

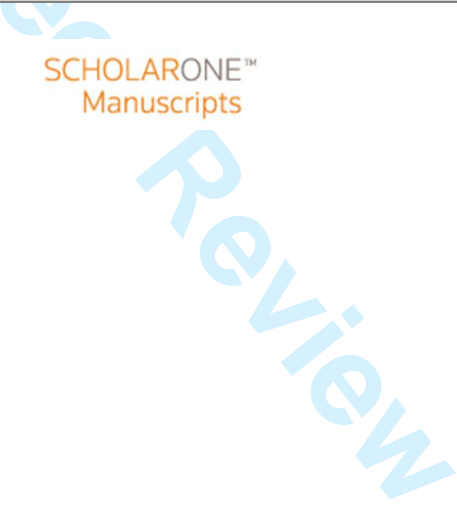
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**The effects of on-pump and off-pump coronary artery bypass surgery on respiratory function in the early post-operative period.**

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Keywords:	cardiac surgery, intensive care, pao2 fio2 ratio, critical care, arterial blood gas
Abstract:	Background: Respiratory complications are common after cardiac surgery and the use of extracorporeal circulation is one of the main causes of lung injury. We hypothesized a better postoperative respiratory function in OFF-pump coronary-artery bypass grafting (OPCABG) as compared with "ON-

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	<p>pump” (ONCABG).</p> <p>Methods: This is a retrospective, single centre study at a Cardiothoracic intensive care unit (ICU) in a Tertiary University Hospital. Consecutive data on 339 patients undergoing elective CABG (n=215 ONCABG, n=124 OPCABG) were collected for one-year from the ICU electronic medical records. We compared respiratory variables (PaO2, PaO2/FiO2 ratio, SaO2 and PaCO2) at seven predefined time-points (ICU admission, 1st-3rd-6th-12th-18th-24th postoperative hour). We also evaluated time-to-extubation, rates of re-intubation and use of non-invasive ventilation (NIV). We used mixed-effects linear regression models (with time as random-effect for clustering of repeated measures) adjusted for a pre-determined set of covariates.</p> <p>Results: The values of PaO2 and PaO2/FiO2 were significantly higher in the OPCABG group only at ICU admission (mean differences: 9.7 mmHg, 95%CI 3.1-16.2; and 27, 95%CI 6.1-47.7, respectively). The OPCABG group showed higher PaCO2, overall (p=0.02) and at ICU admission (mean difference 1.8 mmHg, 95%CI 0.6-3), although mean values were always within normal range in both groups. No differences were seen in SaO2 values, time-to-extubation, rate of re-intubation rate and use of postoperative NIV. Extubation rate was higher in OPCABG only at the 12th postoperative hour (92% vs ONCABG 82%, p=0.02).</p> <p>Conclusions: OPCABG showed only marginal improvements of unlikely clinical meaning.in oxygenation as compared to ONCABG in elective low-risk patients.</p>



# The effects of on-pump and off-pump coronary artery bypass surgery on respiratory function in the early post-operative period.

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**The effects of on-pump and off-pump coronary artery bypass surgery on respiratory function in the early post-operative period.**

**ABSTRACT**

**Background:** Respiratory complications are common after cardiac surgery and the use of extracorporeal circulation is one of the main causes of lung injury. We hypothesized a better postoperative respiratory function in OFF-pump coronary-artery bypass grafting (OPCABG) as compared with “ON-pump” (ONCABG).

**Methods:** This is a retrospective, single centre study at a Cardiothoracic intensive care unit (ICU) in a Tertiary University Hospital. Consecutive data on 339 patients undergoing elective CABG (n=215 ONCABG, n=124 OPCABG) were collected for one-year from the ICU electronic medical records. We compared respiratory variables (PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, SaO<sub>2</sub> and PaCO<sub>2</sub>) at seven predefined time-points (ICU admission, 1<sup>st</sup>-3<sup>rd</sup>-6<sup>th</sup>-12<sup>th</sup>-18<sup>th</sup>-24<sup>th</sup> postoperative hour). We also evaluated time-to-extubation, rates of re-intubation and use of non-invasive ventilation (NIV). We used mixed-effects linear regression models (with time as random-effect for clustering of repeated measures) adjusted for a pre-determined set of covariates.

**Results:** The values of PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> were significantly higher in the OPCABG group only at ICU admission (mean differences: 9.7 mmHg, 95%CI 3.1-16.2; and 27, 95%CI 6.1-47.7, respectively). The OPCABG group showed higher PaCO<sub>2</sub>, overall (p=0.02) and at ICU admission (mean difference 1.8 mmHg, 95%CI 0.6-3), although mean values were always within normal range in both groups. No differences were seen in SaO<sub>2</sub> values, time-to-extubation, rate of re-intubation rate and use of postoperative NIV. Extubation rate was higher in OPCABG only at the 12<sup>th</sup> postoperative hour (92% vs ONCABG 82%, p=0.02).

**Conclusions:** OPCABG showed only marginal improvements of unlikely clinical meaning.in oxygenation as compared to ONCABG in elective low-risk patients.

**Keywords:** Cardiac surgery; intensive care; critical care; pao2 fio2 ratio; arterial blood gas.

## The effects of on-pump and off-pump coronary artery bypass surgery on respiratory function in the early post-operative period.

### INTRODUCTION

Respiratory dysfunction is common during the postoperative period after cardiac surgery and its incidence varies according to the criteria used for diagnosis<sup>1</sup>, but it can be reasonably estimated in the order of 10%<sup>2</sup>. The most common postoperative lung complications are atelectasis, pleural effusion and pneumonia<sup>3</sup> and they may persist over the first days after surgery and one study showed that incidence of hypoxia or hypercarbia 24 hours after discharge from intensive care (ICU) can be as high as 79% and 38%, respectively<sup>4</sup>.

The occurrence of pulmonary complications is affected by several factors, both preoperative lung function<sup>5</sup>, smoking history<sup>6</sup> and intra-operative factors; among the latter, lung collapse during cardiopulmonary bypass (CPB) is a key-factor in determining acute lung injury<sup>7</sup>. Moreover CPB triggers a systemic inflammatory response with a cascade of cytokines that may further exacerbate lung injury<sup>8</sup>. Off- pump coronary artery grafting (OPCABG) has been introduced with the idea of decreasing complications after cardiac surgery, in particular those related to CPB. However, three large randomized trials have shown no difference in mortality and in composite outcomes between OPCABG and the standard on-pump technique (ONCABG)<sup>9-11</sup>. The largest of such trials reported a lower 30-day incidence of respiratory failure or infection in the population undergoing OPCABG as compared with the ONCABG group<sup>10</sup>. Moreover, lower quality evidence suggests improvements of the respiratory function with OPCABG as compared with conventional on-pump approach from respiratory perspectives, as demonstrated by reduced incidence of postoperative hypoxemia<sup>12</sup>, pneumonia<sup>12</sup>, prolonged mechanical ventilation<sup>13</sup> and acute respiratory distress syndrome<sup>14</sup>, as well as decreasing the incidence of postoperative radiological changes<sup>15</sup>. One study reported also higher plasma values of lung epithelium-specific proteins (markers of lung injury) at the end of ONCABG as compared with OPCABG, although these levels returned at baseline 24 hours after surgery<sup>16</sup>, and another found a better maintained endothelium-dependent vasodilation<sup>17</sup>. On the other side Montes

et al. found that restrictive changes of lung function happen after both ONCABG and OPCABG, with no differences between the two groups<sup>18</sup>. Since no studies have focused on a detailed course of gases exchanges after CABG, we sought to evaluate this outcome by means of the course of arterial O<sub>2</sub> pressure (PaO<sub>2</sub>), arterial carbon dioxide pressure (PaCO<sub>2</sub>) and the ratio of PaO<sub>2</sub> over the inspired fraction of oxygen (FiO<sub>2</sub> - PaO<sub>2</sub>/FiO<sub>2</sub>) over the first day spent in ICU for patient undergoing OPCABG as compared with ONCABG.

For Peer Review

## METHODS

This is a retrospective single centre study performed at the Oxford Heart Centre, John Radcliffe Hospital (Oxford, United Kingdom) and was registered with the Local Ethics Committee which waived the need for informed consent. We included all patients admitted to our 14-bed Cardiothoracic ICU after elective isolated CABG during a period of one-year starting from the 8<sup>th</sup> August 2012 (date of introduction of electronic medical records system). The sample size of 339 was determined by how many patients were admitted during this period. Data were extracted by four authors (FC, TT, CC, CS) and stored in a password-protected database. We already reported the results of metabolic and hemodynamic differences between OPCABG and ONCABG in this patient's population<sup>19</sup>. As previously described by our group, adult patients undergoing elective isolated CABG were divided in two populations according to the use of intraoperative CPB (ONCABG vs OPCABG). We excluded patients undergoing emergency CABG, those returning to operating room within the first 24 hours, patients with moderate and/or severe liver disease and/or with preoperative organ support as defined by: 1) mechanical (intra-aortic balloon pump – IABP) or pharmacological haemodynamic support; 2) renal support with any form of renal replacement therapy; 3) respiratory support with invasive or non-invasive ventilation (NIV).

There was no electronic medical records system for the intraoperative period and therefore we could not accurately report data for such period. As reported in our previous study, at our institution cardiac surgery cases are always led by an experienced anaesthetic consultant with at least 5 years of practice in cardiac surgery. Most of the consultants have at least basic skills in transoesophageal echocardiography, either due to their experience in cardiac anaesthesia or based on a board certification; moreover, at our hospital there is one consultant cardiologist working only in the operating room and performing echocardiogram in each patient undergoing cardiac surgery. In principle cardiac anaesthesia is conducted mostly with volatile agents (isoflurane) or more rarely with propofol. Fentanyl boluses are used to maintain analgesia; pancuronium is the choice muscle relaxant and it is given at the induction of anaesthesia in a single dose (usually between 4 and 6 mg) for the whole intervention. A warming system is connected for intravenous fluid warming in a large

bore cannula and a warming mattress is positioned under the patient. Patients are intraoperatively ventilated mostly with volume-controlled ventilation with protective tidal volumes ( $<8\text{ml/kg}$  based on ideal body weight) and a positive end-expiratory pressure (PEEP) usually set at  $5\text{ cmH}_2\text{O}$ . During CPB, all patients undergoing ONCABG are disconnected from the ventilator. At ICU arrival after surgery our policy was to set the ventilator in synchronized intermittent mandatory ventilation + pressure support modality, with a default PEEP of  $5\text{ cmH}_2\text{O}$  and tidal volumes kept in the range of  $6\text{--}8\text{ ml/kg}$  of ideal body weight.

