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The influence of oxygen delivery during cardiopulmonary bypass on the incidence of delirium in CABG patients; a retrospective study

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Abstract

Introduction: Postoperative delirium is the most common neurological complication of cardiac surgery. Hypoxia has been shown to increase the risk of postoperative delirium. The possibility to continuously monitor oxygen delivery (DO_2) during cardiopulmonary bypass (CPB) offers an adequate approximation of the oxygen status in a patient. This study investigates the role of oxygen delivery during cardiopulmonary bypass in the incidence of postoperative delirium.

Methods: Three hundred and fifty-seven adult patients who underwent normothermic coronary artery bypass grafting (CABG) surgery were included in this retrospective study. The nadir indexed DO_2 (DO_2i) value on bypass, the total time under the critical DO_2i level and the area under the curve (AUC) for critical DO_2i were determined. Delirium was identified by the postoperative administration of haloperidol.

Results: The mean nadir DO_2i significantly differed, comparing the group of patients with postoperative delirium to the group without. Multivariate analysis only identified age, pre-existing cognitive impairment, preoperative kidney dysfunction and cross-clamp time as independent risk factors for delirium. The results also indicated that patients of older age were more sensitive to a declined DO_2i.

Conclusion: A low DO_2i during cardiopulmonary bypass is significantly associated with the incidence of postoperative delirium in CABG patients. However, the role of DO_2 as an independent predictor of delirium could not be proven.

Keywords

oxygen delivery; cardiopulmonary bypass; delirium; CABG

Introduction

Several studies have demonstrated an increased risk for mortality and morbidity related to postoperative delirium. The incidence of delirium following cardiac surgery varies between 3 and 31% in the general patient population, but can reach up to 50% in patients over 60 years old.[1,2] Regarding coronary artery bypass grafting (CABG) surgery in specific, delirium has been associated with an increased long-term risk for death and stroke.[3] Previously, literature-reported independent risk factors for delirium include; age, left ventricular ejection fraction (LVEF), diabetes, cerebrovascular disease, peripheral vascular disease, pre-existent cognitive impairment, type of surgery and duration of surgery.[1,4] Regarding pathophysiology, it is known that brain insults, such as hypoxia, stroke and metabolic abnormalities can result in delirium.[5] Since the oxygen supply to the brain during cardiopulmonary bypass (CPB) is mainly determined by hematocrit levels and pump flow, oxygen delivery (DO_2) is a potential factor related to postoperative delirium. The effect of diminished DO_2 during CPB has been studied in relation to its influence on kidney function. A study by Ranucci in CABG patients designated the nadir DO_2i during surgery as an independent risk factor for acute kidney injury (AKI),

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with a critical value of 272 ml/min/m².[6] Subsequent research by De Somer showed a nadir DO_2 level below 262 mL/min/m² during CPB to be independently associated with AKI.[7]

In December 2014, our heart-lung machines were equipped with the Goal Directed Perfusion (GDP) module of the Sorin real-time perfusion charting system Connect. This presented us with the opportunity of continuous measurement and display of DO_2 during CPB. At the end of 2015, collected data were retrospectively audited in an effort to investigate the possible effect of diminished DO_2 during CPB on the incidence of "hypoxia induced" postoperative delirium.

Material and Methods

Study design

This retrospective study, based on data collected at the Catharina Hospital, Eindhoven from January to December 2015, comprised adult patients who underwent elective, first-time, solely CABG surgery with the use of CPB under normothermic conditions with continuous automatic DO_2 registration. Exclusion criteria were: procedures with multiple aortic clamp sessions, usage of haloperidol medication prior to surgery and incomplete preoperative or postoperative records.

The research ethics committee had agreed to the work being undertaken without need of their oversight and waived the need for informed consent.

Procedures

Induction of general anesthesia was achieved using fentanyl, etomidate and rocuronium. On indication, supplements of midazolam or dexamethasone were given. During surgery, anesthesia was maintained using propofol and alfentanil. The procedures used a conventional heart-lung machine with a Sorin custom pack containing the Inspire 6F membrane oxygenator and a Revolution centrifugal pump (LivaNova, Amsterdam, the Netherlands). Arterial flow values were registered by a calibrated flow sensor on the arterial line. CPB was performed under normothermic conditions (patient core temperature ⩾36-C) with arterial blood flow rates between 2.4 L/min/m² to 3.2 L/min/m² to maintain venous oxygen saturation (SvO_2) above 65% and the mean arterial pressure between 50-80 mmHg. Cold crystalloid or warm blood cardioplegia was used according to the surgeon's preference.

