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Carotid artery blood flow velocities during open-heart surgery and its association with delirium
A prospective, observational pilot study

Martin H. Bernardi, MD[a,*], Martin Wahrmann[a], Martin Dworschak, MD[a], Clemens Kietaibl, MD[b], Robin Ristl, PhD[c], Maximilian Edlinger-Stanger, MD[a], Andrea Lassnigg, MD[a], Michael J. Hiesmayr, MD[a], Ulrike Weber, MD, PhD[a]

Abstract

The aim of this prospective observational single-centre pilot study was to evaluate the association between alterations in carotid artery blood flow velocities during cardiac surgery and postoperative delirium.

Carotid artery blood flow velocity was determined perioperatively at 5 different timepoints by duplex sonography in 36 adult cardiac surgical patients. Delirium was assessed using the Confusion Assessment Method for the ICU and the Intensive Care Delirium Screening Checklist. Additionally, blood flow velocities in the middle cerebral arteries, differences in regional cerebral tissue oxygenation and quantity and quality of microemboli were measured.

Delirium was detected in 7 of 36 patients. After cardiopulmonary bypass carotid artery blood flow velocities increased by +23 cm/second (95% confidence interval (CI) 9–36 cm/second) in non-delirious patients compared to preoperative values ($P = .002$), but not in delirious patients (+3 cm/second [95% CI −25 to 32 cm/second], $P = .5781$). Middle cerebral artery blood flow velocities were higher at aortic de-cannulation in non-delirious patients (29 cm/second [inter-quartile range (IQR), 24–36 cm/second] vs 12 cm/second [IQR, 10–19 cm/second]; $P = .017$). Furthermore, brain tissue oxygenation was higher in non-delirious patients during surgery.

Our results suggest that higher cerebral blood flow velocities after aortic de-clamping and probably also improved brain oxygenation might be beneficial to prevent postoperative delirium.

Abbreviations: AoCC = aortic cross-clamp, BMI = body mass index, CA = carotid artery, CAM-ICU = Confusion Assessment Method for the ICU, CBF = cerebral blood flow, CBFV = cerebral blood flow velocity, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CPB = cardiopulmonary bypass, EuroSCORE = European system for cardiac operative risk evaluation score, ICDSC = Intensive Care Delirium Screening Checklist, ICU = intensive care unit, IDDM = insulin-dependent diabetes mellitus, IQR = inter-quartile range, LOS = length of hospital-stay, LOS-ICU = length of ICU-stay, LVEF = left ventricular ejection fraction, MCA = middle cerebral arteries, NIDDM = non-insulin-dependent diabetes mellitus, NIRS = near-infrared spectroscopy, $PaCO_2$ = partial pressure levels of carbon dioxide, PAOD = peripheral arterial obstructive disease, POD = postoperative day, rSO_2 = regional cerebral oxygen saturation, TCD = transcranial Doppler.

Keywords: cardiac surgery, cardiopulmonary bypass, cerebral blood flow velocity, delirium, doppler ultrasonography, transcranial Doppler ultrasonography

1. Introduction

Postoperative delirium is an acute and fluctuating state of confusion and disorientation, characterized by changes in attention, cognition, consciousness, and perception. After cardiac surgery it occurs with an incidence of up to 50%.[1–4] Possible causes for this multifactorial complication are systemic hypoperfusion, cerebral microembolization, and an inflammatory response, which eventually lead to regional or global imbalances between cerebral oxygen demand and supply.[5,6]

Postoperative delirium, an impairment of cerebral function that occurs with a high incidence can have detrimental and long-lasting consequences and remains a serious healthcare burden, particularly due to the associated medical costs, increased morbidity, long-term cognitive deficits, and raised mortality.[1,5,7–9] Unfortunately, up to date, the pathophysiology of postoperative delirium is not fully understood.

