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Published in:
Acta Anaesthesiologica Scandinavica

DOI:
10.1111/aas.13457

Publication date:
2019

Document version:
Accepted manuscript

Citation for pulished version (APA):
Rasmussen, S. R., Kandler, K., Nielsen, R. V., Cornelius Jakobsen, P., Knudsen, N. N., Ranucci, M., Christian Nilsson, J., & Ravn, H. B. (2019). Duration of critically low oxygen delivery is associated with acute kidney injury after cardiac surgery. *Acta Anaesthesiologica Scandinavica*, *63*(10), 1290-1297. https://doi.org/10.1111/aas.13457

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Article type : Clinical investigation

TITLE PAGE

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Short title: Oxygen delivery and acute kidney injury

Word count: 4619

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Abstract

Background. Acute kidney injury is a serious complication following cardiac surgery associated with mortality. Restricted oxygen delivery is a potential risk factor for acute kidney injury. The aim of this study was to investigate the impact of the duration of low oxygen delivery (<272 mL· min^{-1}·m^{-2}), during cardiopulmonary bypass on kidney function.

Methods. Patients undergoing coronary artery bypass graft surgery ± valve repair were included n=1968. Oxygen delivery was monitored during cardiopulmonary bypass. Data were explored using multiple regression analyses regarding association between low oxygen delivery and renal replacement therapy (RRT), acute kidney injury (AKI) and postoperative peak serum creatinine (PPSC).

Results. Postoperative peak serum creatinine, incidence of acute kidney injury, and need for dialysis increased in a dose-dependent manner in relation to duration of a mean oxygen delivery <272 mL· min^{-1}·m^{-2}. Using multiple regression analyses only exposure for at least 30 minutes was independently associated with increased PPSC and AKI. In contrast, both short (1-5 min, OR: 2.58 [1.20, 5.54]; p=0.015) and at least 30 min (OR: 2.85 [1.27-6.41]; p=0.011) exposure to low DO_2 were both independently associated with the need for RRT.

Conclusion. A low oxygen delivery during cardiopulmonary bypass was in a dose-dependent manner associated with an increased risk of renal injury.

Editorial Comment:

Acute kidney injury occurs post-operatively in some cardiac surgery patients. In this single-centre retrospective analysis, both brief and longer exposures to total oxygen delivery below 272 ml min-1 m2 on cardiopulmonary bypass were associated with increased risk for acute kidney injury.

Introduction

Cardiac surgery-associated acute kidney injury (AKI) is a serious complication following heart surgery[1,2]. Large observational studies have described AKI frequencies ranging from 20-50 % in cardiac surgery patients, and this complication is associated with an increased risk of prolonged hospital stay, morbidity, and mortality[3-5]. Even a minor increase in postoperative serum creatinine (sCr) is associated with an increase in morbidity and mortality[6,7].

The aetiology of AKI after cardiac surgery is multifactorial. Numerous pre- and intraoperative risk factors have been identified, including age, sex, nephrotoxic agents, drugs, haemodilution, red blood cell (RBC) transfusions and comorbidities such as chronic kidney disease (CKD), diabetes mellitus and chronic obstructive lung disease (COLD)[8-10]. Only a few of these risk factors are modifiable. In this respect, intraoperative amendable risk factors have gained increased attention. In recent decades, haemodilution during cardiopulmonary bypass (CPB) has been recognised as a risk factor for postoperative AKI and in-hospital mortality[9,11]. In this respect, a critical factor is oxygen delivery (DO_2) during CPB rather than the nadir haematocrit itself. Observational studies have shown that a DO_2 below a critical threshold ranging between 225 $mL \cdot min^{-1} \cdot m^{-2}$ and 272 $mL \cdot min^{-1} \cdot m^{-2}$ is associated with an increased risk of postoperative AKI[12-17], and in the largest retrospective study comprising more than 19,000 cardiac surgery patients, the critical cut-off point was found at approximately 270 $mL \cdot min^{-1} \cdot m^{-2}$. Furthermore, the integral of amount and time below the critical DO_2 limit has been associated with an increased risk of AKI[18]. Indeed, in a newly published randomised controlled trial, patients randomised to maintain DO_2 above 280 $mL \cdot min^{-1} \cdot m^{-2}$ had a reduced rate of AKIN stage I injury[19].

The aim of the present study was to evaluate in a more clinical applicable approach, the association between duration (minutes) with a low DO_2 during CPB and the occurrence of AKI in patients undergoing coronary artery bypass grafting (CABG) with or without valve surgery.

Methods

Study design and patient population

In a retrospective observational study from 2012 to 2014, all adult patients undergoing CABG surgery with or without valve repair, at Rigshospitalet, Copenhagen University Hospital, were included. Exclusion criteria were previous nephrectomy, preoperative sCr >199.7 µmol/L and acute surgery, defined as coronary angiography within 24 hours prior to surgery. In total 2125 patients were screened prior to study inclusion. Patients who did not have available data for DO_2 calculation and/or outcome data were excluded from the study (n=157), leaving 1968 patients available for final analysis. In the remaining analyses, pairwise deletion was used if data were missing.