**Database organization**

We collected the following baseline data: 1) *demographics*: age, sex, height, weight, BMI; 2) *preoperative status*: diabetes, hypertension, hypercholesterolemia, smoking history, creatinine, Euroscore II and left and right ventricular (LV and RV) systolic function; in particular, the LV systolic function was classified according to the ejection fraction as: good ( $>55\%$ ), mildly impaired ( $46\text{--}55\%$ ), moderately impaired ( $36\text{--}45\%$ ) or severely impaired ( $<35\%$ ); 3) *surgical details*: number of grafts performed.

For the interest of this study we recorded the following parameters for all patients admitted to ICU after CABG: arterial blood gases and **arterial O2 saturation ( $\text{SaO}_2$ )**; time to extubation and need for early re-intubation (within the first 24 hours); use of any form of NIV support after extubation within the first 24 hours. This set of parameters was collected at 7 different time-points: ICU admission and at  $1^{\text{st}}$ - $3^{\text{rd}}$ - $6^{\text{th}}$ - $12^{\text{th}}$ - $18^{\text{th}}$ - $24^{\text{th}}$  postoperative hour (choosing the closest recorded value to the established time-point).

Our primary outcomes were the differences in  $\text{PaO}_2$ ,  $\text{PaCO}_2$ ,  $\text{PaO}_2/\text{FiO}_2$  overall and at single time-points. Secondary outcomes were overall and single-time-points differences in  $\text{SaO}_2$ , time to extubation, need for NIV and for early re-intubation.

Other parameters recorded were: pH (alpha-stat method as this values was recorded in the electronic medical records system), lactate and base deficit; mean arterial pressure (MAP), central venous pressure (CVP) and haemodynamic support; postoperative pharmacological cardiovascular support;



fluid administration (crystalloids, colloids and per os fluid intake); urine output and fluid balance; administration of furosemide and sodium bicarbonates, the length of stay (LOS) and mortality in the Cardiothoracic ICU. The differences of such parameters are reported in our previous study.<sup>19</sup>

### Statistical analysis

Statistical analysis was conducted with *Stata Statistical Software: Release 14 (StataCorp. 2015, College Station, TX: StataCorp LP®)*. For baseline comparisons between ONCABG and OPCABG, continuous variables were compared using the Student's t-test and results presented as mean, 95% confidence interval and p-value. Categorical variables are presented as percentage and confidence interval, and the Chi-square test was used for between group comparisons.

Continuous variables that were observed multiple times in the postoperative period were analysed using mixed effects linear regression models with time as a random effect to allow for the clustering of repeated measures within the same patient. Separate models were used, one for each variable of interest (PaO<sub>2</sub>, PaCO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, FiO<sub>2</sub>, SaO<sub>2</sub>). All models were adjusted for the following covariates: age, sex, BMI, number of grafts, LV and RV systolic function, creatinine levels, smoking history, diabetes, hypertension, hypercholesterolemia and EuroSCORE II. Thirty five percent of patients included in the dataset had at least one covariate with missing information. Because these values were likely to be missing at random, and to avoid a loss in efficiency, missing values for BMI, number of grafts, creatinine, smoking history, diabetes, hypertension, hypercholesterolemia and EuroSCORE II were imputed using multiple imputation by chained equations. Twenty imputed datasets were created. Multiple imputation was performed using the mi package in *Stata Statistical Software: Release 14 (StataCorp. 2015, College Station, TX: StataCorp LP®)*. All tests were two-sided and a result of p-value <0.05 was considered statistically significant.

### RESULTS

A total of 363 patients underwent isolated CABG in the period of study. Of these we excluded a total of 24 patients (n=14, emergency cases; n=3, preoperative IABP; n=2, immediate return to **operating room** for suspected bleeding; n=4, mini-invasive CABG; n=1, preoperative dialysis). Among the 339 patients included in the study, 63.4% (n=215) underwent ONCABG and the remaining had OPCABG (36.6%, n=124). The vast majority of OPCABG cases (n=119/124, 96%) were performed by two cardiac surgeon **consultants**. The characteristics of the two groups were similar with the only exceptions of higher number of patients with hypercholesterolemia and number of grafts performed in the ONCABG group; there was also a trend towards more patients with good RV systolic function in the OPCABG group (Table 1).

We found no differences in the overall course of PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> (Figure 1 and 2, respectively) although significant differences were found at ICU admission, when OPCABG group showed significantly higher PaO<sub>2</sub> (mean difference - MD - 9.7 mmHg, 95%CI 3.1-16.2), and PaO<sub>2</sub>/FiO<sub>2</sub> (MD 27, 95%CI 6.1-47.7). The course of overall PaCO<sub>2</sub> showed higher (although always within normal range) values in the OPCABG group (Figure 3, p=0.02). The only significant difference in PaCO<sub>2</sub> was found at ICU admission (MD 1.8 mmHg, 95%CI 0.6-3), with also a trend towards higher PaCO<sub>2</sub> values at the 1<sup>st</sup>, 3<sup>rd</sup>, 18<sup>th</sup> and 24<sup>th</sup> postoperative hour (MD between 1 and 2 mmHg, all p=0.05-0.08). No differences in SaO<sub>2</sub> values over the course of the first 24 hours spent in ICU were seen (Figure 4). The results of the overall and single time-points differences for PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, PaCO<sub>2</sub> and SaO<sub>2</sub> is available as supplemental digital content 1 (for PaO<sub>2</sub> and PaCO<sub>2</sub> values are provided both in mmHg and in kPa).

The mean time to extubation was similar between groups OPCABG and ONCABG (7.0±14 vs 7.8±15.7 hours respectively, p=0.63). No patients required re-intubation in the OPCABG vs four in the ONCABG group (0% vs 2% respectively, p=0.31). The number of patients extubated at all time-points was similar between groups, except at the 12<sup>th</sup> postoperative hour when OPCABG showed better results (n=110/124, 92% vs ONCABG n=172/215, 82%, p=0.02), and no difference were found in the postoperative use of NIV between groups (Table 2).

With regards to other variables of interest for the evaluation of respiratory outcomes, we already reported in our previous study<sup>19</sup> the results of a mixed effects model analysis. In that study we found similar pH values and overall fluid balance between the ONPABG and OPCABG groups at all time-points, with also a similar crystalloids/colloids ratio between groups. The urine output was significantly higher in the OPCABG both in the overall comparison ( $p=0.02$ ) and at the 3<sup>rd</sup>, 6<sup>th</sup>, 12<sup>th</sup> and 24<sup>th</sup> postoperative hour while diuretic therapy was similar between groups.

## DISCUSSION

The performance of OPCABG surgery has received a lot of scrutiny with three large randomized trials showing no benefit in mortality as compared with the traditional on-pump technique<sup>9-11</sup>. We aimed at extending the knowledge on potential respiratory benefits of OPCABG, evaluating the course of gas exchanges over the first day spent in the ICU since no studies has yet focused on a detailed sequential postoperative course. To our knowledge this is the first study comparing serial differences in the postoperative respiratory profile between OPCABG and ONCABG surgery.

We found similar values in oxygenation both overall and at most time-points. Small differences were seen at ICU admission, however this result should be interpreted with caution since during the route to Cardiac ICU the patient is ventilated with a bag-mask, and such approach may have caused inhomogeneity in the ventilation between patients and thus on the arterial blood gas at ICU admission. Moreover, such differences seem very marginal from a clinical perspective. Indeed, the mean differences in PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> ratio favouring the OPCABG group at ICU admission were in the region of 10 mmHg and 27 ratio, respectively.

An interesting finding of our study is that during the first postoperative day the PaO<sub>2</sub>/FiO<sub>2</sub> ratio maintained values within the range of acute lung injury<sup>20</sup>, confirming the presence of a lung insult even in elective low-risk patients undergoing cardiac surgery regardless of the use of CPB as already shown by Montes et al.<sup>18</sup>. Whether the difference in the postoperative course of respiratory variables would have been larger in a population at higher risk (such as more-than-mild **chronic obstructive pulmonary** disease, emergency CABG, patients intubated before surgery, etc) cannot be

addressed by the present study. For instance, a large retrospective analysis conducted in patients undergoing re-do cardiac surgery, OPCABG significantly reduced the incidence of pulmonary complications (4.1% vs 9.5% in the ONCABG group)<sup>12</sup>. On the other side, a smaller study on totally arterial coronary grafts found a trend towards higher degree of respiratory complications in the OPCABG group. The same study found a shorter ventilator support after OPCABG<sup>21</sup>.

The values of PaO<sub>2</sub>/FiO<sub>2</sub> ratio gradually improved in our cohort of patients and this finding is similar to those of Montes et al. that reported a nadir of PaO<sub>2</sub>/FiO<sub>2</sub> ratio at ICU arrival gradually recovering after surgery<sup>18</sup>. Although these authors did not find differences between ON vs OPCABG at ICU arrival, the clinical meaning of a better PaO<sub>2</sub>/FiO<sub>2</sub> ratio immediately after surgery in OPCABG patients reported by our study remains unremarkable from clinical perspectives. Moreover, Montes et al. found restrictive changes in pulmonary function assessed by spirometry both in OPCABG and ONCABG, without differences between groups. In particular, forced expiratory volume in one second and forced vital capacity significantly decreased from ~90% of predicted values to ~50% (with unchanged ratio) 72 hours after surgery, and similarly behaved total lung capacity, dropping from ~105% to ~70%<sup>18</sup>.

The PaCO<sub>2</sub> showed higher values overall and at ICU admission in the OPCABG group but with a mean difference in the range of ~2 mmHg, together with a trend towards lower values at the 1<sup>st</sup>, 3<sup>rd</sup>, 18<sup>th</sup> and 24<sup>th</sup> hours. However, both groups had always mean PaCO<sub>2</sub> values within the normal range, again supporting the presence of only mild lung injury after low-risk cardiac surgery.

In our ICU we have a standardized protocol aiming at early extubation, and we found a difference in time to extubation only at the 12<sup>th</sup> postoperative hour. Importantly, the mean time of extubation in both groups was less than the 8-10 hours cut-off usually investigated<sup>22, 23</sup>, and over 85% and 96% of the whole population extubated by the 12<sup>th</sup> and 24<sup>th</sup> postoperative hour respectively, thus confirming both the low risk population of patients. Similar time to extubation for the two CABG techniques has been already shown<sup>24</sup>, but it is important to note that we investigated a low-risk population and our findings should not be expanded to high-risk patients. In this respect, a small study on re-do CABG showed a beneficial effect of OPCABG in decreasing the occurrence of

prolonged mechanical ventilation (PMV) as compared with ONCABG<sup>13</sup>. Nonetheless there is no full concordance on the association between type of cardiac surgical procedure and PMV: one large study conducted on over 4800 patients found that CABG associated to valve surgery was an independent predictor of PMV<sup>25</sup>, while a smaller one (400 patients) did not identify the type of surgery as a factor linked to postoperative PMV<sup>26</sup>.