Data collection and analysis

The following preoperative variables were collected: age, gender, body surface area (BSA), body mass index (BMI), carotid artery disease, previous cognitive impairment, previous transient ischemic attack/cerebral vascular accident (TIA/CVA), peripheral vessels disease, diabetes mellitus, kidney dysfunction, left ventricular ejection fraction (LVEF) ⩽40% and preoperative hemoglobin level. Preoperative cognitive disorders, brain damage and diagnosis of depression in the medical history as well as confused mental state at admission were scored as previous cognitive impairment.

Kidney dysfunction was based upon the preoperative patient status, defined by a glomerular filtration rate (GFR) <60.

Preoperative creatinine values were collected as part of determining acute kidney injury (AKI). AKI was defined as a 1.5-fold or more increase in postoperative serum creatinine level compared to the preoperative baseline value within 48 hours, which is one of the criteria according to AKIN criteria.[8]

During the procedure, all perfusion-related data were registered in the Sorin Connect™ program and the GDP module was used to directly display the DO_2 during perfusion, which was automatically calculated every 10 seconds by the GDP module from measured arterial pump flow (Q) and inline values for hematocrit (Hct), arterial oxygen saturation (SaO_2) and partial arterial oxygen pressure (PaO_2) measured by the CDI500. Data prior to calibration of the CDI500, as well as after resuming ventilation, were excluded from the analysis. The following equation was used in Connect for DO_2 calculation:

$$DO_2\,[\text{ml/min}] = Q\,[\text{L/min}] \times (\text{Hct}/2{,}94\,[\text{g/dL}] \times 1.36\text{ ml}\,[\text{mlO}_2/\text{gr}] \times SaO_2\,[\%] + 0.003 \times PaO_2\,[\text{mmHg}]\,) \times 10$$

The calculated DO_2 value divided by the BSA in m² provided an indexed DO_2i in ml/min/m².

To assess DO_2i during bypass, a specific three parameters were used:

1. Nadir DO_2i during bypass (ml/min/m²). This value was calculated from the lowest hemoglobin value on bypass combined in the equation with the mean pump flow value during 30 minutes around this point (15 min on every side), similar to Ranucci's research.[6]
2. Time the DO_2i was below the critical value (sec). To study a cumulative effect of a low DO_2i, the total time below the critical level was calculated.
3. Area under the DO_2i curve (AUC, ml/m²). This value was determined as the integral of the amount and time below a critical threshold, to indicate the extent to which the DO_2i was decreased.

Table 1. Population and intraoperative data.

Variable	No delirium (n=314)	Delirium (n=43)	p-value
Age (years)	65.5±8.9	71.3±8.4	0.000[a]
Gender male	264 (84.1%)	40 (93.0%)	0.122[b]
Body surface area (m^2)	1.98±0.18	1.94±0.17	0.218[a]
Body mass index	27.8±3.97	27.1±3.48	0.295[a]
Carotid artery disease	8 (2.5%)	0 (0%)	0.290[b]
Previous cognitive impairment	12 (3.8%)	6 (13.6%)	0.004[b]
Peripheral vascular disease	37 (11.8%)	9 (20.9%)	0.093[b]
Previous TIA/CVA	36 (11.5%)	8 (18.6%)	0.182[b]
Diabetes mellitus	72 (22.9%)	13 (30.2%)	0.292[b]
Kidney dysfunction*	29 (9.2%)	14 (32.6%)	0.000[b]
LVEF ⩽40%	54 (17.2%)	12 (27.9%)	0.090[b]
Blood transfusion	37 (11.8%)	8 (18.6%)	0.206[b]
Preoperative Hb level (g/dl)	14.18±1.4	13.97±1.36	0.399[a]
Nadir Hb level on bypass (g/dl)	9.29±1.27	8.89±1.27	0.053[a]
Cardiopulmonary bypass time (min)	75.0 (28-222)	76.0 (31-145)	0.179[c]
Cross-clamp time (min)	49.5±15.7	55.6±17.9	0.020[a]
Acute kidney injury	3 (1.0%)	3 (7.0%)	0.004[b]

TIA: transient ischemic attack; CVA: cerebral vascular attack; LVEF: left ventricular ejection fraction; Hb: hemoglobin.
*Kidney dysfunction: preoperative glomerular filtration rate (GFR) <60.
Data represents mean±SD, n (%) or median (min-max).
[a]Student's t-test.
[b]Chi-square test.
[c]Mann-Whitney U-test.

