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The association between gender, cognitive function, markers of inflammation and preoperative cerebral oxygen saturation in a cohort of preoperative cardiac surgery patients

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Abstract

Objective: Determination of factors influencing the preoperative cerebral oxygen saturation ($rScO_2$) measured with near infrared spectroscopy in a cohort of cardiac surgical patients.
Methods: Secondary exploratory analysis of 128 preoperative cardiac patients enrolled in a clinical trial determining the cognitive function after sevoflurane- vs propofol-based anesthesia for on-pump cardiac surgery [1] (ISRCTN44821042). Stratification of patient groups was performed by quartiles of preoperative $rScO_2$. Quartile 1 (Q1) $rScO_2$ < 61.0%, Q2 $rScO_2$ = 61.0-64.5%, Q3 $rScO_2$ = 65.0-68.0%, Q4 $rScO_2$ > 68.0%. Preoperative demographic data as well as cognitive tests and laboratory data were compared according to the groups.
Results: Patients in the groups with lower $rScO_2$ were older, had higher EuroScore, and showed higher levels of C-reactive protein. More female patients were in the groups with low $rScO_2$. Patients with low $rScO_2$ had worse results in two of four cognitive tests.
Conclusion: Preoperative $rScO_2$ is associated with several factors that have impact on postoperative outcome and might therefore serve as important non-invasive indicator for postoperative risk.

Key words: cerebral oxygen saturation, risk prediction, cardiac anesthesia

Introduction

Cerebral oxygen saturation measured with near infrared spectroscopy [2] has been shown to be associated with postoperative cognitive dysfunction and clinical outcome in cardiac- [3-5] and non-cardiac surgery [6]. Based on these clinical findings, algorithms have been proposed to maintain adequate cerebral oxygenation during surgery [7]. Several factors to be influenced according to these algorithms are related to cerebral perfusion or oxygen content and therefore oxygen delivery to the brain. Adequate arterial oxygen saturation and hemoglobin are relevant for cerebral oxygenation [8, 9], mean arterial pressure and carbon dioxide tension are equally related to cerebral perfusion [8].

Recent work focuses not only on cerebral oxygen saturation as indicator for intraoperative cerebral perfusion but on the impact of *preoperative* cerebral oxygenation on postoperative outcome [10]. Factors that influence this preoperative cerebral oxygen saturation might therefore be important not only for risk-prediction but for risk-reduction. Again, the *preoperative* cerebral oxygenation has been linked to factors of cerebral perfusion such as left ventricular function, but also to the general severity of preoperative morbidity measured with the EuroScore [10]. Further, Kishi and co-workers connect age and cerebral oxygenation [9] and hereby indicate an association between age-related changes in microcirculation and cerebral oximetry.

A very recently published study by Carlson and co-workers reports an association between cognitive function and cerebral oxygen saturation [11] in a community dwelling elderly population. The cerebral oxygen saturation therefore seems to be related not only to structural but also to functional changes in the brain.

The present study tries to identify *preoperative* patient-related factors influencing the regional cerebral oxygen saturation including cognitive function and markers of inflammation. The exploratory, post-hoc analysis is based on a cohort of cardiac surgical patients that had been enrolled in a clinical trial determining the cognitive function after sevoflurane- vs propofol-based anaesthesia for on-pump cardiac surgery [1] (ISRCTN44821042).

Methods

128 patients scheduled for elective or urgent cardiac surgery with cardiopulmonary bypass had been enrolled in the prospective, randomized trial after approval of the local ethical committee and written informed consent. Exclusion criteria were age below 18 years, overt neurological diseases or dementia, significant stenosis of the carotid arteries, pregnancy, contra-indications for sevoflurane or propofol, insufficient knowledge of the German language, and emergency indication for surgery.

Demographic data were obtained after inclusion.