We also showed no differences in the rate of reintubation between groups, supporting again a good standardized practice with regards to extubation and that postoperative lung injury between groups was similar. Among the four cases of re-intubation, half were not due to respiratory failure (a severe upper gastrointestinal bleeding between after the 18<sup>th</sup> postoperative hour, and a cardiovascular collapse after the 12<sup>th</sup> postoperative hour). The remaining two cases were due to isolated hypoxemic respiratory failure and occurred after the 3<sup>rd</sup> and after the 12<sup>th</sup> postoperative hour respectively. In one of the latter cases, continuous positive airway pressure was unsuccessfully attempted before reintubation.

Also, the similar utilization of postoperative NIV between groups throughout the whole period of study confirms similar degree of lung injury from clinical perspectives and the higher rate of extubation at the 12<sup>th</sup> hour in the OPCABG should be interpreted as a marginal finding in the context of the other results of our study. In one study, the preventive and prolonged (median 16 hours) use of bi-level NIV after extubation of CABG patients significantly reduced hospital LOS and rate of basal atelectasis as compared with standard care<sup>27</sup>; however, in our population it was more frequent the use of continuous positive airway pressure ventilation (up to overall 8% at 24<sup>th</sup> postoperative hour) as compared with the use of bi-level positive airways pressure which was almost unremarkable. This finding is in agreement with deranged PaO<sub>2</sub>/FiO<sub>2</sub> ratio associated to normal PaCO<sub>2</sub> values.

### ***Strengths and limitations***

The strength of this study are mainly the relatively large sample size investigated for the outcome of interest, the electronic data collected during the postoperative period and the statistical approach

allowing for clustering of data at different time-points, and adjusted for several covariates. With regards to the sample size of our observational study, a calculation was not performed in line with the STROBE guidelines for reporting of observational studies<sup>28</sup>. Of note, the 95% CIs were reasonably small and this supports that our sample size was adequate. Nonetheless, even if the sample size of our investigation is relatively large, we analysed a low-risk population and therefore the analysis of certain outcomes such as mortality is probably underpowered.

This study has several limitations. First, it is a single centre study at a University teaching hospital and, although baseline characteristics in the two groups were similar, it was not a randomized study and by definition the retrospective design is potentially subject to biases. However we used electronically collected data and this minimizes the risk of a “recall bias” which is a usual limitation of retrospective studies needing subjective measurements. Indeed, data were accurately downloaded from fully electronic medical charts and the even distribution of preoperative variables (apart from hypercholesterolemia and RV dysfunction) supports that groups were highly comparable at baseline. The difference in number of grafts performed between the two populations is not surprising and incomplete revascularization is a clear challenge for OPCABG technique as shown in the major randomized controlled trials<sup>9-11</sup>.

Second, our study lacks of systematic data on patient’s preoperative and postoperative lung function tests. However such deficiency is reasonable since we investigated a low risk population undergoing cardiac surgery with a mean Euroscore II around 4 points, and performing routine spirometry is not currently recommended in this class of patients. For this reason we could not reliably investigate the presence of chronic obstructive pulmonary disease nor staging it according to the Gold criteria. Our study also misses a systematic evaluation of radiological changes in chest-X ray after surgery. In this regards, one study found a higher mechanical ventilation time and a higher incidence of left band atelectasis in the ONCABG group at 6 days postoperatively as compared with OPCABG<sup>15</sup>.

Third, as no electronic medical records system was available for the intraoperative period, we could not analyse intraoperative data, especially with regards to length of surgery and ventilation strategy

- although this is strongly standardized at our institution. Our analysis lacks also of data on intraoperative fluid administration but is worth mentioning that during the postoperative period the ratio crystalloids/colloids administered was similar between groups.

Fourth, we had missing information on almost a quarter of the total population, but in most cases such missing data was limited to just one covariate (demographics or preoperative comorbidities). To avoid a loss in efficiency of the mixed effects models, we used a multiple imputation approach by chained equations in order to compensate for this lack of data.

## CONCLUSIONS

We found a marginal improvement of no clinical meaning in gas exchanges during the first 24 postoperative hours after OPCABG in comparison to ONCABG for elective low-risk CABG. Better  $\text{PaO}_2$  and  $\text{PaO}_2/\text{FiO}_2$  ratio was found in the OPCABG group only at ICU admission, rate of extubation differed only at the 12<sup>th</sup> postoperative hour and  $\text{PaCO}_2$  values were within normal range in both groups. Whether a population at high risk from respiratory perspectives would have benefit from OPCABG technique remains to be addressed by future studies.

### Details of authors contributions:

FC: database creation; data collection; reference management.

TT: data collection and double-check of typing errors in the database.

CC: database creation; data collection.

CS: database creation; data collection and double-check of typing errors in the database, draft editing.

StG: statistical analysis (mixed effects linear regression models, multiple imputation by chained equations); draft editing.

MA: design of the study; draft editing.

ShG: design of the study; draft editing.

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FS: design of the study; database creation; double-check of typing errors in the database; initial statistical analysis; first draft of the manuscript and final manuscript editing.

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## REFERENCES

1. Wynne R. Variable definitions: implications for the prediction of pulmonary complications after adult cardiac surgery. *Eur J Cardiovasc Nurs*. Apr 2004;3(1):43-52.
2. Filsoufi F, Rahmanian PB, Castillo JG, Chikwe J, Adams DH. Predictors and early and late outcomes of respiratory failure in contemporary cardiac surgery. *Chest*. Mar 2008;133(3):713-721.
3. Jensen L, Yang L. Risk factors for postoperative pulmonary complications in coronary artery bypass graft surgery patients. *Eur J Cardiovasc Nurs*. Sep 2007;6(3):241-246.
4. Lagow EE, Leeper BB, Jennings LW, Ramsay MA. Incidence and severity of respiratory insufficiency detected by transcutaneous carbon dioxide monitoring after cardiac surgery and intensive care unit discharge. *Proc (Bayl Univ Med Cent)*. Oct 2013;26(4):373-375.
5. Nissinen J, Biancari F, Wistbacka JO, et al. Pulmonary function and immediate and late outcome after coronary artery bypass surgery. *J Cardiovasc Surg (Torino)*. Dec 2010;51(6):915-921.
6. Santos NP, Mitsunaga RM, Borges DL, et al. Factors associated to hypoxemia in patients undergoing coronary artery bypass grafting. *Rev Bras Cir Cardiovasc*. Jul-Sep 2013;28(3):364-370.
7. Cislighi F, Condemi AM, Corona A. Predictors of prolonged mechanical ventilation in a cohort of 3,269 CABG patients. *Minerva Anestesiol*. Dec 2007;73(12):615-621.
8. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest*. Sep 1997;112(3):676-692.
9. Diegeler A, Borgermann J, Kappert U, et al. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med*. Mar 28 2013;368(13):1189-1198.
10. Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med*. Apr 19 2012;366(16):1489-1497.
11. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med*. Nov 5 2009;361(19):1827-1837.
12. Mack MJ, Pfister A, Bachand D, et al. Comparison of coronary bypass surgery with and without cardiopulmonary bypass in patients with multivessel disease. *J Thorac Cardiovasc Surg*. Jan 2004;127(1):167-173.
13. Kara I, Cakalagaoglu C, Ay Y, et al. Reoperative coronary artery bypass surgery: the role of on-pump and off-pump techniques on factors affecting hospital mortality and morbidity. *Ann Thorac Cardiovasc Surg*. 2013;19(6):435-440.
14. Sa MP, Lima LP, Rueda FG, et al. Comparative study between on-pump and off-pump coronary artery bypass graft in women. *Rev Bras Cir Cardiovasc*. Apr-Jun 2010;25(2):238-244.
15. Narayan P, Caputo M, Jones J, Al-Tai S, Angelini GD, Wilde P. Postoperative chest radiographic changes after on- and off-pump coronary surgery. *Clin Radiol*. Jun 2005;60(6):693-699.
16. Engels GE, Gu YJ, van Oeveren W, Rakhorst G, Mariani MA, Erasmus ME. The utility of lung epithelium specific biomarkers in cardiac surgery: a comparison of biomarker profiles in on- and off-pump coronary bypass surgery. *J Cardiothorac Surg*. 2013;8:4.
17. Angdin M, Settergren G, Vaage J. Better preserved pulmonary endothelium-dependent vasodilation with off-pump coronary surgery. *Scand Cardiovasc J*. Sep 2001;35(4):264-269.
18. Montes FR, Maldonado JD, Paez S, Ariza F. Off-pump versus on-pump coronary artery bypass surgery and postoperative pulmonary dysfunction. *J Cardiothorac Vasc Anesth*. Dec 2004;18(6):698-703.
19. Sanfilippo F, Chiarenza F, Cassisi C, et al. The Effects of On-Pump and Off-Pump Coronary Artery Bypass Surgery on Metabolic Profiles in the Early Postoperative Period. *J Cardiothorac Vasc Anesth*. Feb 12 2016.
20. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. Oct 2012;38(10):1573-1582.
21. Berdat PA, Muller K, Schmidli J, et al. Totally arterial off-pump vs. on-pump coronary revascularization: comparison of early outcome. *Interact Cardiovasc Thorac Surg*. Mar 2004;3(1):176-181.
22. Habib RH, Zacharias A, Engoren M. Determinants of prolonged mechanical ventilation after coronary artery bypass grafting. *Ann Thorac Surg*. Oct 1996;62(4):1164-1171.
23. Wong DT, Cheng DC, Kustra R, et al. Risk factors of delayed extubation, prolonged length of stay in the intensive care unit, and mortality in patients undergoing coronary artery bypass graft with fast-track cardiac anesthesia: a new cardiac risk score. *Anesthesiology*. Oct 1999;91(4):936-944.
24. Legare JF, Buth KJ, King S, et al. Coronary bypass surgery performed off pump does not result in lower in-hospital morbidity than coronary artery bypass grafting performed on pump. *Circulation*. Feb 24 2004;109(7):887-892.
25. Branca P, McGaw P, Light R. Factors associated with prolonged mechanical ventilation following coronary artery bypass surgery. *Chest*. Feb 2001;119(2):537-546.
26. Yende S, Wunderink R. Causes of prolonged mechanical ventilation after coronary artery bypass surgery. *Chest*. Jul 2002;122(1):245-252.
27. Al Jaaly E, Fiorentino F, Reeves BC, et al. Effect of adding postoperative noninvasive ventilation to usual care to prevent pulmonary complications in patients undergoing coronary artery bypass grafting: a randomized controlled trial. *J Thorac Cardiovasc Surg*. Oct 2013;146(4):912-918.

28. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med.* Oct 16 2007;147(8):W163-194.

Figure 1. Graph showing PaO<sub>2</sub> mean values (mmHg) at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

Figure 2. Graph showing PaO<sub>2</sub>/FiO<sub>2</sub> ratio mean values at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

Figure 3. Graph showing PaCO<sub>2</sub> mean values (mmHg) at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

Figure 4. Graph showing SaO<sub>2</sub> mean values (%) at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

Table 1. Univariate analysis of demographics co-morbidities, number of graft performed and arterial blood gases results at baseline (pre-operatively). Two populations undergoing “off-pump” and “on-pump” coronary artery bypass grafting are compared (results reported in mean and 95% Confidence Interval). Values are expressed as mean (standard deviation) or as percentages. BMI=Body mass index; RV=Right ventricle; LV= left ventricle.

Table 2. Number of patients extubated and of patients receiving respiratory non-invasive ventilation support. BiPAP: Bi-level positive airway pressure; CPAP: continuous positive airway pressure; HFO: high-flow oxygen. \*=*p*<0.05.

## The effects of on-pump and off-pump coronary artery bypass surgery on respiratory function in the early post-operative period.

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**The effects of on-pump and off-pump coronary artery bypass surgery on respiratory function in the early post-operative period.**

**ABSTRACT**

**Background:** Respiratory complications are common after cardiac surgery and the use of extracorporeal circulation is one of the main causes of lung injury. We hypothesized a better postoperative respiratory function in OFF-pump coronary-artery bypass grafting (OPCABG) as compared with “ON-pump” (ONCABG).

**Methods:** This is a retrospective, single centre study at a Cardiothoracic intensive care unit (ICU) in a Tertiary University Hospital. Consecutive data on 339 patients undergoing elective CABG (n=215 ONCABG, n=124 OPCABG) were collected for one-year from the ICU electronic medical records. We compared respiratory variables (PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, SaO<sub>2</sub> and PaCO<sub>2</sub>) at seven predefined time-points (ICU admission, 1<sup>st</sup>-3<sup>rd</sup>-6<sup>th</sup>-12<sup>th</sup>-18<sup>th</sup>-24<sup>th</sup> postoperative hour). We also evaluated time-to-extubation, rates of re-intubation and use of non-invasive ventilation (NIV). We used mixed-effects linear regression models (with time as random-effect for clustering of repeated measures) adjusted for a pre-determined set of covariates.

**Results:** The values of PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> were significantly higher in the OPCABG group only at ICU admission (mean differences: 9.7 mmHg, 95%CI 3.1-16.2; and 27, 95%CI 6.1-47.7, respectively). The OPCABG group showed higher PaCO<sub>2</sub>, overall (p=0.02) and at ICU admission (mean difference 1.8 mmHg, 95%CI 0.6-3), although mean values were always within normal range in both groups. No differences were seen in SaO<sub>2</sub> values, time-to-extubation, rate of re-intubation rate and use of postoperative NIV. Extubation rate was higher in OPCABG only at the 12<sup>th</sup> postoperative hour (92% vs ONCABG 82%, p=0.02).

**Conclusions:** OPCABG showed only marginal improvements of unlikely clinical meaning.in oxygenation as compared to ONCABG in elective low-risk patients.

**Keywords:** Cardiac surgery; intensive care; critical care; pao2 fio2 ratio; arterial blood gas.

## The effects of on-pump and off-pump coronary artery bypass surgery on respiratory function in the early post-operative period.

### INTRODUCTION

Respiratory dysfunction is common during the postoperative period after cardiac surgery and its incidence varies according to the criteria used for diagnosis<sup>1</sup>, but it can be reasonably estimated in the order of 10%<sup>2</sup>. The most common postoperative lung complications are atelectasis, pleural effusion and pneumonia<sup>3</sup> and they may persist over the first days after surgery and one study showed that incidence of hypoxia or hypercarbia 24 hours after discharge from intensive care (ICU) can be as high as 79% and 38%, respectively<sup>4</sup>.

The occurrence of pulmonary complications is affected by several factors, both preoperative lung function<sup>5</sup>, smoking history<sup>6</sup> and intra-operative factors; among the latter, lung collapse during cardiopulmonary bypass (CPB) is a key-factor in determining acute lung injury<sup>7</sup>. Moreover CPB triggers a systemic inflammatory response with a cascade of cytokines that may further exacerbate lung injury<sup>8</sup>. Off- pump coronary artery grafting (OPCABG) has been introduced with the idea of decreasing complications after cardiac surgery, in particular those related to CPB. However, three large randomized trials have shown no difference in mortality and in composite outcomes between OPCABG and the standard on-pump technique (ONCABG)<sup>9-11</sup>. The largest of such trials reported a lower 30-day incidence of respiratory failure or infection in the population undergoing OPCABG as compared with the ONCABG group<sup>10</sup>. Moreover, lower quality evidence suggests improvements of the respiratory function with OPCABG as compared with conventional on-pump approach from respiratory perspectives, as demonstrated by reduced incidence of postoperative hypoxemia<sup>12</sup>, pneumonia<sup>12</sup>, prolonged mechanical ventilation<sup>13</sup> and acute respiratory distress syndrome<sup>14</sup>, as well as decreasing the incidence of postoperative radiological changes<sup>15</sup>. One study reported also higher plasma values of lung epithelium-specific proteins (markers of lung injury) at the end of ONCABG as compared with OPCABG, although these levels returned at baseline 24 hours after surgery<sup>16</sup>, and another found a better maintained endothelium-dependent vasodilation<sup>17</sup>. On the other side Montes

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et al. found that restrictive changes of lung function happen after both ONCABG and OPCABG, with no differences between the two groups<sup>18</sup>. Since no studies have focused on a detailed course of gases exchanges after CABG, we sought to evaluate this outcome by means of the course of arterial O<sub>2</sub> pressure (PaO<sub>2</sub>), arterial carbon dioxide pressure (PaCO<sub>2</sub>) and the ratio of PaO<sub>2</sub> over the inspired fraction of oxygen (FiO<sub>2</sub> - PaO<sub>2</sub>/FiO<sub>2</sub>) over the first day spent in ICU for patient undergoing OPCABG as compared with ONCABG.

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## METHODS

This is a retrospective single centre study performed at the Oxford Heart Centre, John Radcliffe Hospital (Oxford, United Kingdom) and was registered with the Local Ethics Committee which waived the need for informed consent. We included all patients admitted to our 14-bed Cardiothoracic ICU after elective isolated CABG during a period of one-year starting from the 8<sup>th</sup> August 2012 (date of introduction of electronic medical records system). The sample size of 339 was determined by how many patients were admitted during this period. Data were extracted by four authors (FC, TT, CC, CS) and stored in a password-protected database. We already reported the results of metabolic and hemodynamic differences between OPCABG and ONCABG in this patient's population<sup>19</sup>. As previously described by our group, adult patients undergoing elective isolated CABG were divided in two populations according to the use of intraoperative CPB (ONCABG vs OPCABG). We excluded patients undergoing emergency CABG, those returning to operating room within the first 24 hours, patients with moderate and/or severe liver disease and/or with preoperative organ support as defined by: 1) mechanical (intra-aortic balloon pump – IABP) or pharmacological haemodynamic support; 2) renal support with any form of renal replacement therapy; 3) respiratory support with invasive or non-invasive ventilation (NIV).

There was no electronic medical records system for the intraoperative period and therefore we could not accurately report data for such period. As reported in our previous study, at our institution cardiac surgery cases are always led by an experienced anaesthetic consultant with at least 5 years of practice in cardiac surgery. Most of the consultants have at least basic skills in transoesophageal echocardiography, either due to their experience in cardiac anaesthesia or based on a board certification; moreover, at our hospital there is one consultant cardiologist working only in the operating room and performing echocardiogram in each patient undergoing cardiac surgery. In principle cardiac anaesthesia is conducted mostly with volatile agents (isoflurane) or more rarely with propofol. Fentanyl boluses are used to maintain analgesia; pancuronium is the choice muscle relaxant and it is given at the induction of anaesthesia in a single dose (usually between 4 and 6 mg) for the whole intervention. A warming system is connected for intravenous fluid warming in a large



bore cannula and a warming mattress is positioned under the patient. Patients are intraoperatively ventilated mostly with volume-controlled ventilation with protective tidal volumes ( $<8\text{ml/kg}$  based on ideal body weight) and a positive end-expiratory pressure (PEEP) usually set at  $5\text{ cmH}_2\text{O}$ . During CPB, all patients undergoing ONCABG are disconnected from the ventilator. At ICU arrival after surgery our policy was to set the ventilator in synchronized intermittent mandatory ventilation + pressure support modality, with a default PEEP of  $5\text{ cmH}_2\text{O}$  and tidal volumes kept in the range of  $6\text{--}8\text{ ml/kg}$  of ideal body weight.

**Database organization**

We collected the following baseline data: 1) *demographics*: age, sex, height, weight, BMI; 2) *preoperative status*: diabetes, hypertension, hypercholesterolemia, smoking history, creatinine, Euroscore II and left and right ventricular (LV and RV) systolic function; in particular, the LV systolic function was classified according to the ejection fraction as: good ( $>55\%$ ), mildly impaired ( $46\text{--}55\%$ ), moderately impaired ( $36\text{--}45\%$ ) or severely impaired ( $<35\%$ ); 3) *surgical details*: number of grafts performed.

For the interest of this study we recorded the following parameters for all patients admitted to ICU after CABG: arterial blood gases and arterial  $\text{O}_2$  saturation ( $\text{SaO}_2$ ); time to extubation and need for early re-intubation (within the first 24 hours); use of any form of NIV support after extubation within the first 24 hours. This set of parameters was collected at 7 different time-points: ICU admission and at  $1^{\text{st}}$ - $3^{\text{rd}}$ - $6^{\text{th}}$ - $12^{\text{th}}$ - $18^{\text{th}}$ - $24^{\text{th}}$  postoperative hour (choosing the closest recorded value to the established time-point).