Adequate blood supply to the brain depends on sufficient cerebral blood flow (CBF) via the vertebral arteries and the internal carotid arteries. The latter carry almost two-thirds of the CBF and are easily accessible for blood flow examination with Doppler ultrasound.[10]

The primary aim of this single-center pilot study was to investigate whether perioperative CBF velocity (CBFV) in the carotid artery (CA) differs between patients who would be diagnosed with delirium after open-heart surgery and those without delirium. Furthermore, we assessed whether CBFV in the middle cerebral artery (MCA) differs between patients in both groups. Also, we examined group differences in the magnitude of cerebral microemboli by transcranial Doppler (TCD), and bilateral regional cerebral oxygenation (rSO₂) of the frontal lobes by near-infrared spectroscopy (NIRS). Moreover, we tested the impact of cardiopulmonary bypass (CPB) – associated inflammation (defined as raised interleukin-6 (IL-6) levels) on delirium,[11,12] length of hospital and intensive care unit (ICU)-stay (LOS, LOS-ICU) and 30-day mortality.

2. Methods

2.1. Ethics approval

This study was approved by the Ethics committee of the Medical University of Vienna (Ref: 1964/2016) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03117712, Principal investigator: Ulrike Weber, M.D., Date of registration: April 18, 2017).

2.2. Study design, setting, and participants

In this prospective observational single-center pilot study we included 40 elective cardiac surgical patients undergoing open-heart surgery (valve replacement or repair, combined procedures, atrial or ventricular septal defect repair) on CPB. The study was conducted between May 8, 2017, and June 5, 2018 and adhered to the applicable CONSORT guidelines. We excluded the following interventions or conditions: declined informed consent, emergency procedures, postoperative need for extracorporeal cardiac assist device, untreated or uncontrolled preoperative arterial hypertension (i.e., blood pressure >140/90 mm Hg), planned profound hypothermic CPB (body temperature <34°C), history of preoperative dementia or cognitive impairment, history of stroke, significant carotid artery disease (i.e., >50% stenosis of

the internal carotid artery), age <18 years, and chronic renal replacement therapy.

2.3. Procedure

Patients were enrolled the day before surgery. Anesthesia was induced with propofol (1.0–1.5 mg/kg), fentanyl (3–10 μg/kg), and cis-atracurium (0.2 mg/kg) and maintained with sevoflurane (target BIS value 40–50)[13] and fentanyl (0.05–0.1 μg/kg/min). Patients received tranexamic acid according to their kidney function. Anticoagulation was achieved with heparin (400 IU/kg) to reach an activated clotting time >480 seconds. CPB was performed using non-pulsatile flow targeting 100% calculated cardiac output (i.e., 2.0–2.4 L/m²/min). Mean arterial pressure was maintained between 55 and 70 mm Hg throughout CPB. The intraoperative trigger for the transfusion of packed red blood cells was a hematocrit of ≤22%.[14] Blood glucose levels were kept between 80 and 150 mg/dL intra- and postoperatively. Patients were sedated on ICU with propofol until extubation. On the ICU all patients received interventions known to reduce the incidence or reduce the duration of postoperative delirium according to institutional standards. These included early mobilization and appropriate environmental stimuli (i.e., use of glasses and hearing aids). Postoperative pain control was performed with a combination of opioid and non-opioid analgesics and hyperactive delirium was treated with dexmedetomidine in combination with atypical antipsychotics.

2.4. Outcomes

2.4.1. Primary outcome. We investigated differences in CBFV in the CA during open-heart surgery between patients with and without postoperative delirium.

2.4.2. Secondary outcomes. As secondary outcomes we assessed group differences in: (A) CBFV in the MCA; (B) the magnitude of cerebral microemboli by TCD; (C) the association between levels of rSO₂; (D) in CPB-associated inflammation (determined by elevated IL-6 levels 2 hours postoperatively and on the first postoperative day); (E) LOS and LOS-ICU; and (F) 30-day mortality.

2.5. Data collection

Preoperative patient data (age, sex, body mass index (BMI), European system for cardiac operative risk evaluation score [EuroSCORE]), comorbidities (history of myocardial infarction, asthma, chronic obstructive pulmonary disease [COPD], insulin or non-insulin-dependent diabetes mellitus [IDDM, NIDDM], chronic kidney disease [CKD], recent cardiac decompensation [i.e., within 24 hours before surgery], peripheral arterial obstructive disease [PAOD], atrial fibrillation, stable and unstable angina pectoris, arterial hypertension, left ventricular ejection fraction [LVEF]), preoperative medication (statins, β-Blocker, α2-adrenergic-agonist, calcium channel-blockers), surgery- and procedure-related factors (i.e., diagnosis, surgical procedure, duration of anesthesia and surgery, duration of CBP and aortic cross-clamp time [AoCC], hematocrit, arterial partial pressure levels of carbon dioxide [PaCO₂]), and postoperative data (LOS, LOS-ICU, length of mechanical ventilation, IL-6 levels) were collected.