Cognitive tests were performed on the day prior to surgery by three trained investigators. The test-battery included the Abbreviated-Mental-Test (AMT) for assessment of global cognitive function [12], the Stroop-Test for determination of directed attention and interference [13], a version of the Trail-making test, and a word-list for short-term memory. Most of the tests are taken from the 'Nuremberg Geriatric Inventory (NGI)' [13] in order to shorten and adapt to the clinical situation. The German self-report inventory BSKE (Befindlichkeitsskalierung anhand von Kategorien und Eigenschaftswoertern) [14] was used to measure the positive and the negative mood.

Preoperative blood test included creatinine, white and red blood cell count, high sensitive troponin I, C-reactive protein and N-terminal pro brain natriuretic peptide (NTproBNP).

The preoperative regional oxygen saturation ($rScO_2$) was obtained by bi-hemispheric application of the non-invasive optodes, immediately before induction of anaesthesia using the INVOS 5100 Cerebral Oximeter (Covidien Germany GmbH, Neustadt, Germany). The mean of both hemispheres was used as "preoperative $rScO_2$" for the present analysis.

All patients received anesthesia and surgery according to the institutional standard. The present analysis included merely preoperative values.

The present analysis has to be understood as a merely exploratory, hypothesis-generating approach. For the statistical analysis the preoperative $rScO_2$-values were stratified in quartiles and the relevant factors were compared according to the groups. After Kolmogorov-Smirnov-tests for equality of distribution, one-way analysis of variance for continuous data and chi-square-test for categorical data were performed as appropriate.

Results

118 patients could be included in the analysis, in 10 patients values were missing or surgery has been cancelled.

Distribution of the preoperative $rScO_2$ is shown in figure 1. Quartiles were defined as

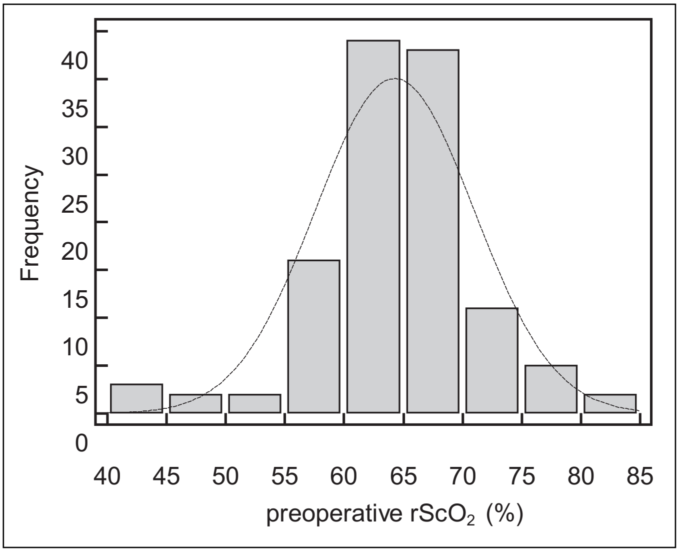

Figure 1: Distribution of preoperative regional cerebral oxygen saturation

follows: Quartile 1 (Q1): $rScO_2$ < 61.0%, quartile 2 (Q2): $rScO_2$ = 61.0 to 64.5%, quartile 3 (Q3): $rScO_2$ = 65.0 to 68.0%, quartile 4 (Q4): $rScO_2$ > 68.0%.

Table 1 shows the demographic data and data of preoperative morbidity. Patients in the lowest quartile for preoperative $rScO_2$ (Q1) were older than those in the highest quartile (Q4), and had higher EuroScores than those in Q3 and Q4. There were more females in the lowest quartile. The groups did differ by trend in the number of patients with diabetes, the numerical differences in the incidence of chronic kidney disease and cerebrovascular disease did not reach statistical significance. We found no group differences in the planned type of surgery.

Figure 2 illustrates the cognitive test performance. Patients with low preoperative rScO2 showed worse test results in the two of four cognitive tests that focused at speed in task performance. There were no differences in mood (data not shown).