The risk factor investigated was the time below a critical DO_2, which in the present study was defined as the number of minutes below a threshold value of 272 $mL \cdot min^{-1} \cdot m^{-2}$. The critical DO_2 value used was based on Ranucci et al.'s original findings[12]. The primary outcome was AKI defined by the KDIGO (Kidney Disease: Improving Global Outcomes) criteria[20].
The KDIGO classification was calculated as the difference between sCr, measured prior to surgery (baseline) and the peak value on one of the first two postoperative days. KDIGO stage 1 was defined as an increase in sCr level of 150% to 190% or an absolute increase of 26.5 µmol. Stage 2 was defined as an increase in sCr level of 200% to 290% and stage 3 was 300% or above baseline. From the KDIGO criteria we made a binary AKI variable defined as either no AKI or any stage of KDIGO (no/yes). Secondary outcomes were postoperative peak serum creatinine (PPSC; µmol/L) measured within the first 48 hours after surgery and acute renal failure defined as kidney failure requiring renal replacement therapy (RRT). RRT was deployed at the discretion of the intensivist.

Data

The following preoperative data were registered from patient charts: age (years), gender, height (meter), weight (kg), body surface area (BSA, m^2). Co-morbidity data were obtained from the admission notes, including diabetes (no/NIDDM/IDDM), ejection fraction (categorised into four groups >50%, 50-31%, 30-21%, <21%), smoking status (no/yes/former), preoperative sCr (µmol/L)

and the following categorical entities (no/yes); peripheral artery disease (PAD), chronic obstructive lung disease (COLD), arterial hypertension, hypercholesterolemia, neurological disease/events, chronic kidney disease (CKD), preoperative Renin-angiotensin-aldosterone-system (RAAS) blockers and preoperative diuretics.

The following variables were collected from the electronic perfusion charts: type of surgery (CABG +/- valve), duration of CPB (minutes), mean arterial pressure (MAP, mmHg) and aortic cross-clamp time (minutes). Furthermore, pump flow ($L \cdot min^{-1} \cdot m^{-2}$), haematocrit (Hct), oxygen-saturation (SaO_2) and arterial oxygen tension (PaO_2; mmHg) were measured every minute on the monitor during CPB. DO_2 was afterwards calculated according to the following equation, where 1.36 (mL/g) is the oxygen carrying capacity of haemoglobin and 0.003 (mL/dL/mmHg) is the solubility constant for oxygen. Multiplier 10 is used to convert CaO_2 (PaO_2 x 0.003) from mL/dL to mL/L:

$$DO_2 = \text{pump flow} \times [((Hct/3) \times 1.36 \times SaO_2) + (PaO_2 \times 0.003) \times 10].$$

RBC transfusions given the same day as surgery were registered. In addition, post-operative re-operation within 48 hours (no/yes) was registered.

Anaesthesia, surgical procedures and CPB management

All patients received triazolam (0.125-0.250 mg) prior to surgery. Anaesthesia was induced with fentanyl (10 µg/kg), propofol (1-2 mg/kg), and cisatracurium (0.1 mg/kg) and maintained with sevoflurane (0.5-3.0%) and a continuous infusion of remifentanil (15-30 µg/kg/h). Arterial blood pressure was monitored with a cannula placed in the left radial artery.

The CABG started with a median sternotomy, cannulation in the ascending aorta and insertion of a two-stage venous cannula through the right atrial appendage. Heparinisation was provided to obtain an activated clotting time >480 sec. All surgical procedures employed CPB with membrane oxygenation and roller pumps with non-pulsatile flow and a normothermic bladder temperature (36.5 - 37.0 ^oC). Pump flow was set to 2.4 $L/min/m^2$.

Statistical analyses

Statistical analyses were performed using SPSS 22.0 (IBM SPSS. Armonk, NY). Univariable analyses of the pre- and intraoperative variables were performed to investigate associations with the primary outcome AKI. Analyses were repeated with the secondary outcome, RRT. All normally distributed continuous variables are expressed as mean ± standard deviation (SD) and compared with an unpaired two-sample Student's t-test. Skewed right distributed data underwent log-transformation. Categorical variables are expressed as count and percentage of total and compared with the Pearson's Chi-squared test.

Regarding the third and continuous outcome (difference of mean PPSC), univariable analyses were performed using the unpaired Students t-test for analysing the association with categorical pre- and intraoperative variables, while the association with continuous pre- and intraoperative variables was investigated using linear regression. Residual plots were visually assessed for testing goodness of fit for all linear regression models. All data were analysed for normal distribution with the Kolmogorov–Smirnov test.