2.5.1. Carotid duplex sonography. Carotid duplex sonography for estimation of CBFV was evaluated at 5 different time points: (A) before induction of anesthesia; (B) before sternotomy and

CPB; (C) 10 minutes after AoCC; (D) after CPB and chest closure, when stable hemodynamics were achieved; and again (E) on postoperative day (POD) 1. CA-CBFV was derived as the peak CBFV [cm/second] within the vessel using a pulsed-wave Doppler. All patients were examined in the supine position. After having identified the common CA in a transverse plane the transducer was rotated into a sagittal plane. The sample volume was adjusted in the center of the vessel and an angle correction was performed. This measurement can be performed independently of flow conditions (laminar or pulsatile). Due to restricted access to the patients' neck during surgery, we were not able to insonnate the internal CA. To avoid further interferences, we focused on CBFV in the left common CA since all central venous lines were inserted in the right jugular vein.

2.5.2. Delirium assessment.

The Confusion Assessment Method for the ICU (CAM-ICU)[15] and the Intensive Care Delirium Screening Checklist (ICDSC)[16] were used for the diagnosis of delirium. Assessment by the CAM-ICU was performed by trained nurses and members of the study team at least once daily and when obvious mental alterations were noted.

The ICDSC evaluates the level of consciousness, inattention, disorientation, hallucinations, psychomotor activity, speech or mood disturbance, sleep disturbance, and fluctuation of symptoms.[17] Patients are considered to have delirium when at least 4 of the above 8 items are deviant. Patients with scores between 1 and 3 are diagnosed as having sub-syndromal delirium.[16,18] One single investigator (MHB) completed the scale based on the information from the last 24 hours, collecting data from patient's interrogation and the evaluation and observation of the ICU nurse. We recorded the CAM-ICU and the ICDSC at the following 3 timepoints: on POD 1, POD 2 and POD 5.

2.5.3. Transcranial Doppler.

During the time the patient's aorta was cannulated both MCAs were insonnated with a pulse-wave transducer at both 2 and 2.5 MHz. For this purpose, we used a multi-frequency pulsed TCD to detect and differentiate high-intensity transient signals in real-time into either artefact, solid or gaseous microemboli (Doppler BoxX, Compumedics Germany GmbH, DWL, Singen, Germany). The TCD software is based on an algorithm described by Devuyst and colleagues.[19] To avoid dislocation of the transducer during continuous recording we mounted a size-adjustable probe holder bi-laterally over the temporal bone window with a head frame (DiaMon, Compumedics GmbH, DWL, Singen, Germany).

Examination criteria were as follows: insonnation depth between 55 and 70 mm, threshold for ME registration set to 9 dB, a sample volume length of 8 mm and a pulse repetition frequency of 7 kHz. The mean MCA-CBFV was concurrently assessed. The TCD examinations were carried out in compliance with the guidelines from the International Consensus Group on Microembolus detection.[20,21] TCD was recorded for 10 minutes at 4 different time points: (A) during cannulation of the ascending aorta; (B) during AoCC; (C) during release of the AoCC; (D) during de-cannulation.

2.5.4. Near-infrared spectroscopy.

A NIRS device (INVOS 5100C, Medtronic, Minneapolis, USA) was used to determine rSO_2 over both frontal lobes in real-time. The respective optodes were placed laterally above the eyebrow and attached using the manufacturer's adhesive holder. NIRS was recorded intraoperatively at the same time points as the TCD evaluations.