The results of the laboratory tests are shown in table 2. There were no significant differences in hemoglobin, leucocyte count, high sensitive troponin, or creatinine. The group with low $rScO_2$ did differ significantly in C-reactive protein from the group with high $rScO_2$. The numerical differences in NTproBNP did not reach statistical significance due to the extremely large variances.

Table 1: Demographic data and data of preoperative morbidity according to preoperative regional cerebral oxygen saturation quartiles. If not mentioned otherwise, data is given as means (standard deviation)

	Q1 **rScO2 < 61%** **N=33**	**Q2** **rScO2 =** **61- 64.5%** **N=29**	**Q3** **rScO2 =** **65.0 - 68%** **N=27**	**Q4** **rScO2 > 68%** **N=29**	**P**
Age (years)	67.6 (9.1)	65.4 (6.0)	61.6 (7.2)	63.7 (9.3)	0.038[a] Q1 ≠ Q4
Gender	Female n=16 (48%)	Female n=7 (24%)	Female n=5 (19%)	Female n=4 (14%)	0.010[b]
Body mass index	27.5 (3.8)	28.4 (2.9)	29.1 (3.8)	28.7 (4.9)	0.425[a]
Educational level	0: n=3 (9%) 1: n=18 (55%) 2: n=0 (0%) 3: n=1 (3%) 4: n=2 (6%) 5: n=3 (9%) Missing n=6 (18%)	0: n=0 (0%) 1: n=14 (48%) 2: n=5 (17%) 3: n=1 (4%) 4: n=3 (10%) 5: n=4 (14%) Missing n=2 (7%)	0: n=1(4%) 1: n=8 (30%) 2: n=11 (40%) 3: n=0 (0%) 4: n=1 (4%) 5: n=1 (4%) Missing n=5 (18%)	0: n=1 (4%) 1: n=13 (45%) 2: n=6 (21%) 3: n=1 (4%) 4: n=3 (10%) 5: n=2 (7%) Missing n=3 (10%)	0.082[b]
Euroscore	5.4 (3.3)	3.6 (2.3)	3.2 (2.6)	3.3 (3.0)	0.011[a] Q1 ≠ Q3 &Q4
Diabetes	Insulin n=6 (18%) No insulin n=8 (24%)	Insulin n=1 (4%) No insulin n=2 (7%)	Insulin n=2 (7%) No insulin n=3 (11%)	Insulin n=7 (24%) No insulin n=3 (10%)	0.050[b]
Chronic kidney disease	n=19 (59.4%)	n=14 (48.3%)	n=11 (40.7%)	n=9 (31.0%)	0.153[b]
Chronic obstructive lung disease	n=3 (9.1%)	n=3 (10.3%)	n=0 (0%)	n=1 (3.4%)	0.305[b]
Cerebrovascular insufficiency	n=4 (12.1%)	n= (6.9%)	n=2 (7.4%)	n=0 (0%)	0.306[b]
Type of surgery	CABG n=20 (60.6%) Valve n=5 (15.2%) Combined n=8 (24.2%)	CABG n=19 (65.5%) Valve n=5 (17.5%) Combined n=5 (17.5%)	CABG n=16 (59.3%) Valve n=6 (22.2%) Combined n=5 (18.5%)	CABG n=19 (65.5%) Valve n=3 (10.3%) Combined n=7 (24.1%)	0.921[b]

[a]: One-way analysis of variance (ANOVA); [b]: Chi-Square-Test
Educational level: 0 = no graduation; 1 = compulsory school; 2 = secondary school; 3 = general qualification for university entrance; 4 = technical college; 5 = university degree

