dedicated monitor, with specific algorithms for DO2 and VCO2 measurement. For patients in the GDP group the perfusionist will have direct view of the GDP monitor data, to allow a compliance to the GDP protocol. For patients in the Control group, the screen of the GDP monitor will be adequately blinded to the perfusionist, to avoid any “intention to treat” based on GDP monitor data in the group that is intended to be treated following a conventional strategy. All data will be recorded in a centralized electronic platform located at the IRCCS Policlinico San Donato.

Each Institution will provide a minimum of 40 and a maximum of 80 patients. 11 Institutions will be initially involved, based in Europe, Australia, New Zealand, Canada and US. Coordinating Institution will be the IRCCS Policlinico San Donato (Milan).

The general study coordinator is Marco Ranucci (IRCCS PSD). Each Institution will express a Principal Investigator and a number of sub-investigators. The GIFT steering group (and writing committee) is composed by the Study Coordinator and Principle Investigators

6. Ethics

Each Institution will submit the protocol to their Local Ethic Com or Institutional Review Board. A written informed consent is required. The study will be conducted according to the GCP rules.

The GIFT will be registered in the clinicaltrial.gov registry.

The study is a spontaneous RCT

7. Data analysis

All data are properties of the participating Institutions. The GIFT database is property of the GIFT Steering Group. Data will be analyzed by statisticians at the IRCCS PSD. 3 interim analysis are planned, at 25% (175 patients), 50% (350 patients) and 75% (525 patients) of the patients enrollment.

Specific stopping rules (for futility, safety, and efficacy) are settled and will be applied after the second interim analysis.

Stopping rule for futility: the trial will be stopped for futility in presence of a relative risk for the primary outcome (any AKI) not including the hypothesized value of 0.6 within a 99% CI at the 50% interim analysis or 95% CI at the 75% interim analysis.
Stopping rule for efficacy: the trial will be stopped for efficacy in presence of a difference for the primary outcome (any AKI) in favour of the GDP group at a P value of 0.01 at the 25% interim analysis or 0.05 at the 50% and 75% interim analyses.
Stopping rule for safety in presence of a difference for the primary outcome (any AKI) in favour of the control group at a P value of 0.01 at the 25% interim analysis or 0.05 at the 50 - 75% interim analysis.

The analysis will be based on an intention-to-treat analysis. Based on the length of CPB, the patients will be excluded by the analysis in case of too short (< 60 min) or too long (> 90th percentile) CPB duration. This, to avoid an insignificant effect of CPB or a renal dysfunction due to causes other than CPB (difficult weaning from CPB, inotropic drug use).
Post-hoc analyses will include:

- A per-protocol analysis (including only the patients who reached the goal in the GDP group and those who did not in the Control group). Patients with transfusion protocol violation will be excluded from this analysis.
- A subgroup analysis including only patients at high-risk for AKI, based on an AKI risk score (10)

8. References