One of the critical values used to assess the DO_2i was 272 ml/min/m^2, established by Ranucci.[6]

An additionally chosen cut-off value was 310 ml/min/m^2, which was determined using a receiver operating characteristic (ROC) curve.

Other operative values collected were nadir hemoglobin level on bypass, CPB time, aortic cross-clamp time and the number of homologous blood transfusions. The administration of packed cells during surgery and in the Post-Anesthetic Care Unit (PACU) or Intensive Care Unit (ICU) was registered as blood transfusion.

The occurrence of delirium was defined by the postoperative administration of haloperidol, which was the primary drug of choice at the Catharina Hospital, in the case of a positive delirium screening test like a confusion assessment method (CAM) or CAM-ICU and multidisciplinary consultation. The group of patients was split into age categories: <50, 50-59, 60-69, 70-79 and >79 for further investigation of the role of age in this patient population.

Statistics

Statistical analyses were performed using an SPSS software package (IBM SPSS version 23.0, Armonk, NY, USA). Continuous variables were tested using either the Student t-test, or, in the case of a non-normal distribution, the Mann-Whitney U test. Categorical data was tested using the Pearson Chi-square test. For each variable, the skewness and kurtosis values were used to analyze whether there was a normal distribution of data. Data, analyzed using the Mann-Whitney U test, were expressed as median values completed with the minimum and maximum. All other data were presented as mean values, with either the standard deviation for continuous variable data or the percentage of the total for categorical data. Values of $p<0.05$ were considered statistically significant. For univariate and multivariate analysis, a binary logistic regression analysis was used. A ROC curve with its corresponding area under the curve value was used to determine a predictive nadir DO_2i value for postoperative delirium in our study population.

Results

Finally, 357 patients out of 402 eligible for the study completed our audit. Excluded were 45 patients due to incomplete data (40), preoperative haloperidol (3) or multiple aorta occlusions (2). From the study population, 43 patients (12.0%) were diagnosed with delirium. Table 1 shows the patients and intraoperative characteristics. Age and previous cognitive impairment were more frequent in the delirium group. Also, patients with preoperative kidney dysfunctions suffered more often from postoperative delirium. Although CPB time did

Table 2. Nadir DO_2i and delirium.

Variable	No delirium (n=314)	Delirium (n=43)	p-value
Nadir DO_2i (ml/min/m^2)	321.6±41.5	301.5±41.5	0.003

Data represents mean±SD. Student's t-test.

Table 3. DO_2i and delirium using 272 (ml/min/m^2) AKI threshold.

Variable	No delirium (n=314)	Delirium (n=43)	p-value
Time DO_2i<272 (sec)	10 (0-3750)	20 (0-3280)	0.097
AUC DO_2i<272 (ml/m^2)	3.7 (0-2750.1)	8.9 (0-2201.8)	0.157

Data represents median (min-max). Mann-Whitney U-test.

Table 4. DO_2i and delirium using 310 (ml/min/m^2) threshold.

Variable	No delirium (n=314)	Delirium (n=43)	p-value
Time DO_2i < 310 (sec)	60 (0-6000)	780 (0-5520)	0.039
AUC DO_2i < 310 (ml/m^2)	66.3 (0-4675.5)	197.1 (0-4925.4)	0.034

Data represents median (min-max). Mann-Whitney U-test. AUC: area under the curve.

not differ between the groups, there was a significant difference in cross-clamp time (p=0.02), with disadvantage for the delirium group. Of hemoglobin-related characteristics, only nadir hemoglobin on bypass clearly differed between the groups, but just failed statistical significance (p=0.053). Of all patients, 1.7% developed AKI. The incidence of AKI in the group with delirium was significantly higher than in the group without (p=0.004).

Table 2 shows that the nadir DO_2i on bypass was negatively associated with postoperative delirium, with a significantly lower mean value in the delirium group compared to the no-delirium group (p=0.003).

In Table 3, the calculated parameters of "time below the critical value" and "area under the curve" of DO_2i are presented for the 272 ml/min/m^2 AKI threshold. The differences for both parameters related to this threshold were not significant.

In the analysis of a ROC curve, a cut-off DO_2i value of 310 ml/min/m^2 was determined using the curve coordinates with an area under the curve of 0.634 with a specificity of 65% and sensitivity of 62%. This revised critical value was used for further analysis. In Table 4, the data for parameters "time below the critical value" and "area under the curve" are shown calculated using the value of 310 ml/min/m^2. Here, both parameters were significantly higher in the delirium group (p=0.039 and p=0.034). Still, in the no-delirium group, 271 out of 314 (86%) patients were measured at least once under the threshold, in the delirium group 38 out of 43 (88%).