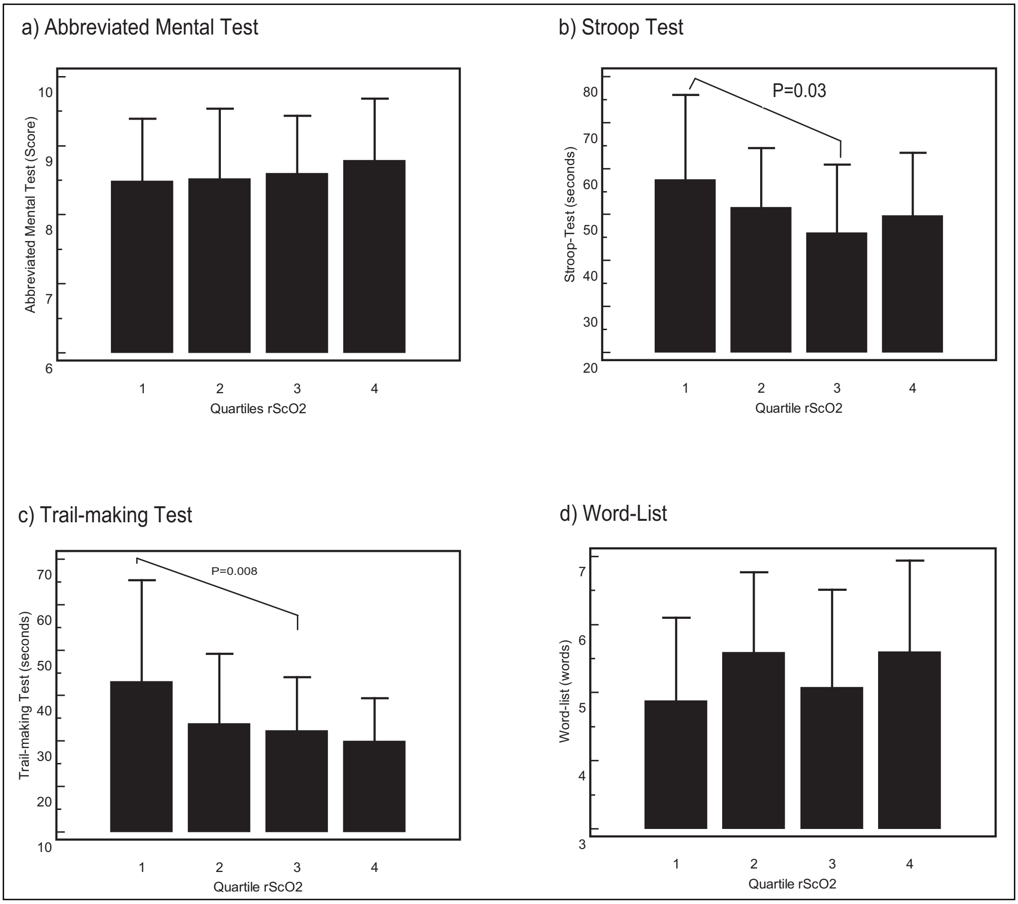

Figure 2: Cognitive test-scores for patients in different quartiles of preoperative $rScO_2$. Quartile 1: $rScO_2$ < 61.0%, quartile 2: $rScO_2$ = 61.5 - 64.5%, quartile 3: $rScO_2$ = 65.0 to 68.0%, quartile 4: $rScO_2$ > 68.0%

Table 2: Comparison of laboratory results in patients with different baseline regional cerebral oxygen saturation. Data is given in mean (standard deviation), significance is tested with one-way ANOVA and post hoc Bonferroni-analysis.

	Q1 $rScO_2$ < 61% N=33	Q2 $rScO_2$ = 61- 64.5% N=29	Q3 $rScO_2$ = 65.0 - 68% N=27	Q4 $rScO_2$ > 68% N=29	P
Hb (g/l)	135.5 (15.5)	139.5 (15.3)	144.3 (12.7)	144.4 (13.6)	0.056
Leucocytes (/µl)	7887 (2282)	7593 (2318)	7039 (1579)	7917 (2300)	0.397
CRP (mg/dl)	16.6 (22.6)	9.0 (10.6)	7.5 (8.2)	6.0 (7.4)	0.017 Q1 ≠ Q4
hsTrop (pg/ml)	86.4 (256.0)	20.1 (27.9)	39.3 (96.4)	45.3 (178.6)	0.518
NTproBNP (pg/ml)	1292 (1538)	886 (1973)	464 (684)	473 (114)	0.089
Creatinine (µmol/l)	82.1 (25.6)	88.5 (29.9)	85.2 (22.1)	78.8 (10.3)	0.425