A simple rolling mean of DO_2 was calculated from perfusion charts for every 1-5, 10, 15, and 30 minutes of the duration on bypass. For each patient, the lowest 1-5, 10, 15, and 30 minutes mean DO_2 was identified. From this, binary categorical variables were constructed for each of the time intervals, based on whether the patient's mean DO_2 was below 272 $mL \cdot min^{-1} \cdot m^{-2}$ in 0, or for at least 1, 10, 15 or 30 minutes. The implication of this is that i.e. patients with a low DO_2 for 15 min will be included in the groups with a lower duration, but not in the 30-min group, thereby reflecting the dose-response relation. In contrast, patients were assigned exclusively to one group prior to the multiple regression analysis, which enables a strict comparison of each individual patient's exposure to a low DO_2. However, this approach weakens the statistical power due to a lower number of patients in the intermediate groups.

All variables significantly associated ($p < 0.05$) with the outcomes AKI or RRT in the univariable analyses were included in a multiple binary logistic stepwise-backward regression model as co-variates. A similar analysis was performed with multiple linear regression with PPSC as the outcome. Categorical data were introduced in the multiple regression models as an indicator first manner, meaning that covariate not-present (0) is used as reference to covariate present (1).

For each outcome four models were analysed with each model containing one of the following dichotomous variables; any given 1-5, 10, 15 or 30 minutes with a mean DO_2 below the critical level. This procedure was done to prevent the coupling between these variables. An exception was the transfusion of RBC products. RBC transfusions are given due to a low haematocrit; hence low DO_2. Indeed, when we performed a collinearity analysis, we found a correlation between DO_2 and RBC transfusion with a tolerance value ranging between 0.101 to 0.322 for the four groups; 1-5, 10, 15 or 30 minutes with a mean DO_2 below the critical level. We therefore excluded the RBC transfusion variable from our multivariable model. All logistic regression models were post hoc tested with the Hosmer-Lemeshow goodness of fit test.

Ethics & Approval

The study was approved by the Danish Health Authority (registration number: 3-3013-1188/1) and the Danish Data Protection Agency (registration number: RH-2015-251). Due to the retrospective study design, the need for written informed consent was waived.

Results

Among the 1,969 patients included in the study from 2012 through 2014, 577 patients (29.3%) developed AKI and 57 patients (2.9%) required RRT after CABG surgery.

Univariable analyses

Demographics, pre-, intra- and postoperative variables are shown by AKI status in Table 1. Patients diagnosed with AKI were significantly older and had more frequently COLD, hypertension, CKD and PAD. Furthermore, they received more frequently preoperative treatment with diuretics and had a higher baseline sCr compared to patients who did not develop AKI postoperatively.
During surgery, patients developing AKI more frequently underwent reoperation, had a lower haematocrit, and more often needed RBC transfusion. Furthermore, the duration of CPB was longer and the mean DO_2 was significantly lower (345.8 ± 69.7 vs. 363.9 ± 70.6 mL· min^{-1}·m^{-2}, $p < 0.001$) in these patients.

Duration of critically low DO_2

A mean DO_2 <272 mL· min^{-1}·m^{-2} during CPB was associated with a significantly higher PPSC level (Figure 1), a higher incidence of AKI (Figure 2), and need for RRT postoperatively (Figure 3),

compared to patients whose DO_2 was >272 $mL \cdot min^{-1} \cdot m^{-2}$ during the entire CPB run. For all three renal outcomes, the incidence increased stepwise in relation to a prolonged exposure to a critically low DO_2 (Figure 1-3).

Multiple regression analyses

Multiple linear regression analyses demonstrated that only exposure to a low DO_2 for at least 30 minutes was significantly associated with a higher PPSC and occurrence of AKI (Table 2). In contrast, exposure to a low DO_2 in 1-5 and 30 minutes were both associated with an increased risk of requiring RRT (Table 2). For the complete multiple regression analyses see Table A, B, & C in the supplementary material.

For PPSC as outcome: the regression coefficient (RC) was 8.31 in the 30 minutes group. The following covariates were independent risk factors for a higher PPSC; age, CKD, PAD, pre-operative use of diuretics, re-operation, and mean MAP.

For the outcome AKI, 30 minutes below the DO_2 threshold were independently increasing the risk of AKI with an odds ratio of 1.50 (Table 2). Age, PAD, CKD, arterial hypertension, pre-operative use of diuretics and re-operation were all independent risk factors for AKI.

With RRT as outcome: 1-5 minutes and 30 minutes below the critical DO_2 were both independent risk factors, with an odds ratio of 2.58 and 2.85, respectively ($p<0.02$). Other independent risk factors for RRT were age, pre-operative use of diuretics and pre-operative s-creatinine.

Discussion

In the present study, we found that the frequency of AKI was 29.3% and the need for RRT was 2.9%, similar to previous studies[5,6,18,19]. Overall, the occurrence of all three outcomes increased with the duration of DO_2 below the critical level. Using multiple regression analyses, we found that a mean DO_2 <272 $mL \cdot min^{-1} \cdot m^{-2}$ for 30 min or more was independently associated with a higher PPSC and AKI. In contrast, both a short (1-5 min) and extended period (30 min) with a low DO_2 were both independently associated with the need for RRT.