To recognize the potential risk factors for postoperative delirium in our study population univariate and multivariate logistic regression analysis were performed. In the univariate analysis, all parameters of DO_2i were significant; nadir DO_2i p=0.045, time DO_2i <310 p=0.010 and AUC DO_2i <310 p=0.008. Age, preoperative kidney dysfunction, previous cognitive impairment and cross-clamp time, being known delirium risk factors from the literature as well as proven significant factors in our patients, were included in multivariate analysis and shown to be independent predictors of delirium. Nadir DO_2i, as well as the remaining DO_2 parameters, were not identified as independent predictors of delirium (Table 5).

In Table 6, the incidence of delirium in the different age categories of patients is shown. None of the patients younger than 50 years old were diagnosed with postoperative delirium. As for the other patients, the percentage diagnosed with delirium climbed with age. In the group of patients older than 79 years, 53.8% were diagnosed with delirium after CABG. Nadir DO_2i was calculated for the different age categories (Table 7). The differences in the mean of the nadir DO_2i between the groups were not statistically significant, most likely due to low patient numbers per category. The results for nadir DO_2i demonstrate that oxygen delivery during bypass was lower, overall, in older patients. The mean nadir DO_2i of the delirium and non-delirium groups differed the most for patients of 79 years and older.

Discussion

This retrospective study demonstrated a significantly lower mean nadir DO_2i on bypass in patients who suffered postoperative delirium compared to the delirium-free study population. For the 272 ml/min/m^2 AKI threshold, no significant difference was found for "time of DO_2i below the critical value" and "area under the curve" parameters, which could indicate that information about the duration and depth of low DO_2 was not specifically accurate in the prediction of postoperative delirium in our study population. However, further exploration of the study data revealed an enormous skewness in the distribution for all but the nadir DO_2i data.

We decided to additionally determine the critical DO_2i value valid in our normothermic patients since Ranucci's

Table 5. Multivariate logistic regression analysis for delirium risk factors.

Risk factor	p-value	Odds ratio	95% C.I. Lower	95% C.I. Upper
(Constant)	0.023	0.004		
Age (years)	0.014	1.058	1.011	1.108
Kidney dysfunction	0.004	3.397	1.475	7.825
Previous cognitive impairment	0.005	5.250	1.667	16.54
Cross-clamp time (min)	0.014	1.025	1.005	1.046
Nadir DO_2i (ml/min/m^2)	0.148	0.993	0.984	1.002
(Constant)	0.000	0.000		
Age (years)	0.011	1.061	1.014	1.110
Kidney dysfunction	0.003	3.565	1.543	8.241
Previous cognitive impairment	0.004	5.499	1.739	17.392
Cross-clamp time (sec)	0.029	1.023	1.002	1.044
Time DO_2i <310 ml/min/m^2	0.324	1.000	1.000	1.000
(Constant)	0.000	0.000		
Age (years)	0.010	1.062	1.014	1.111
Kidney dysfunction	0.003	3.559	1.537	8.241
Previous cognitive impairment	0.004	5.523	1.744	17.488
Cross-clamp time (sec)	0.022	1.024	1.003	1.044
AUC <310 ml/min/m^2	0.363	1.000	1.000	1.000

C. I. = confidence interval.

study was performed using mild hypothermia and concerned the kidneys instead of the brain.[6] A critical threshold value of 310 ml/min/m^2 was established for this study population. This higher value is most likely due to the higher oxygen consumption under normothermic circumstances. In the study population, 86% of patients at least once displayed a DO_2i below 310 ml/min/m^2 and only 12% developed postoperative delirium. However, for this threshold, "time of DO_2i below the critical value" and "area under the curve" did demonstrate significant association with postoperative delirium. Ideally, to avoid a type 1 error, further analysis of this newly determined threshold should not be performed in the same set of data. However, we did not state the value of 310 ml/min/m^2 to be an exact threshold, but, instead, wanted to create awareness that the critical DO_2 value is not a fixed value and that the 272 ml/min/m^2 threshold currently used in practice may not be the optimal value to reduce the risk of hypoxia-induced delirium.

Although clearly associated with delirium, none of the DO_2 parameters could be identified as an independent risk factor for postoperative delirium in this study population. Multivariate analysis did identify age, peripheral vascular disease, preoperative kidney dysfunction and cross-clamp time as independent risk factors.