2.6. Statistical analysis

As neither suitable data for the primary outcome measure, that is differences in CBFV in the CA during open-heart surgery, nor previous data on the incidence of postoperative delirium at our intensive care unit were available during study planning, we considered a mean difference of 1 standard deviation in CBFV in the CA between both study groups (delirium/no delirium) to represent a clinically relevant effect. Also, we assumed a 50% incidence of delirium between POD 1 and POD 5, according to current literature.[1–3]

Under these assumptions, 17 individuals per group would be required to achieve a significance level of 5% in the t-test with a power of 80%. Therefore, we planned to recruit a total of 40 patients to allow for a 20% drop-out rate.

Metric variables are presented as median with inter-quartile range (IQR) and categorial variables as absolute frequencies. Differences between groups were analyzed by using the Student's t test for normally distributed, the Mann–Whitney U-test for non-normally distributed continuous variables. The χ^2-test was employed for categorical variables. To describe the correlation between CBFV and rSO_2 we calculated the Spearman's correlation coefficient.

A P-value of $\leq$.05 was considered statistically significant. Statistical analysis and plots were performed using R 3.4.3 (http://www.R-project.org/).

3. Results

3.1. Patient cohort and characteristics

A total of 40 patients were included in the pilot study. Four patients dropped out of the study after inclusion: 1 patient developed hemodynamic instability after weaning from CPB leading to an unplanned treatment with extracorporeal membrane oxygenation; another patient required unscheduled intraoperative deep hypothermic cardiac arrest; in 1 patient the procedure was changed to a minimally-invasive approach with venous drainage being achieved via percutaneous cannulation of the superior vena cava through the right internal jugular vein with the central venous line being placed in the left internal jugular vein, which did not allow us to perform carotid duplex sonography intra-operatively; and in 1 patient the procedure was re-booked for another day when the study team was not available. Therefore, merely 36 patients could be analyzed (Supplemental Fig. 1, http://links.lww.com/MD/D432).

Patients' mean age was 66 ± 12 years, 36% were females, and mean EuroSCORE was 4.7 ± 4.1. Postoperative delirium was found in 7 patients (19%). In 4 patients (57%) delirium occurred on POD1, in 1 patient (14%) on POD 2 and in 2 patients (29%) on POD 5. Among the 29 patients (81%) without delirium, 9 patients (31%) were diagnosed with sub-syndromal delirium. Median BIS values were equal between patients with and those without delirium, 40 (IQR, 39–41) and 42 (IQR, 38–44), respectively (P=.2586). 30-day mortality was 0%. We found a significantly higher proportion of PAOD (P=.041) in delirious patients. Patients with delirium had significantly lower hematocrit levels before CPB (31% [IQR, 27–32%]) than patients without delirium (36% [IQR, 32–39%]; P=.038). This was also the case after AoCC (28% [IQR, 25–29%] and (30% [IQR, 28–33%], respectively; P=.015). Delirium was associated with a significantly longer LOS-ICU (6 days [IQR, 3–11 days] vs 1 day [IQR, 1–3 days]; P=.002), and a prolonged LOS (21

Patient and surgical characteristics.