A low DO_2 as an overall risk factor for AKI has previously been reported[12,14,15,17,19]. Ranucci et al.[12], were the first to describe a low DO_2 as a risk factor, they calculated nadir DO_2 from arterial blood gas measurements taken every 30 minutes and observed an association with both acute renal failure and PPSC. Retrospective studies applying AKIN or KDIGO as outcome parameters have also reported a low DO_2 to be an independent risk factor, when calculating DO_2 from blood samples taken every 10 and 15 minutes[14,15]. The two studies did not calculate the mean of low DO_2 values, but used the single lowest DO_2 measurement[14,15]. Recently, Mukaida et al. demonstrated that the integral of duration and severity of a DO_2 <300 mL· min^{-1}·m^{-2} was an independent predictor of AKI[18]. In the present study, we took advantage of the continuous data recordings every minute from the bypass machine's monitoring system, making it possible to investigate the impact of a DO_2 <272 mL· min^{-1}·m^{-2} in various time spans. Although, the integral of severity and duration of a low DO2 is probably a better way to predict the risk of AKI, this approach is not clinically applicable, since the integral is not readily available during CPB. Therefore, we chose to evaluate the importance of extended exposure to a low DO_2 with a prespecified cut-off level at 272 mL· min^{-1}·m^{-2}. The PPSC increased in a dose-dependent manner as the duration of a low DO_2 was prolonged, which was further confirmed by an increase in the occurrence of AKI by 23% and increased need for renal replacement therapy by 34% from the shortest (1-5 min) to the longest (≥30 min) duration of a DO_2 below the threshold. Using multiple regression analyses, the impact of a low DO_2 was independently associated with PPSC and AKI only in the group with at least 30 min exposure to a low DO_2. A potential explanation for the lack of association with outcome in the groups with a shorter exposure may be the limited number of patients within the individual time intervals. Another explanation may be related to variation in severity of a low DO_2 in the individual groups. With an extended duration (30 min) of a mean DO_2 below 272 mL· min^{-1}·m^{-2} could represent more severely reduced oxygen delivery compared to a mean DO_2 below 272 mL· min^{-1}·m^{-2} in 1-5 min. Furthermore, association between AKI and duration of a low DO_2 at various thresholds has shown high individual variability. At threshold levels below 300 and 280 mL· min^{-1}·m^{-2}, the median (IQR) duration of a low DO_2 among patients with AKI was 34.7 (16.0-61.0) minutes and 7.7 (1.6-28.0) minutes, respectively[18]. These observations clearly demonstrate the multifactorial aetiology underlying the pathophysiology of AKI following cardiac surgery.

Even under adequate DO_2 levels, several other factors affect whether or not the kidneys and especially the medulla develop hypoxia during CPB. One study found a considerable shunting away from the kidneys reducing the renal DO_2 by 20% despite a satisfactory global DO_2[21]. A recent

proof-of-concept study on eighteen cardiac surgery patients found, that the decrease in renal DO_2 during CPB was mainly caused by haemodilution, whereas renal blood flow remained unchanged even in the presence of an increased renal vascular resistance. The reduction in renal DO_2 led to a significant increase in oxygen extraction compared to pre-CPB, which probably was aggravated by an increased renal oxygen consumption during and after CPB[21]. Among the eighteen patients included in the study, four developed AKI, but unfortunately the authors did not provide detailed data on their renal DO_2.

As can be seen from the DO_2 equation, it is a multiplex of several factors. Oxygen saturation is almost always 100%, while on CPB, leaving the remaining two modifiable factors, namely blood flow and haemoglobin.

To counteract the reduction in global DO_2, there are two major options: 1: Increasing the haemoglobin level, which is not attractive since transfusion of RBCs on its own increases the risk of renal impairment[22,23], or 2: Increasing the systemic blood flow to increase the overall DO_2. This approach was applied in the GIFT trial, where patients were randomised to either a goal-directed perfusion strategy, where DO_2 should be maintained > 280 $mL \cdot min^{-1} \cdot m^{-2}$ by increasing blood flow during CPB or a conventional perfusion strategy based on body surface area and temperature. A significant reduction in AKI of any kind was observed, which was mainly related to an improvement in the occurrence of AKI stage 1, whereas more severe AKI stage 2 and 3 were not significantly different between the two groups[19]. The GIFT study included 350 patients, so it was not powered to detect any difference in mortality, morbidity or hospital stay of length.