Our primary outcomes were the differences in  $\text{PaO}_2$ ,  $\text{PaCO}_2$ ,  $\text{PaO}_2/\text{FiO}_2$  overall and at single time-points. Secondary outcomes were overall and single-time-points differences in  $\text{SaO}_2$ , time to extubation, need for NIV and for early re-intubation.

Other parameters recorded were: pH (alpha-stat method as this values was recorded in the electronic medical records system), lactate and base deficit; mean arterial pressure (MAP), central venous pressure (CVP) and haemodynamic support; postoperative pharmacological cardiovascular support;



fluid administration (crystalloids, colloids and per os fluid intake); urine output and fluid balance; administration of furosemide and sodium bicarbonates, the length of stay (LOS) and mortality in the Cardiothoracic ICU. The differences of such parameters are reported in our previous study.<sup>19</sup>

### Statistical analysis

Statistical analysis was conducted with *Stata Statistical Software: Release 14* (StataCorp. 2015, College Station, TX: StataCorp LP®). For baseline comparisons between ONCABG and OPCABG, continuous variables were compared using the Student's t-test and results presented as mean, 95% confidence interval and p-value. Categorical variables are presented as percentage and confidence interval, and the Chi-square test was used for between group comparisons.

Continuous variables that were observed multiple times in the postoperative period were analysed using mixed effects linear regression models with time as a random effect to allow for the clustering of repeated measures within the same patient. Separate models were used, one for each variable of interest (PaO<sub>2</sub>, PaCO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, FiO<sub>2</sub>, SaO<sub>2</sub>). All models were adjusted for the following covariates: age, sex, BMI, number of grafts, LV and RV systolic function, creatinine levels, smoking history, diabetes, hypertension, hypercholesterolemia and EuroSCORE II. Thirty five percent of patients included in the dataset had at least one covariate with missing information. Because these values were likely to be missing at random, and to avoid a loss in efficiency, missing values for BMI, number of grafts, creatinine, smoking history, diabetes, hypertension, hypercholesterolemia and EuroSCORE II were imputed using multiple imputation by chained equations. Twenty imputed datasets were created. Multiple imputation was performed using the mi package in *Stata Statistical Software: Release 14* (StataCorp. 2015, College Station, TX: StataCorp LP®). All tests were two-sided and a result of p-value <0.05 was considered statistically significant.

### RESULTS

A total of 363 patients underwent isolated CABG in the period of study. Of these we excluded a total of 24 patients (n=14, emergency cases; n=3, preoperative IABP; n=2, immediate return to operating room for suspected bleeding; n=4, mini-invasive CABG; n=1, preoperative dialysis). Among the 339 patients included in the study, 63.4% (n=215) underwent ONCABG and the remaining had OPCABG (36.6%, n=124). The vast majority of OPCABG cases (n=119/124, 96%) were performed by two cardiac surgeon consultants. The characteristics of the two groups were similar with the only exceptions of higher number of patients with hypercholesterolemia and number of grafts performed in the ONCABG group; there was also a trend towards more patients with good RV systolic function in the OPCABG group (Table 1).

We found no differences in the overall course of PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> (Figure 1 and 2, respectively) although significant differences were found at ICU admission, when OPCABG group showed significantly higher PaO<sub>2</sub> (mean difference - MD - 9.7 mmHg, 95%CI 3.1-16.2), and PaO<sub>2</sub>/FiO<sub>2</sub> (MD 27, 95%CI 6.1-47.7). The course of overall PaCO<sub>2</sub> showed higher (although always within normal range) values in the OPCABG group (Figure 3, p=0.02). The only significant difference in PaCO<sub>2</sub> was found at ICU admission (MD 1.8 mmHg, 95%CI 0.6-3), with also a trend towards higher PaCO<sub>2</sub> values at the 1<sup>st</sup>, 3<sup>rd</sup>, 18<sup>th</sup> and 24<sup>th</sup> postoperative hour (MD between 1 and 2 mmHg, all p=0.05-0.08). No differences in SaO<sub>2</sub> values over the course of the first 24 hours spent in ICU were seen (Figure 4). The results of the overall and single time-points differences for PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, PaCO<sub>2</sub> and SaO<sub>2</sub> is available as supplemental digital content 1 (for PaO<sub>2</sub> and PaCO<sub>2</sub> values are provided both in mmHg and in kPa).

The mean time to extubation was similar between groups OPCABG and ONCABG (7.0±14 vs 7.8±15.7 hours respectively, p=0.63). No patients required re-intubation in the OPCABG vs four in the ONCABG group (0% vs 2% respectively, p=0.31). The number of patients extubated at all time-points was similar between groups, except at the 12<sup>th</sup> postoperative hour when OPCABG showed better results (n=110/124, 92% vs ONCABG n=172/215, 82%, p=0.02), and no difference were found in the postoperative use of NIV between groups (Table 2).

With regards to other variables of interest for the evaluation of respiratory outcomes, we already reported in our previous study<sup>19</sup> the results of a mixed effects model analysis. In that study we found similar pH values and overall fluid balance between the ONPABG and OPCABG groups at all time-points, with also a similar crystalloids/colloids ratio between groups. The urine output was significantly higher in the OPCABG both in the overall comparison ( $p=0.02$ ) and at the 3<sup>rd</sup>, 6<sup>th</sup>, 12<sup>th</sup> and 24<sup>th</sup> postoperative hour while diuretic therapy was similar between groups.

## DISCUSSION

The performance of OPCABG surgery has received a lot of scrutiny with three large randomized trials showing no benefit in mortality as compared with the traditional on-pump technique<sup>9-11</sup>. We aimed at extending the knowledge on potential respiratory benefits of OPCABG, evaluating the course of gas exchanges over the first day spent in the ICU since no studies has yet focused on a detailed sequential postoperative course. To our knowledge this is the first study comparing serial differences in the postoperative respiratory profile between OPCABG and ONCABG surgery.

We found similar values in oxygenation both overall and at most time-points. Small differences were seen at ICU admission, however this result should be interpreted with caution since during the route to Cardiac ICU the patient is ventilated with a bag-mask, and such approach may have caused inhomogeneity in the ventilation between patients and thus on the arterial blood gas at ICU admission. Moreover, such differences seem very marginal from a clinical perspective. Indeed, the mean differences in PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> ratio favouring the OPCABG group at ICU admission were in the region of 10 mmHg and 27 ratio, respectively.

An interesting finding of our study is that during the first postoperative day the PaO<sub>2</sub>/FiO<sub>2</sub> ratio maintained values within the range of acute lung injury<sup>20</sup>, confirming the presence of a lung insult even in elective low-risk patients undergoing cardiac surgery regardless of the use of CPB as already shown by Montes et al.<sup>18</sup>. Whether the difference in the postoperative course of respiratory variables would have been larger in a population at higher risk (such as more-than-mild chronic obstructive pulmonary disease, emergency CABG, patients intubated before surgery, etc) cannot be

addressed by the present study. For instance, a large retrospective analysis conducted in patients undergoing re-do cardiac surgery, OPCABG significantly reduced the incidence of pulmonary complications (4.1% vs 9.5% in the ONCABG group)<sup>12</sup>. On the other side, a smaller study on totally arterial coronary grafts found a trend towards higher degree of respiratory complications in the OPCABG group. The same study found a shorter ventilator support after OPCABG<sup>21</sup>.

The values of PaO<sub>2</sub>/FiO<sub>2</sub> ratio gradually improved in our cohort of patients and this finding is similar to those of Montes et al. that reported a nadir of PaO<sub>2</sub>/FiO<sub>2</sub> ratio at ICU arrival gradually recovering after surgery<sup>18</sup>. Although these authors did not find differences between ON vs OPCABG at ICU arrival, the clinical meaning of a better PaO<sub>2</sub>/FiO<sub>2</sub> ratio immediately after surgery in OPCABG patients reported by our study remains unremarkable from clinical perspectives. Moreover, Montes et al. found restrictive changes in pulmonary function assessed by spirometry both in OPCABG and ONCABG, without differences between groups. In particular, forced expiratory volume in one second and forced vital capacity significantly decreased from ~90% of predicted values to ~50% (with unchanged ratio) 72 hours after surgery, and similarly behaved total lung capacity, dropping from ~105% to ~70%<sup>18</sup>.

The PaCO<sub>2</sub> showed higher values overall and at ICU admission in the OPCABG group but with a mean difference in the range of ~2 mmHg, together with a trend towards lower values at the 1<sup>st</sup>, 3<sup>rd</sup>, 18<sup>th</sup> and 24<sup>th</sup> hours. However, both groups had always mean PaCO<sub>2</sub> values within the normal range, again supporting the presence of only mild lung injury after low-risk cardiac surgery.

In our ICU we have a standardized protocol aiming at early extubation, and we found a difference in time to extubation only at the 12<sup>th</sup> postoperative hour. Importantly, the mean time of extubation in both groups was less than the 8-10 hours cut-off usually investigated<sup>22, 23</sup>, and over 85% and 96% of the whole population extubated by the 12<sup>th</sup> and 24<sup>th</sup> postoperative hour respectively, thus confirming both the low risk population of patients. Similar time to extubation for the two CABG techniques has been already shown<sup>24</sup>, but it is important to note that we investigated a low-risk population and our findings should not be expanded to high-risk patients. In this respect, a small study on re-do CABG showed a beneficial effect of OPCABG in decreasing the occurrence of

prolonged mechanical ventilation (PMV) as compared with ONCABG<sup>13</sup>. Nonetheless there is no full concordance on the association between type of cardiac surgical procedure and PMV: one large study conducted on over 4800 patients found that CABG associated to valve surgery was an independent predictor of PMV<sup>25</sup>, while a smaller one (400 patients) did not identify the type of surgery as a factor linked to postoperative PMV<sup>26</sup>.

We also showed no differences in the rate of reintubation between groups, supporting again a good standardized practice with regards to extubation and that postoperative lung injury between groups was similar. Among the four cases of re-intubation, half were not due to respiratory failure (a severe upper gastrointestinal bleeding between after the 18<sup>th</sup> postoperative hour, and a cardiovascular collapse after the 12<sup>th</sup> postoperative hour). The remaining two cases were due to isolated hypoxemic respiratory failure and occurred after the 3<sup>rd</sup> and after the 12<sup>th</sup> postoperative hour respectively. In one of the latter cases, continuous positive airway pressure was unsuccessfully attempted before reintubation.