	No delirium (N=29)	Delirium (N=7)	P-value
Preoperative characteristics			
Age (y)	68 [59;74]	73 [67;76]	.144
Male	19 (65.5%)	4 (57.1%)	.686
Female	10 (34.5%)	3 (42.9%)	
BMI (kg/m^2)	27.8 (3.9)	26.6 (4.7)	.548
EuroSCORE	3.00 [1.30;5.50]	6.40 [2.82;9.40]	.254
Hematocrit (%)	40 [37;44]	37 [35; 39]	.058
Comorbidities			
Asthma	1 (3.45%)	1 (14.3%)	.838
COPD	2 (6.90%)	2 (28.6%)	.414
NIDDM	6 (20.7%)	3 (42.9%)	.466
IDDM	1 (3.45%)	2 (28.6%)	.163
CKD	3 (10.3%)	1 (14.3%)	1.000
Cardiac decompensation	0 (0.00%)	1 (14.3%)	.434
PAOD	0 (0.00%)	2 (28.6%)	.041
Atrial fibrillation	11 (37.9%)	2 (28.6%)	.981
No Angina pectoris	26 (89.7%)	6 (85.7%)	.087
Angina pectoris (stable)	3 (10.3%)	0 (0.00%)	
Angina pectoris (unstable)	0 (0.00%)	1 (14.3%)	
Arterial hypertension	17 (58.6%)	5 (71.4%)	.773
LVEF >50%	25 (86.2%)	4 (57.1%)	
LVEF 30–50%	3 (10.3%)	2 (28.6%)	.209
LVEF <30%	1 (3.45%)	1 (14.3%)	
Medication			
Statins	10 (34.5%)	4 (57.1%)	.502
β-blockers	16 (55.2%)	5 (71.4%)	.722
α2-adrenergic-agonists	1 (3.45%)	0 (0.00%)	1.000
Calcium channel blockers	3 (10.3%)	2 (28.6%)	.520
Intraoperative characteristics			
Valve replacement/repair	18 (62.1%)	6 (85.7%)	.480
Combined procedure	10 (34.5%)	1 (14.3%)	
Ventricular septal defect repair	1 (3.45%)	0 (0.00%)	
Anesthesia time (min)	366 [327;438]	363 [320;436]	.675
Surgery time (min)	289 [250;353]	282 [240;343]	.658
CPB time (min)	155 [122;198]	131 [108;198]	.857
AoCC (min)	112 [81.0;131]	96.0 [81.5;148]	.936
Hematocrit pre CPB (%)	35.5 [32.3;38.9]	31.4 [26.7;31.8]	.038
Hematocrit during AoCC (%)	29.6 [27.6;33.2]	28.3 [24.9;28.9]	.015
Hematocrit post CPB (%)	30.3 [27.3;32.8]	28.8 [28.4;29.3]	.117
IL-6 2 h post CPB (pg/mL)	150 [99.0;294]	180 [55.4;374]	.920
Postoperative characteristics			
Mechanical ventilation (h)	12.5 [10.6;14.8]	25.6 [8.94;34.7]	.480
IL-6 POD 1 (pg/mL)	151 [75.0;256]	178 [130;440]	.289
Hematocrit POD 1 (%)	34.5 [33.4;36.1]	32.9 [30.1;34.5]	.337
LOS-ICU (d)	1 [1;3]	6 [3;11]	.002
LOS-Hospital (d)	10 [9;18]	21.0 [16;25]	.039

Values are presented as number (n), percentage (%), and median [inter-quartile range]. The listed P values of statistical tests were calculated by using t-test for normal distributed continuous and the Mann–Whitney U-test for non-normal distributed continuous and the χ^2-test for categorical variables.

AoCC = aortic cross-clamp, BMI = body mass index, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CPB = cardiopulmonary bypass, European system for cardiac operative risk evaluation = EuroSCORE, ICU = intensive care unit, IDDM = insulin-dependent diabetes mellitus, IL-6 = interleukin 6, LOS = length of stay, LVEF = left ventricular ejection fraction, NIDDM = non-insulin-dependent diabetes mellitus, PAOD = peripheral artery occlusive disease, POD = postoperative day.

[IQR 16–25 days] vs 10 [IQR 9–18 days]; P = .039) compared to patients without delirium. Detailed results are shown in Table 1.

3.2. Primary outcome variable

Preoperative baseline levels for CA-CBFV were 56 cm/second (IQR, 49–62 cm/second) in patients with delirium and 59 cm/second (IQR, 47–66 cm/second) in patients without delirium (P = .802). CA-CBFV before CPB was 53 cm/second (IQR, 40–60

cm/second) in delirious patients and 63 cm/second (IQR, 49–72 cm/second) in non-delirious patients (P = .037). It decreased to nadir levels in both groups during CPB (39 cm/second [IQR, 24–43 cm/second] vs 36 cm/second [IQR, 26–50 cm/second], respectively; P = .610). After CPB, CA-CBFV increased steadily to peak on POD 1 at 73 cm/second (IQR, 71–81 cm/second) in delirious patients and 91 cm/second (IQR, 73–115 cm/second) in non-delirious patients (P = .272; Table 2 and Fig. 1a).

CA-CBFV did not increase after CPB in patients with delirium relative to preoperative values (+3 cm/second [95% CI −25 to

Cerebral perfusion velocities [cm/s].