AKI defined by the KDIGO criteria is based on serum creatinine, a late and indirect biomarker of kidney damage. Serum creatinine is reflecting other non-renal factors such as gender, muscle mass, hydration status, altered metabolism etc. We only registered serum creatinine on the first two postoperative days. Considering the delayed increase in serum creatinine, we may have lost important information, potentially affecting the true occurrence of AKI. Another limitation in the present study is the inability to differentiate between the various stages of AKI, which have considerably impact on the clinical outcome. But due to the retrospective nature of this study, without extended monitoring of the postoperative plasma creatinine level, we decided not to differentiate between the individual stages of kidney injury.

In the present study, we included patients receiving transfusions on the day of surgery (29% of the patients received RBC transfusion). Nevertheless, we excluded the transfusion variable since low DO_2 and transfusion of RBCs demonstrated co-linearity. Although it is not without concern to remove transfusions from the model; RBC transfusions may be harmful besides being a surrogate for anaemia, through immunological and 'storage lesion' effects. Stored RBC has been described to be depleted of the 2,3 DPG, thus altering the oxygen dissociation curve and accumulate haemolysed erythrocytes leading to an increase of free pro-inflammatory molecules, a high concentration of free haemoglobin and iron, known to be toxic the kidney[24,25]. Further studies are warranted to elucidate transfusion of blood products as an independent risk factor.

Another variable not registered, but potentially influencing the outcome, is temperature. Hypothermia has been found to be a risk factor in some studies[26]. At Rigshospitalet, cardiac surgery is carried out at normothermia. Nevertheless, fluctuations during surgery may occur hence influencing the outcomes.
In the present study, the mean MAP was 44.1 mmHg in patients without AKI and 45.7 mmHg in the group developing AKI, which although it was a statistically significant difference, is unlikely to play a role in clinical practice with a mean difference of less than 2 mmHg between the two groups. To further explore the impact of blood pressure, we included MAP in our multivariate regression models, but this variable was not a significant risk factor. Even though arterial pressure during CPB remains a matter of controversy, to our knowledge no observational nor randomised study has found a clear relationship between MAP during CPB and post-operative AKI[27,28].

A major strength of the present study is the ability to monitor DO_2 continuously every minute, making it possible to investigate the importance of the duration of a low DO_2. Secondly, our study comprises more patients than previous dose-response studies, resulting in a more robust estimate of the individual renal outcome and DO_2.

In conclusion, a DO_2 below 272 $mL \cdot min^{-1} \cdot m^{-2}$was associated with an increased the risk of developing AKI. PPSC, occurrence of AKI and need for RRT all increased with prolonged exposure to a low DO_2. However, only 30 minutes exposure of a low DO_2 was independently associated with AKI.

Acknowledgements

The authors have no conflicts of interest. No funding was received for this study.

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Table 1. Preoperative, Intraoperative and Postoperative Variables by AKI				
Variable	Total	AKI	No AKI	p - value
Number of patients	1968	577 (29.3)	1391 (70.7)	
Preoperative				
Age (years)	67.6 ± 9.4	71.5 ± 8.5	65.9 ± 9.3	**0.001**
Gender, male	1612 (81.9)	472 (81.8)	1140 (81.9)	0.961
Body Mass Index (kg/m^2)	27.4 ± 4.3	27.5 ± 4.4	27.4 ± 4.2	0.389
Chronic obstructive lung disease	185 (9.4)	75 (13.1)	110 (7.9)	**<0.001**
Cerebral disease	217 (11.1)	64 (11.1)	153 (11.0)	0.811
NIDDM	470 (23.9)	152 (26.4)	318 (22.9)	0.096
IDDM	48 (2.4)	15 (2.6)	33 (2.4)	0.763
Hypertension	1385 (70.6)	477 (77.9)	938 (67.5)	**<0.001**
Hypercholesterolemia	1468 (75.7)	424 (73.9)	1062 (76.5)	0.375
Chronic kidney disease	81 (4.1)	46 (8.0)	35 (2.5)	**<0.001**
Peripheral arterial disease	219 (11.2)	86 (15.0)	133 (9.6)	**0.001**
Smoker	443 (22.6)	101 (17.7)	342 (24.6)	**0.001**
RAAS blocker	1009 (52.0)	315 (55.5)	694 (50.5)	**0.047**
Diuretics	703 (36.2)	280 (49.4)	423 (30.8)	**<0.001**
Ejection fraction (<30%)	225 (11.4)	83 (14.4)	142 (10.2)	**0.007**
Baseline serum creatinine (µmol/L)	94.6 ± 30.5	98.8 ± 29.3	92.8 ± 30.9	**<0.001**
Intra- and postoperative variables				
Peak postoperative serum creatinine (µmol/L)	98.0 (79.0 – 126.0)	148.0 (123.0 – 182.0)	87.0 (74.0 – 102.0)	**<0.001**
Reoperation (within 48 hours)	87 (4.4)	42 (7.3)	45 (3.2)	**<0.001**
Red blood cell transfusion (same day as operation)	560 (28.4)	270 (46.8)	290 (20.8)	**<0.001**
CPB duration (minutes)	90.4 ± 43.0	103 ± 52.9	84.7 ± 36.5	**<0.001**
Mean MAP during CPB (mmHg)	44.6 ± 6.9	45.7 ± 7.3	44.1 ± 6.6	**<0.001**
Mean haematocrit (%)	29.6 ± 4.0	28.6 ± 4.1	30.0 ± 3.9	**<0.001**
Pump flow, indexed ($L/min/m^2$)	2.65 ± 0.31	2.64 ± 0.3	2.66 ± 0.3	0.362
Mean DO_2, indexed ($mL/min/m^2$)	358.6 ± 70.7	345.8 ± 69.7	363.9 ± 70.6	**<0.001**
AKI = Acute kidney injury, according to KDIGO criteria. NIDDM = Non-insulin-dependent diabetes mellitus, IDDM = Insulin-dependent diabetes mellitus, RAAS = Renin–angiotensin–aldosterone system, CPB = Cardiopulmonary bypass, DO_2 = Oxygen delivery. All normally distributed continuous variables were expressed as mean ± standard deviation. Categorical variables are expressed as count and percentage of the				