Also, the similar utilization of postoperative NIV between groups throughout the whole period of study confirms similar degree of lung injury from clinical perspectives and the higher rate of extubation at the 12<sup>th</sup> hour in the OPCABG should be interpreted as a marginal finding in the context of the other results of our study. In one study, the preventive and prolonged (median 16 hours) use of bi-level NIV after extubation of CABG patients significantly reduced hospital LOS and rate of basal atelectasis as compared with standard care<sup>27</sup>; however, in our population it was more frequent the use of continuous positive airway pressure ventilation (up to overall 8% at 24<sup>th</sup> postoperative hour) as compared with the use of bi-level positive airways pressure which was almost unremarkable. This finding is in agreement with deranged PaO<sub>2</sub>/FiO<sub>2</sub> ratio associated to normal PaCO<sub>2</sub> values.

### ***Strengths and limitations***

The strength of this study are mainly the relatively large sample size investigated for the outcome of interest, the electronic data collected during the postoperative period and the statistical approach

allowing for clustering of data at different time-points, and adjusted for several covariates. With regards to the sample size of our observational study, a calculation was not performed in line with the STROBE guidelines for reporting of observational studies<sup>28</sup>. Of note, the 95% CIs were reasonably small and this supports that our sample size was adequate. Nonetheless, even if the sample size of our investigation is relatively large, we analysed a low-risk population and therefore the analysis of certain outcomes such as mortality is probably underpowered.

This study has several limitations. First, it is a single centre study at a University teaching hospital and, although baseline characteristics in the two groups were similar, it was not a randomized study and by definition the retrospective design is potentially subject to biases. However we used electronically collected data and this minimizes the risk of a “recall bias” which is a usual limitation of retrospective studies needing subjective measurements. Indeed, data were accurately downloaded from fully electronic medical charts and the even distribution of preoperative variables (apart from hypercholesterolemia and RV dysfunction) supports that groups were highly comparable at baseline. The difference in number of grafts performed between the two populations is not surprising and incomplete revascularization is a clear challenge for OPCABG technique as shown in the major randomized controlled trials<sup>9-11</sup>.

Second, our study lacks of systematic data on patient’s preoperative and postoperative lung function tests. However such deficiency is reasonable since we investigated a low risk population undergoing cardiac surgery with a mean Euroscore II around 4 points, and performing routine spirometry is not currently recommended in this class of patients. For this reason we could not reliably investigate the presence of chronic obstructive pulmonary disease nor staging it according to the Gold criteria. Our study also misses a systematic evaluation of radiological changes in chest-X ray after surgery. In this regards, one study found a higher mechanical ventilation time and a higher incidence of left band atelectasis in the ONCABG group at 6 days postoperatively as compared with OPCABG<sup>15</sup>.

Third, as no electronic medical records system was available for the intraoperative period, we could not analyse intraoperative data, especially with regards to length of surgery and ventilation strategy

- although this is strongly standardized at our institution. Our analysis lacks also of data on intraoperative fluid administration but is worth mentioning that during the postoperative period the ratio crystalloids/colloids administered was similar between groups.

Fourth, we had missing information on almost a quarter of the total population, but in most cases such missing data was limited to just one covariate (demographics or preoperative comorbidities). To avoid a loss in efficiency of the mixed effects models, we used a multiple imputation approach by chained equations in order to compensate for this lack of data.

## CONCLUSIONS

We found a marginal improvement of no clinical meaning in gas exchanges during the first 24 postoperative hours after OPCABG in comparison to ONCABG for elective low-risk CABG. Better  $\text{PaO}_2$  and  $\text{PaO}_2/\text{FiO}_2$  ratio was found in the OPCABG group only at ICU admission, rate of extubation differed only at the 12<sup>th</sup> postoperative hour and  $\text{PaCO}_2$  values were within normal range in both groups. Whether a population at high risk from respiratory perspectives would have benefit from OPCABG technique remains to be addressed by future studies.

### Details of authors contributions:

FC: database creation; data collection; reference management.

TT: data collection and double-check of typing errors in the database.

CC: database creation; data collection.

CS: database creation; data collection and double-check of typing errors in the database, draft editing.

StG: statistical analysis (mixed effects linear regression models, multiple imputation by chained equations); draft editing.

MA: design of the study; draft editing.

ShG: design of the study; draft editing.

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FS: design of the study; database creation; double-check of typing errors in the database; initial statistical analysis; first draft of the manuscript and final manuscript editing.

For Peer Review



## REFERENCES

1. Wynne R. Variable definitions: implications for the prediction of pulmonary complications after adult cardiac surgery. *Eur J Cardiovasc Nurs*. Apr 2004;3(1):43-52.
2. Filsoufi F, Rahmanian PB, Castillo JG, Chikwe J, Adams DH. Predictors and early and late outcomes of respiratory failure in contemporary cardiac surgery. *Chest*. Mar 2008;133(3):713-721.
3. Jensen L, Yang L. Risk factors for postoperative pulmonary complications in coronary artery bypass graft surgery patients. *Eur J Cardiovasc Nurs*. Sep 2007;6(3):241-246.
4. Lagow EE, Leeper BB, Jennings LW, Ramsay MA. Incidence and severity of respiratory insufficiency detected by transcutaneous carbon dioxide monitoring after cardiac surgery and intensive care unit discharge. *Proc (Bayl Univ Med Cent)*. Oct 2013;26(4):373-375.
5. Nissinen J, Biancari F, Wistbacka JO, et al. Pulmonary function and immediate and late outcome after coronary artery bypass surgery. *J Cardiovasc Surg (Torino)*. Dec 2010;51(6):915-921.
6. Santos NP, Mitsunaga RM, Borges DL, et al. Factors associated to hypoxemia in patients undergoing coronary artery bypass grafting. *Rev Bras Cir Cardiovasc*. Jul-Sep 2013;28(3):364-370.
7. Cislighi F, Condemi AM, Corona A. Predictors of prolonged mechanical ventilation in a cohort of 3,269 CABG patients. *Minerva Anesthesiol*. Dec 2007;73(12):615-621.
8. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest*. Sep 1997;112(3):676-692.
9. Diegeler A, Borgermann J, Kappert U, et al. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med*. Mar 28 2013;368(13):1189-1198.
10. Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med*. Apr 19 2012;366(16):1489-1497.
11. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med*. Nov 5 2009;361(19):1827-1837.
12. Mack MJ, Pfister A, Bachand D, et al. Comparison of coronary bypass surgery with and without cardiopulmonary bypass in patients with multivessel disease. *J Thorac Cardiovasc Surg*. Jan 2004;127(1):167-173.
13. Kara I, Cakalagaoglu C, Ay Y, et al. Reoperative coronary artery bypass surgery: the role of on-pump and off-pump techniques on factors affecting hospital mortality and morbidity. *Ann Thorac Cardiovasc Surg*. 2013;19(6):435-440.
14. Sa MP, Lima LP, Rueda FG, et al. Comparative study between on-pump and off-pump coronary artery bypass graft in women. *Rev Bras Cir Cardiovasc*. Apr-Jun 2010;25(2):238-244.
15. Narayan P, Caputo M, Jones J, Al-Tai S, Angelini GD, Wilde P. Postoperative chest radiographic changes after on- and off-pump coronary surgery. *Clin Radiol*. Jun 2005;60(6):693-699.
16. Engels GE, Gu YJ, van Oeveren W, Rakhorst G, Mariani MA, Erasmus ME. The utility of lung epithelium specific biomarkers in cardiac surgery: a comparison of biomarker profiles in on- and off-pump coronary bypass surgery. *J Cardiothorac Surg*. 2013;8:4.
17. Angdin M, Settergren G, Vaage J. Better preserved pulmonary endothelium-dependent vasodilation with off-pump coronary surgery. *Scand Cardiovasc J*. Sep 2001;35(4):264-269.
18. Montes FR, Maldonado JD, Paez S, Ariza F. Off-pump versus on-pump coronary artery bypass surgery and postoperative pulmonary dysfunction. *J Cardiothorac Vasc Anesth*. Dec 2004;18(6):698-703.
19. Sanfilippo F, Chiarenza F, Cassisi C, et al. The Effects of On-Pump and Off-Pump Coronary Artery Bypass Surgery on Metabolic Profiles in the Early Postoperative Period. *J Cardiothorac Vasc Anesth*. Feb 12 2016.
20. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. Oct 2012;38(10):1573-1582.
21. Berdat PA, Muller K, Schmidli J, et al. Totally arterial off-pump vs. on-pump coronary revascularization: comparison of early outcome. *Interact Cardiovasc Thorac Surg*. Mar 2004;3(1):176-181.
22. Habib RH, Zacharias A, Engoren M. Determinants of prolonged mechanical ventilation after coronary artery bypass grafting. *Ann Thorac Surg*. Oct 1996;62(4):1164-1171.
23. Wong DT, Cheng DC, Kustra R, et al. Risk factors of delayed extubation, prolonged length of stay in the intensive care unit, and mortality in patients undergoing coronary artery bypass graft with fast-track cardiac anesthesia: a new cardiac risk score. *Anesthesiology*. Oct 1999;91(4):936-944.
24. Legare JF, Buth KJ, King S, et al. Coronary bypass surgery performed off pump does not result in lower in-hospital morbidity than coronary artery bypass grafting performed on pump. *Circulation*. Feb 24 2004;109(7):887-892.
25. Branca P, McGaw P, Light R. Factors associated with prolonged mechanical ventilation following coronary artery bypass surgery. *Chest*. Feb 2001;119(2):537-546.
26. Yende S, Wunderink R. Causes of prolonged mechanical ventilation after coronary artery bypass surgery. *Chest*. Jul 2002;122(1):245-252.
27. Al Jaaly E, Fiorentino F, Reeves BC, et al. Effect of adding postoperative noninvasive ventilation to usual care to prevent pulmonary complications in patients undergoing coronary artery bypass grafting: a randomized controlled trial. *J Thorac Cardiovasc Surg*. Oct 2013;146(4):912-918.

28. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med.* Oct 16 2007;147(8):W163-194.

Figure 1. Graph showing PaO<sub>2</sub> mean values (mmHg) at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

Figure 2. Graph showing PaO<sub>2</sub>/FiO<sub>2</sub> ratio mean values at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

Figure 3. Graph showing PaCO<sub>2</sub> mean values (mmHg) at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

Figure 4. Graph showing SaO<sub>2</sub> mean values (%) at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

Table 1. Univariate analysis of demographics co-morbidities, number of graft performed and arterial blood gases results at baseline (pre-operatively). Two populations undergoing “off-pump” and “on-pump” coronary artery bypass grafting are compared (results reported in mean and 95% Confidence Interval). Values are expressed as mean (standard deviation) or as percentages. BMI=Body mass index; RV=Right ventricle; LV= left ventricle.