	No delirium (N = 29)	Delirium (N = 7)	P-value
Common carotid artery			
Preoperative	59 [47;66]	56 [49;62]	.802
Before CPB	63 [49;72]	53 [40;60]	.037
During AoCC	36 [26;50]	39 [24;43]	.610
After CPB	81 [56;110]	51 [46;80]	.070
POD 1	91 [73;115]	73 [71;81]	.272
Middle cerebral artery			
Cannulation	26 [19;45]	21 [19;28]	.402
Cross-clamping	28 [20;38]	22 [19;26]	.201
De-clamping	27 [23;34]	22 [12;28]	.084
De-cannulation	29 [24;36]	12 [10;19]	.017

Values are presented as median [inter-quartile range]. The listed P values of statistical tests were calculated by using the Student's t test for normally distributed, the Mann–Whitney U-test for non-normally distributed continuous variables.
AoCC = aortic cross-clamp, CPB = cardiopulmonary bypass, POD = postoperative day.

32 cm/second]; $P = .5781$) or relative to pre CPB values (+10 cm/second [95% CI −12 to 33 cm/second]; $P = .3053$).

In contrast, CA-CBFV increased in non-delirious patients after CPB by 23 cm/second (95% CI 9–36 cm/second) compared to preoperative values ($P = .002$) and by 17 cm/second (95% CI 3–31 cm/second) compared to values before CPB ($P = .023$; Table 3).

3.3. Secondary outcome variables

Perioperative MCA-CBFV showed only slight variations in non-delirious patients starting from a baseline MCA-CBFV of 26 cm/second (IQR, 19–45 cm/second) at cannulation to 29 cm/second (IQR, 24–36 cm/second) during de-cannulation. In patients with delirium MCA-CBFV started at a somewhat lower level (21 cm/second [19–28 cm/second]) and decreased significantly on CPB until de-cannulation (12 cm/second [IQR, 10–19 cm/second],

$P = .017$; Fig. 1b). We did not find any correlation between mean arterial pressure and MCA-CBFV (Supplemental Table 1, http://links.lww.com/MD/D435 and Supplemental Fig. 2, http://links.lww.com/MD/D433).

Intraoperative rSO_2 ranged between 64% (IQR, 57–72%) and 70% (IQR, 63–78%) in patients without delirium. In patients with delirium we found consistently lower levels of rSO_2 (i.e., between 50% [IQR, 50–57%] and 57% [IQR, 48–66%]) that ranged significantly below those of non-delirious patients during surgery (Fig. 2). We, however, found only a mediocre positive correlation between CA-CBFV and rSO_2 as well as MCA-CBFV and rSO_2 during CPB ($r = 0.31$ and $r = 0.27$, respectively; Fig. 3).

Perioperative $PaCO_2$ levels were significantly lower after CPB in patients with delirium (32 mm Hg [30–36 mm Hg]) compared to those without delirium (40 mm Hg [38–42 mm Hg], respectively; $P = .006$; Table 4). We did not find any correlation between perioperative $paCO_2$ levels and mean arterial pressure (Supplemental Fig. 3, http://links.lww.com/MD/D434).

We did not observe any group differences in the quantity or quality of perioperative microemboli (Fig. 4).

4. Discussion

Our pilot study revealed different CA-CBFV before CPB and a more pronounced increase in CA-CBFV after CPB in non-delirious patients compared to those who presented with postoperative delirium. Recovery of CA-CBFV immediately after CPB was significantly augmented in non-delirious patients compared to preoperative values while it did not change in patients with delirium. Furthermore, we found lower MCA-CBFV and rSO_2-values at comparable time points in patients with postoperative delirium.