AKI subgroup. Skewed data are expressed as median and interquartile ranges (IQR) of the respective group.

Table 2. Multiple regression analyses

	Model 1 - Critical 1-5 min		Model 2 - Critical 10 min		Model 3 - Critical 15 min		Model 4 - Critical 30 min	
Risk factor	RC (95%CI)	p - value	RC (95%CI)	p - value	RC (95%CI)	p - value	RC (95%CI)	p - value

Multiple Stepwise Backward Linear Regression Analyses with PPSC as outcome								
Critical DO_2 1-5 min (n= 302)	-	NS						
Critical DO_2 10 min (n= 48)			-	NS				
Critical DO_2 15 min (n=116)					-	NS		
Critical DO_2 30 min (n= 218)							8.31 (2.38-14.25)	**0.006**
Multiple Stepwise Backward Logistic Regression Analyses with AKI as outcome								
	OR (95%CI)	p - value	OR (95%CI)	p - value	OR (95%CI)	p - value	OR (95%CI)	p - value
Critical DO_2 1-5 min (n= 302)	1.18 (0.87, 1.59)	NS						
Critical DO_2 10 min (n= 48)			1.26 (0.65, 2.45)	NS				
Critical DO_2 15 min (n=116)					1.01 (0.64, 1.60)	NS		
Critical DO_2 30 min (n= 218)							1.50 (1.07, 2.10)	**0.018**
Multiple Stepwise Backward Logistic Regression Analyses with RRT as outcome								
	OR (95%CI)	p - value	OR (95%CI)	p - value	OR (95%CI)	p - value	OR (95%CI)	p - value
Critical DO_2 1-5 min (n= 302)	2.58 (1.20, 5.54)	**0.015**						
Critical DO_2 10 min (n= 48)			0.00 (0.00, -)	NS				
Critical DO_2 15 min (n=116)					0.95 (0.21, 4.34)	NS		
Critical DO_2 30 min (n= 218)							2.85 (1.27, 6.41)	**0.011**

Figure 1

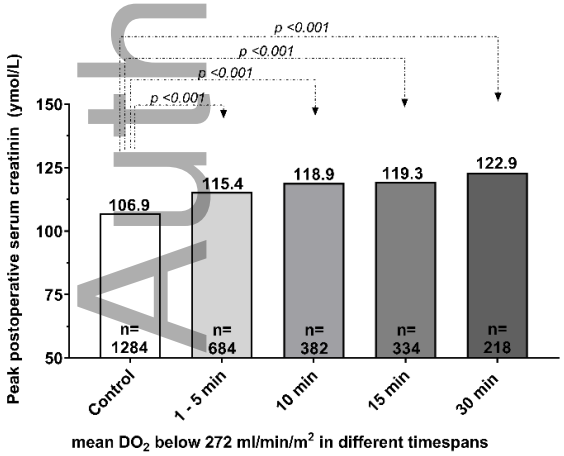

Figure 1: Association between the duration of a lower DO_2 and peak postoperative serum creatinine levels. Data are analysed using transformed logarithmic data and Students t-test, comparing the control group to different time intervals. The number above the bar is the mean for the group.

Figure 2

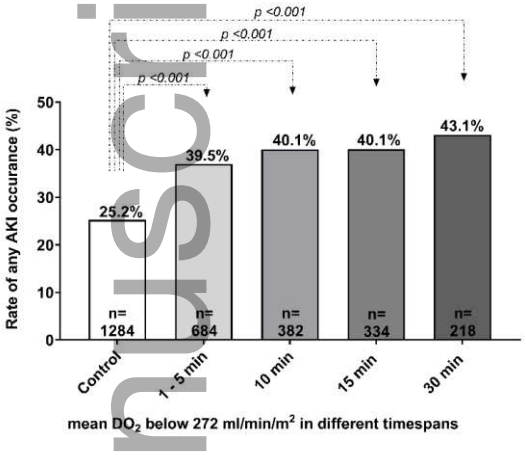

Figure 2: Association between the duration of a lower DO2 and acute kidney injury. Data are analysed using chi square analysis, comparing the control group to different time intervals. The percentage refers to the fraction with AKI of individuals exposed (n=) within each time span.