Table 2. Number of patients extubated and of patients receiving respiratory non-invasive ventilation support. BiPAP: Bi-level positive airway pressure; CPAP: continuous positive airway pressure; HFO: high-flow oxygen. \*=p<0.05.

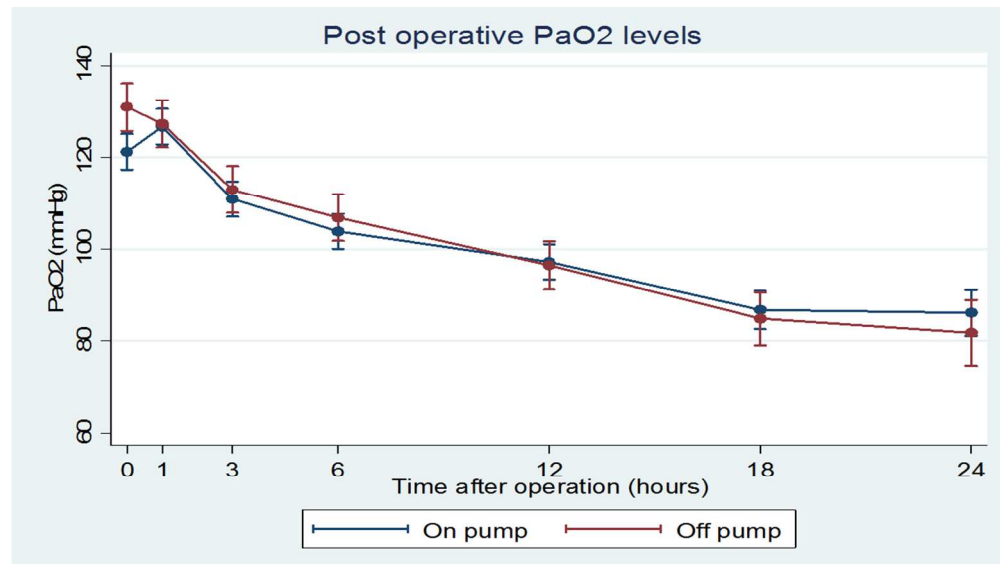


Figure 1. Graph showing PaO<sub>2</sub> mean values (mmHg) at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

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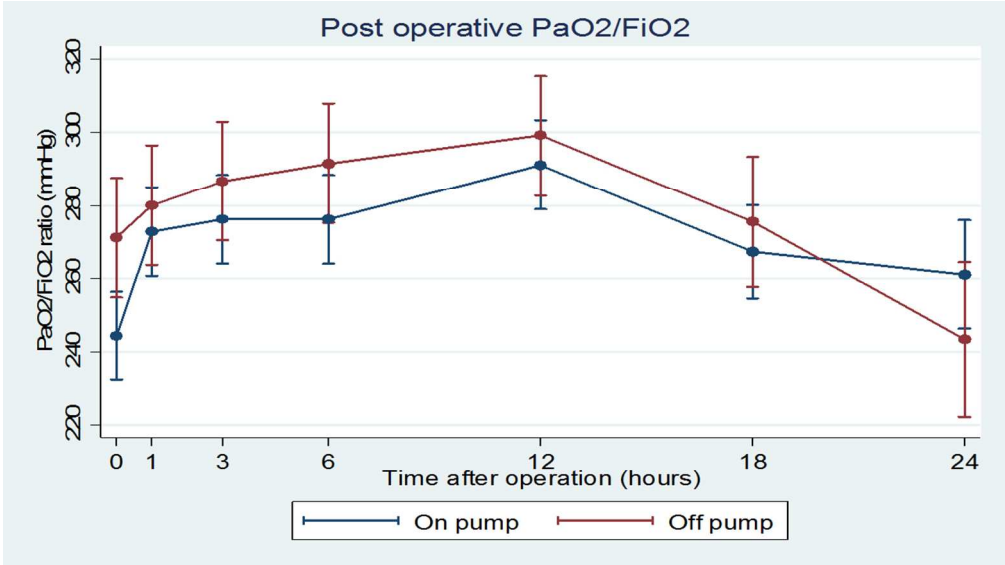


Figure 2. Graph showing PaO2/FiO2 ratio mean values at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

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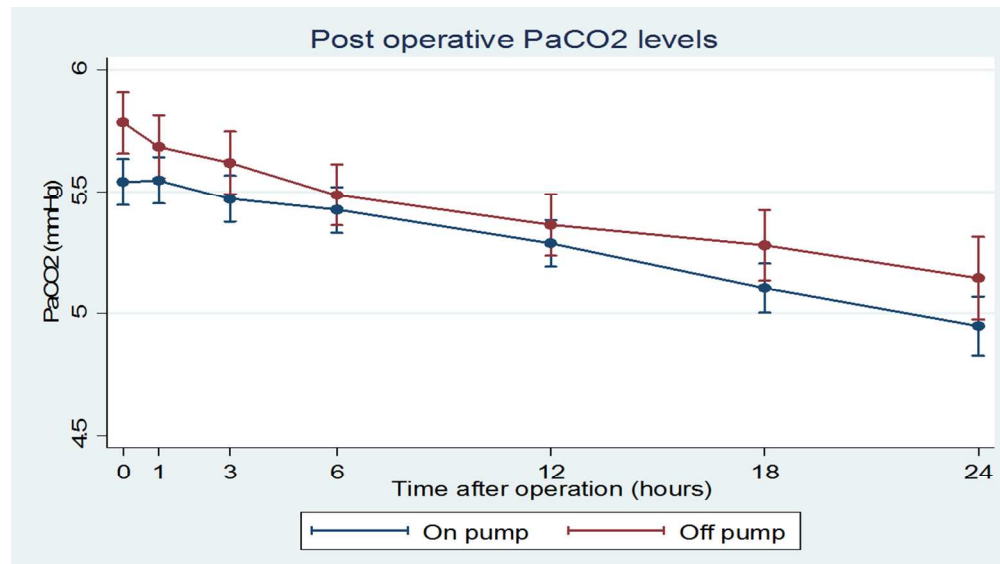


Figure 3. Graph showing PaCO<sub>2</sub> mean values (mmHg) at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

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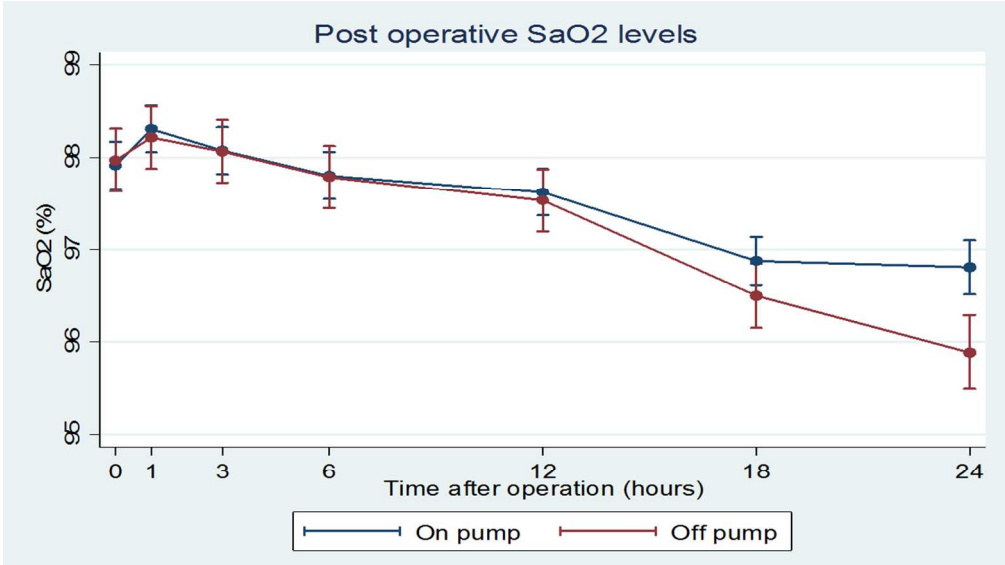


Figure 4. Graph showing SaO2 mean values (%) at each postoperative time-point starting from the time of admission to ICU, along with 95% confidence interval in two populations, on- and off-pump coronary artery bypass grafting. Results are from mixed effects linear regression models.

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	On-pump	Off-pump	p-value
Age (years)	66 (65.0, 67.6)	67.0 (65.3, 68.8)	0.49
Males (%)	87.0 (85.2, 88.6)	81.5 (78.7, 84.0)	0.17
Height (cm)	172.0 (170.8, 173.2)	171.4 (169.9, 172.9)	0.56
Weight (kg)	85.6 (83.4, 87.8)	85.0 (82.3, 87.7)	0.71
BMI (Kg/m <sup>2</sup> )	28.9 (28.3, 29.5)	28.9 (28.0, 29.8)	0.97
Hypertension (%)	74.9 (72.5, 77.1)	72.5 (69.3, 75.5)	0.64
Creatinine (μmol/L)	88.1 (84.4, 91.8)	91.1 (84.5, 97.6)	0.40
Diabetes (%)	29.9 (27.5, 32.3)	27.9 (24.9, 31.0)	0.70
Hypercholesterolemia (%)	86.4 (84.3, 88.3)	74.2 (70.8, 77.5)	<b>0.01</b>
Actual smoker (%)	18.7 (16.6, 20.9)	19.3 (16.6, 22.2)	0.90
Ex-smoker (%)	47.6 (44.9, 50.3)	53.5 (50.0, 57.0)	0.32
Good RV systolic function (%)	95.4 (94.2, 96.4)	99.2 (98.3, 99.7)	0.05
Good LV systolic function (%)	86.5 (84.7, 88.2)	89.5 (87.3, 91.5)	0.42
Euroscore II	4.0 (3.4, 4.5)	4.3 (3.3, 5.3)	0.53
Number of grafts performed	3.0 (2.9, 3.1)	2.4 (2.3, 2.5)	<b>&lt;0.01</b>
Pre-operative lactate (mmol/L)	1.3 (1.2, 1.4)	1.3 (1.2, 1.4)	0.69
Pre-operative base deficit	-0.1 (-0.3, 0.2)	0.2 (-0.2, 0.6)	0.25
Pre-operative pH	7.4 (7.4, 7.4)	7.4 (7.4, 7.4)	0.65
Pre-operative chloride (mmol/L)	108.3 (107.8, 108.8)	108.7 (108.0, 109.4)	0.39

*Table 1. Univariate analysis of demographics co-morbidities, number of graft performed and arterial blood gases results at baseline (pre-operatively). Two populations undergoing “off-pump” and “on-pump” coronary artery bypass grafting are compared (results reported in mean and 95% Confidence Interval). Values are expressed as mean (standard deviation) or as percentages. BMI=Body mass index; RV=Right ventricle; LV= left ventricle.*

	Postop. Hour Group	3 <sup>rd</sup> n (%)	6 <sup>th</sup> n (%)	12 <sup>th</sup> n (%)	18 <sup>th</sup> n (%)	24 <sup>th</sup> n (%)
Patients extubated	ONCABG (n=215)	44 (20%)	125 (58%)	176 (82%)*	195 (91%)	204 (95%)
	OPCABG (n=124)	17 (14%)	82 (66%)	114 (92%)*	119 (96%)	122 (98%)
CPAP or HFO	ONCABG (n=215)	2 (0.9%)	6 (2.8%)	11 (5.1%)	13 (6.0%)	20 (9.3%)
	OPCABG (n=124)	2 (1.6%)	2 (1.6%)	5 (4.0%)	8 (6.4%)	9 (7.3%)
BiPAP	ONCABG (n=215)	3 (1.4%)	0	1 (0.5%)	0	1 (0.5%)
	OPCABG (n=124)	0	0	0	1 (0.8%)	0

Table 2. Number of patients extubated and of patients receiving respiratory non-invasive ventilation support. BiPAP: Bi-level positive airway pressure; CPAP: continuous positive airway pressure; HFO: high-flow oxygen. \*=p<0.05.