Discussion

The present analysis explored several factors that might influence preoperative cerebral oxygen saturation. Preoperative cerebral oxygenation measured with near infrared spectroscopy has been shown to be associated with postoperative morbidity and mortality [10, 15]. Identifying factors that influence cerebral oxygenation could contribute to risk-prediction or even risk-reduction.

The association of age and cerebral oxygenation that was found in the present analysis has been shown by other authors [9]. This can be explained by reduced cerebral oxygen delivery in higher age [16], as well as changes in cerebral micro-circulation [17], that lead to a higher cerebral oxygen extraction from the capillaries [18]. The higher cerebral oxygen extraction impairs cerebral oxygen balance and reduces the mainly venous cerebral oxygen saturation [8].

Interestingly in our cohort, more women had low cerebral oxygen saturation values. This finding stays in contrast to other publications [9] but might be the expression of higher morbidity in female patients presenting for cardiac surgery [19]. The higher risk of cardiac surgery for female patients has been accounted for in the EuroScore [20], a tool to predict postoperative mortality after cardiac surgery. The EuroScore compiles several patient- and surgery related factors, including gender, age, renal impairment, and left-ventricular function. In the present study, patients with low cerebral oxygen saturation had higher EuroScores. This data supports the assumption, that cerebral oxygenation might serve as an index for the overall severity of illness and subsequently impaired regional tissue perfusion [21].

The association of cognitive function and cerebral oxygenation is an interesting finding and supports the data published by Carlson and co-workers in a community-dwelling cohort of elderly people [11]. In neurosciences, cerebral oximetry using near infrared spectroscopy (NIRS) is used to image cerebral activation [22, 23]. Functional multi-channel NIRS detects regional increases in cerebral blood flow and changes in regional oxygen balance [24]. Reduced cerebrovascular reactivity due to impaired cerebral micro-circulation might in this context alter the normal increase in regional cerebral blood flow as reaction to functional activation [24]. Our observation that patients with impaired regional cerebral perfusion, i.e. low cerebral oxygenation, show worse results in cognitive function tests might therefore be an expression of impaired ability to adapt cerebral blood flow to functional demands [25].

Preoperative levels of C-reactive protein have been associated with postoperative outcome in cardiac surgery [26, 27]. The relation between inflammation and cardiovascular disease has been extensively studied [28]. The association of cerebral oxygenation and levels of C-reactive protein in the present analysis can therefore again be explained by the severity of cardiac illness in the groups of patients with different ranges of cerebral oxygen saturation.

Limitations

The present study reports an exploratory analysis of a cohort of no more than 128 patients. The small sample size and the methodology is certainly the major limitation for the interpretation of the results. However, the information given can be considered in the planning of further studies aiming at improvement of preoperative condition in order to reduce preoperative risk.

Conclusion

The preoperative regional cerebral oxygen saturation has been shown to be associated with postoperative outcome [10]. It has further been related to postoperative delirium [29]. The present study adds to this knowledge by showing the association between cerebral oxygenation and cognitive function as well as inflammation. Taking together these findings the present study supports the hypothesis that the cerebral oxygen saturation is a non-invasive, easily obtainable index for preoperative severity of illness.

Most of the identified factors influencing the cerebral oxygenation are unchangeable, i.e. age or gender, but further studies should investigate approaches to improve cerebral oxygenation preoperatively by improvement of the global hemodynamic situation and/or regional tissue perfusion with the aim of reducing perioperative risk in cardiac surgery.

Conflict of interest

The authors J.S. and M.H. receive honoraria for lectures from Covidien Germany GmbH. The other authors declare that they have no conflicts of interest.

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