Figure 3

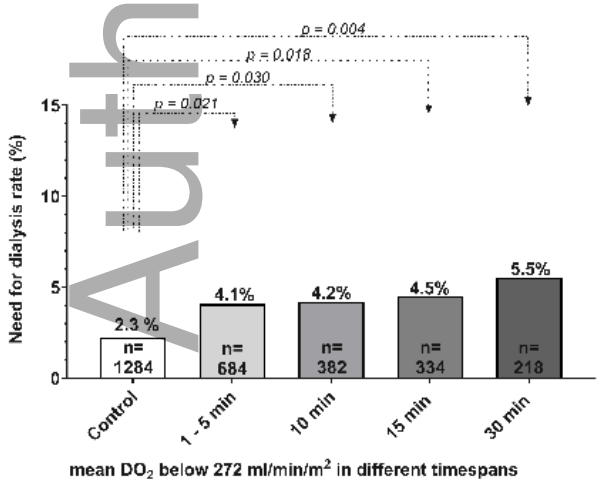

Figure 3: Association between the duration of a lower DO2 and renal replacement therapy. Data are analysed using chi square analysis, comparing the control group to different time intervals. The percentage number is the percentage of the group with lowest mean DO2.

Table 1. Preoperative, Intraoperative and Postoperative Variables by AKI

Variable	Total	AKI	No AKI	*p* - value
Number of patients	1968	577 (29.3)	1391 (70.7)	
Preoperative				
Age (years)	67.6 ± 9.4	71.5 ± 8.5	65.9 ± 9.3	**0.001**
Gender, male	1612 (81.9)	472 (81.8)	1140 (81.9)	0.961
Body Mass Index (kg/m^2)	27.4 ± 4.3	27.5 ± 4.4	27.4 ± 4.2	0.389
Chronic obstructive lung disease	185 (9.4)	75 (13.1)	110 (7.9)	**<0.001**
Cerebral disease	217 (11.1)	64 (11.1)	153 (11.0)	0.811
NIDDM	470 (23.9)	152 (26.4)	318 (22.9)	0.096
IDDM	48 (2.4)	15 (2.6)	33 (2.4)	0.763
Hypertension	1385 (70.6)	477 (77.9)	938 (67.5)	**<0.001**
Hypercholesterolemia	1468 (75.7)	424 (73.9)	1062 (76.5)	0.375
Chronic kidney disease	81 (4.1)	46 (8.0)	35 (2.5)	**<0.001**
Peripheral arterial disease	219 (11.2)	86 (15.0)	133 (9.6)	**0.001**
Smoker	443 (22.6)	101 (17.7)	342 (24.6)	**0.001**
RAAS blocker	1009 (52.0)	315 (55.5)	694 (50.5)	**0.047**
Diuretics	703 (36.2)	280 (49.4)	423 (30.8)	**<0.001**
Ejection fraction (<30%)	225 (11.4)	83 (14.4)	142 (10.2)	**0.007**
Baseline serum creatinine (µmol/L)	94.6 ± 30.5	98.8 ± 29.3	92.8 ± 30.9	**<0.001**
Intra- and postoperative variables				
Peak postoperative serum creatinine (µmol/L)	98.0 (79.0 – 126.0)	148.0 (123.0 – 182.0)	87.0 (74.0 – 102.0)	**<0.001**
Reoperation (within 48 hours)	87 (4.4)	42 (7.3)	45 (3.2)	**<0.001**
Red blood cell transfusion (same day as operation)	560 (28.4)	270 (46.8)	290 (20.8)	**<0.001**
CPB duration (minutes)	90.4 ± 43.0	103 ± 52.9	84.7 ± 36.5	**<0.001**
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AKI = Acute kidney injury, according to KDIGO criteria. NIDDM = Non-insulin-dependent diabetes mellitus, IDDM = Insulin-dependent diabetes mellitus, RAAS = Renin–angiotensin–aldosterone system, CPB = Cardiopulmonary bypass, DO_2 = Oxygen delivery. All normally distributed continuous variables were expressed as mean ± standard deviation. Categorical variables are expressed as count and percentage of the AKI subgroup. Skewed data are expressed as median and interquartile ranges (IQR) of the respective group.