PaO <sub>2</sub> (mmHg) levels	On pump Mean (95% CI)	Off pump Mean (95% CI)	Difference (95% CI)	Overall p-value
ICU admission	121 (117, 125)	131 (126, 136)	9.7 (3.1, 16.3)	0.441
1 <sup>st</sup> postoperative hour	127 (123, 131)	127 (122, 133)	0.7 (-5.8, 7.3)	
3 <sup>rd</sup> postoperative hour	111 (107, 115)	113 (108, 118)	2.1 (-4.4, 8.6)	
6 <sup>th</sup> postoperative hour	104 (100, 108)	107 (102, 112)	3.0 (-3.5, 9.5)	
12 <sup>th</sup> postoperative hour	97 (93, 101)	96 (91, 102)	-0.8 (-7.3, 5.8)	
18 <sup>th</sup> postoperative hour	87 (83, 91)	85 (79, 91)	-1.9 (-9.1, 5.3)	
24 <sup>th</sup> postoperative hour	86 (81, 91)	82 (75, 89)	-4.3 (-13.2, 4.5)	

PaO <sub>2</sub> (kPa) levels	On pump Mean (95% CI)	Off pump Mean (95% CI)	Difference (95% CI)	Overall p-value
ICU admission	16.2 (15.6, 16.7)	17.5 (16.7, 18.1)	1.3 (0.4, 2.2)	0.441
1 <sup>st</sup> postoperative hour	16.9 (16.4, 17.4)	17.0 (16.3, 17.7)	0.1 (-0.8, 1.0)	
3 <sup>rd</sup> postoperative hour	14.8 (14.3, 15.3)	15.1 (14.4, 15.7)	0.3 (-0.6, 1.1)	
6 <sup>th</sup> postoperative hour	13.9 (13.34, 14.37)	14.3 (13.6, 14.9)	0.4 (-0.5, 1.3)	
12 <sup>th</sup> postoperative hour	13.0 (12.4, 13.5)	12.9 (12.2, 13.5)	-0.1 (-1.0, 0.8)	
18 <sup>th</sup> postoperative hour	11.6 (11.0, 12.1)	11.3 (10.5, 12.1)	-0.2 (-1.2, 0.7)	
24 <sup>th</sup> postoperative hour	11.5 (10.8, 12.1)	10.9 (9.9, 11.9)	-0.6 (-1.8, 0.6)	

**Supplemental Digital Content 1 and 2. Comparison of PaO<sub>2</sub> (values shown in mmHg or in kPa) between on- and off-pump at each postoperative time-point. Results are from a mixed effects linear regression model taking into account the repeated measures, adjusting for age, sex, BMI, number of grafts, LV and RV systolic function, creatinine levels, smoking history, diabetes, hypertension, hypercholesterolemia and EuroSCORE II. The p-value represents the overall comparison between on and off pump, and shows whether or not the difference shown here is significant or not. ICU=intensive care unit.**

PaO <sub>2</sub> /FiO <sub>2</sub> ratio	On pump Mean (95% CI)	Off pump Mean (95% CI)	Difference (95% CI)	Overall p-value
ICU admission	244 (232, 256)	271 (255, 288)	26.9 (6.1, 47.7)	0.212
1 <sup>st</sup> postoperative hour	273 (261, 285)	280 (264, 296)	7.2 (-13.7, 28.0)	
3 <sup>rd</sup> postoperative hour	276 (264, 288)	287 (270, 303)	10.4 (-10.2, 31.1)	
6 <sup>th</sup> postoperative hour	276 (264, 288)	291 (275, 308)	15.3 (-5.4, 36.0)	
12 <sup>th</sup> postoperative hour	291 (279, 303)	299 (283, 315)	8.1 (-12.7, 28.9)	
18 <sup>th</sup> postoperative hour	267 (255, 280)	275 (258, 293)	8.1 (-14.2, 30.4)	
24 <sup>th</sup> postoperative hour	261 (246, 276)	243 (222, 264)	-17.8 (-44.0, 8.4)	

**Supplemental Digital Content 3. Comparison of PaO<sub>2</sub>/FiO<sub>2</sub> ratio between on- and off-pump at each postoperative time-point. Results are from a mixed effects linear regression model taking into account the repeated measures, adjusting for age, sex, BMI, number of grafts, LV and RV systolic function, creatinine levels, smoking history, diabetes, hypertension, hypercholesterolemia and EuroSCORE II. The p-value represents the overall comparison between on and off pump, and shows whether or not the difference shown here is significant or not. ICU=intensive care unit.**

PaCO <sub>2</sub> (kPa) levels	On pump Mean (95% CI)	Off pump Mean (95% CI)	Difference (95% CI)	Overall p-value
ICU admission	5.5 (5.4, 5.6)	5.8 (5.7, 5.9)	0.2 (0.1, 0.4)	0.016
1 <sup>st</sup> postoperative hour	5.5 (5.4, 5.6)	5.7 (5.6, 5.8)	0.1 (-0.0, 0.3)	
3 <sup>rd</sup> postoperative hour	5.5 (5.4, 5.6)	5.6 (5.5, 5.7)	0.1 (-0.0, 0.3)	
6 <sup>th</sup> postoperative hour	5.4 (5.3, 5.5)	5.5 (5.4, 5.6)	0.1 (-0.1, 0.2)	
12 <sup>th</sup> postoperative hour	5.3 (5.2, 5.4)	5.4 (5.2, 5.5)	0.1 (-0.1, 0.2)	
18 <sup>th</sup> postoperative hour	5.1 (5.0, 5.2)	5.3 (5.1, 5.4)	0.2 (0.0, 0.3)	
24 <sup>th</sup> postoperative hour	4.9 (4.8, 5.1)	5.1 (5.0, 5.3)	0.2 (-0.0, 0.4)	

PaCO <sub>2</sub> (mmHg) levels	On pump Mean (95% CI)	Off pump Mean (95% CI)	Difference (95% CI)	Overall p-value
ICU admission	41 (41, 42)	43 (42, 44)	1.8 (0.6, 3.0)	0.016
1 <sup>st</sup> postoperative hour	42 (41, 42)	43 (42, 44)	1.0 (-0.2, 2.2)	
3 <sup>rd</sup> postoperative hour	41 (40, 42)	41 (41, 43)	1.1 (-0.8, 2.3)	
6 <sup>th</sup> postoperative hour	41 (40, 41)	41 (40, 42)	0.4 (-0.7, 1.6)	
12 <sup>th</sup> postoperative hour	40 (39, 40)	40 (39, 41)	0.6 (-0.7, 1.8)	
18 <sup>th</sup> postoperative hour	38 (37, 39)	40 (38, 41)	1.3 (0.0, 2.6)	
24 <sup>th</sup> postoperative hour	37 (36, 38)	39 (37, 40)	1.5 (-0.8, 3.8)	

**Supplemental Digital Content 4 and 5. Comparison of PaCO<sub>2</sub> (values shown in mmHg or in kPa) between on- and off-pump at each postoperative time-point. Results are from a mixed effects linear regression model taking into account the repeated measures, adjusting for age, sex, BMI, number of grafts, LV and RV systolic function, creatinine levels, smoking history, diabetes, hypertension, hypercholesterolemia and EuroSCORE II. The p-value represents the overall comparison between on and off pump, and shows whether or not the difference shown here is significant or not. ICU=intensive care unit.**

SaO <sub>2</sub> (%) levels	On pump Mean (95% CI)	Off pump Mean (95% CI)	Difference (95% CI)	Overall p-value
ICU admission	98 (97.7, 98.2)	98 (97.6, 98.3)	0.1 (-0.4, 0.5)	0.228
1 <sup>st</sup> postoperative hour	98 (98.0, 98.6)	98 (97.9, 98.5)	-0.1 (-0.5, 0.3)	
3 <sup>rd</sup> postoperative hour	98 (97.8, 98.3)	98 (97.7, 98.4)	-0.0 (-0.4, 0.4)	
6 <sup>th</sup> postoperative hour	98 (97.6, 98.1)	98 (97.4, 98.1)	-0.0 (-0.4, 0.4)	
12 <sup>th</sup> postoperative hour	98 (97.4, 97.9)	97 (97.2, 97.9)	-0.1 (-0.5, 0.3)	
18 <sup>th</sup> postoperative hour	97 (96.6, 97.1)	96 (96.2, 96.8)	-0.4 (-0.8, 0.1)	
24 <sup>th</sup> postoperative hour	97 (96.5, 97.1)	96 (95.5, 96.3)	-0.9 (-1.4, -0.4)	

**Supplemental Digital Content 6. Comparison of SaO<sub>2</sub> values between on- and off-pump at each postoperative time-point. Results are from a mixed effects linear regression model taking into account the repeated measures, adjusting for age, sex, BMI, number of grafts, LV and RV systolic function, creatinine levels, smoking history, diabetes, hypertension, hypercholesterolemia and EuroSCORE II. The p-value represents the overall comparison between on and off pump, and shows whether or not the difference shown here is significant or not. ICU=intensive care unit.**