In this study, unlike DO_2i, preoperative hemoglobin and blood transfusion did not significantly differ between the groups, while nadir hemoglobin on bypass just failed to reach significance. In an initial study by Kazmierski, a direct association between anemia and delirium was found: patients with anemia had a fourfold increased risk of postoperative delirium, but red blood cell transfusion was not an independent predictor.[9] However, later research demonstrated that nadir intraoperative hemoglobin does not predict delirium in CABG patients.[10,11] Whenever necessary to keep a sufficient SvO_2 according to standard protocol, the pump flow in our study population was increased as well.

Delirium is a condition that occurs mainly in patients aged above 65 years and affects as much as 50% of elderly people, which is in accordance with our findings.[12] There is a very strong level of evidence for age as an independent predictor for postoperative delirium with surgery in general,[13-16] as well as cardiac surgery, specifically.[1,4,17] Lower DO_2i values in the older patient categories are paired with a higher occurrence of postoperative delirium. The older patients in our population had lower values for preoperative hemoglobin and nadir hemoglobin on bypass, which could explain the lower DO_2i values. Moreover, instead of increasing pump flow to compensate for their low hematocrit, it could be that this is accepted in older patients since their metabolism is considered lower. Cerebral blood flow and oxygen utilization have, indeed, been shown to decrease with age, approximately 0.5% per year, yet not enough to prevent a low DO_2 from causing harm.[18] As a consequence, an increased oxygen supply could be required in elderly patients. However, to investigate this theory further, more elderly patients should be included.

In a recent article by Magruder, both nadir DO_2i on bypass and postoperative hypotension were identified as

Table 6. Incidence of delirium in different age groups.

Patients n	Age	No delirium (n=314)	Delirium (n=43)
16	<50	16 (100%)	0 (0%)
70	50-59	65 (92.9%)	5 (7.1%)
127	60-69	115 (90.6%)	12 (9.4%)
131	70-79	112 (85.5%)	19 (14.5%)
13	>79	6 (46.2%)	7 (53.8%)

Data represents number (n) and (% of age group).

Table 7. Oxygen delivery values in different age groups.

Variable	Age	No delirium	Delirium	p-value
Nadir DO_2i (ml/min/m^2)	50-59	329.4±40.4	339.0±53.0	0.711[a]
	60-69	328.5±40.6	315.7±29.7	0.289[a]
	70-79	307.8±39.5	290.9±39.0	0.096[a]
	>79	300.3±28.3	277.6±41.3	0.280[a]

Data represents mean ± SD
[a]Student's t-test

risk factors for AKI after cardiac surgery.[19] Regarding delirium, a mean arterial pressure (MAP) below 60 mmHg for over 15 minutes is known to disrupt autoregulation of cerebral blood flow.[20] This could, subsequently, influence the oxygen delivery to the brain, however, evidence in research is conflicting.[21] Since MAP data during CPB were not included in this study, the influence of hypotension on the occurrence of delirium could not be investigated. In addition to MAP data, the status of cerebral autoregulation during surgery would also be useful information in a follow-up study on delirium.

Study limitations

The main limitation in this retrospective, observational, single-center study is that preoperative data were retrieved from the clinical standard screening records, not specific for the purpose of the study. Additionally, we consider using the administration of haloperidol to define postoperative delirium to be suboptimal, however, the retrospective character of this research did not leave many alternatives. However, the procedure was the same in all patients: only after multidisciplinary consultation was haloperidol prescribed. Still, we do emphasize the importance of execution and registration of a proper delirium diagnosing tool like CAM (-ICU) and regard this a key point for any follow-up research on this topic.

The definition used in our research should, in theory, include hyperactive, hypoactive and the mixed form of delirium. However, even CAM-ICU has been shown to present a lower sensitivity in the hypoactive subtype of delirium compared to the hyperactive or mixed subtypes.[22] One should, therefore, keep in mind that the actual incidence of delirium might be somewhat higher than 12%. The definition used for AKI was largely based on AKIN criteria, yet could not fully meet requirements due to the lack of urine output data.

The main strength of this study is that it was performed on the CABG population under normothermic conditions, which prevents interference of additional delirium risk factors associated with valve or aorta surgery and possible temperature-related effects. In addition, this study uses more comprehensive parameters to determine DO_2, alternative to a single nadir DO_2 value.

Conclusion

In conclusion, this study showed significant differences between nadir DO_2i levels during CPB in patients with and without postoperative delirium after normothermic CABG. In multivariate analysis, DO_2i parameters could not be identified as independent predictors for delirium.

Declaration of Conflicting Interests

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