Table 2. Multiple regression analyses

	Model 1 - Critical 1-5 min		Model 2 - Critical 10 min		Model 3 - Critical 15 min		Model 4 - Critical 30 min	
Risk factor	RC (95%CI)	*p - value*	RC (95%CI)	*p - value*	RC (95%CI)	*p - value*	RC (95%CI)	*p - value*
Multiple Stepwise Backward Linear Regression Analyses with PPSC as outcome								
Critical DO_2 1-5 min (n= 302)	-	NS						
Critical DO_2 10 min (n= 48)			-	NS				
Critical DO_2 15 min (n=116)					-	NS		
Critical DO_2 30 min (n= 218)							8.31 (2.38-14.25)	**0.006**
Multiple Stepwise Backward Logistic Regression Analyses with AKI as outcome								
	OR (95%CI)	*p - value*	OR (95%CI)	*p - value*	OR (95%CI)	*p - value*	OR (95%CI)	*p - value*
Critical DO_2 1-5 min (n= 302)	1.18 (0.87, 1.59)	NS						
Critical DO_2 10 min (n= 48)			1.26 (0.65, 2.45)	NS				
Critical DO_2 15 min (n=116)					1.01 (0.64, 1.60)	NS		
Critical DO_2 30 min (n= 218)							1.50 (1.07, 2.10)	**0.018**
Multiple Stepwise Backward Logistic Regression Analyses with RRT as outcome								
	OR (95%CI)	*p - value*	OR (95%CI)	*p - value*	OR (95%CI)	*p - value*	OR (95%CI)	*p - value*
Critical DO_2 1-5 min (n= 302)	2.58 (1.20, 5.54)	**0.015**						
Critical DO_2 10 min (n= 48)			0.00 (0.00, -)	NS				
Critical DO_2 15 min (n=116)					0.95 (0.21, 4.34)	NS		
Critical DO_2 30 min (n= 218)							2.85 (1.27, 6.41)	**0.011**

Figure 1

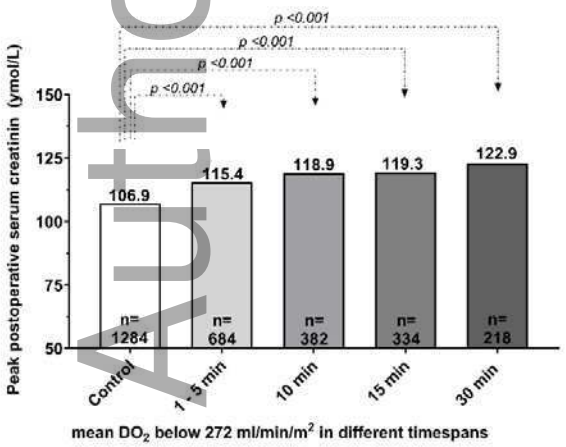

Figure 1: Association between the duration of a lower DO_2 and peak postoperative serum creatinine levels. Data are analysed using transformed logarithmic data and Students t-test,

comparing the control group to different time intervals. The number above the bar is the mean for the group.

Figure 2

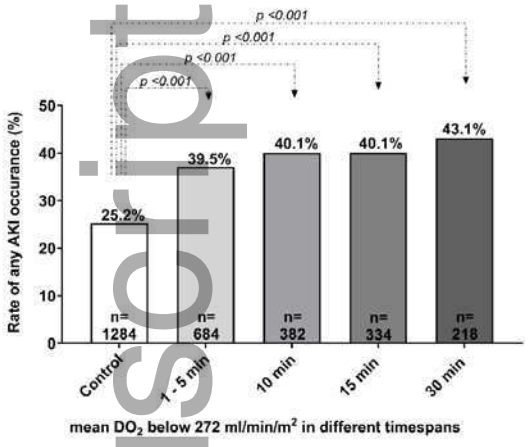

Figure 2: Association between the duration of a lower DO2 and acute kidney injury. Data are analysed using chi square analysis, comparing the control group to different time intervals. The percentage refers to the fraction with AKI of individuals exposed (n=) within each time span.

Figure 3

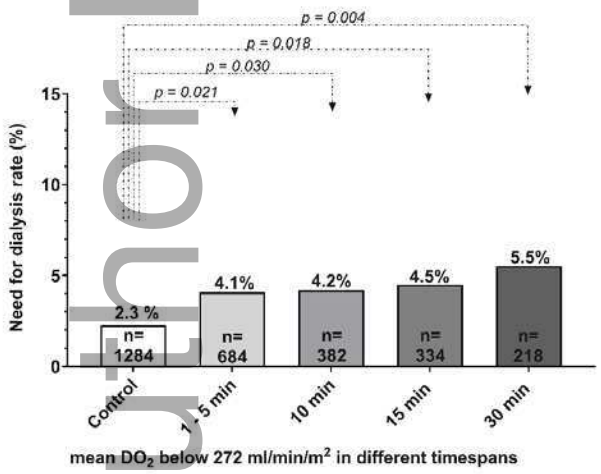

Figure 3: Association between the duration of a lower DO2 and renal replacement therapy. Data are analysed using chi square analysis, comparing the control group to different time intervals. The percentage number is the percentage of the group with lowest mean DO2.