Impaired cerebral autoregulation in patients with delirium after cardiac surgery is currently a focus of research.[22] Caldas et al[23] found deranged cerebral autoregulation up to 7 days in patients with postoperative delirium. This potentially contributed to our finding of a slower recovery of CA-CBFV immediately
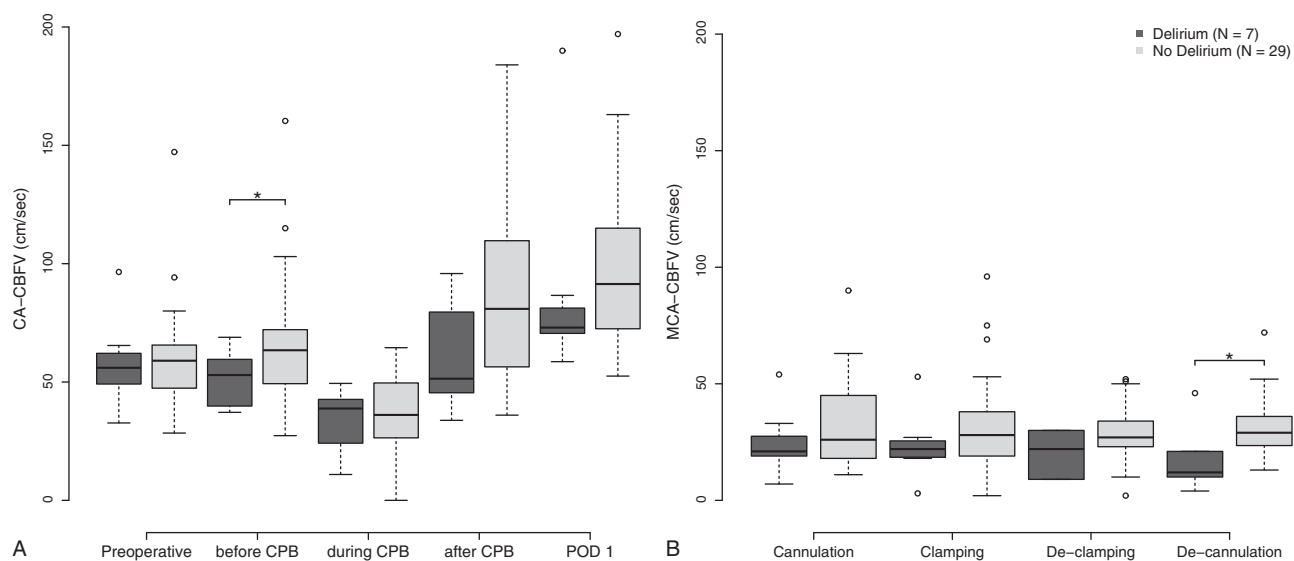

Figure 1. (a) Comparison of carotid artery blood flow velocity (CA-CBFV) and (b) middle cerebral artery blood flow velocity (MCA-CBFV) in cm/s. Dark gray boxes indicate patients with postoperative delirium, light gray boxes indicate patients without postoperative delirium. Asterisks mark significant differences between the 2 groups at $P < .05$.

Table 3

Perioperative carotid artery flow alterations [cm/s].

	Preoperative	Before CPB	During AoCC	After CPB
No delirium (N=29)				
Preoperative	0			
Before CPB	6 [−3;15]	0		
During AoCC	−24 [−32;−16]*	−30 [−40;−20]*	0	
After CPB	23 [9;36]*	17 [3;31]*	47 [34;60]*	0
POD 1	37 [25;50]*	31 [16;46]*	61 [46;76]*	14 [−4;33]
Delirium (N=7)				
Preoperative	0			
Before CPB	−7 [−34;20]	0		
During AoCC	−25 [−43;−7]*	−18 [−40;4]	0	
After CPB	3 [−25;32]	10 [−12;33]	28 [7;49]*	0
POD 1	31 [−14;77]*	38 [−2;79]*	56 [6;107]*	28 [−23;79]

Values are presented as mean difference and 95% confidence interval. Values were compared within columns to the respective baseline (0) by using the paired Student's *t* test. Asterisks mark *P*-values of statistical significance (*P*≤.05).

AoCC=aortic cross-clamp, CPB=cardiopulmonary bypass, POD=postoperative day.

Figure 2. Comparison of regional cerebral oxygen saturation (rSO$_2$) determined by near-infrared spectroscopy. Dark gray boxes indicate patients with postoperative delirium, light gray boxes indicate patients without postoperative delirium. Asterisks mark significant differences between the 2 groups at *P*<.05.

after CPB in delirious patients. Furthermore, Chan and Anemann[24] demonstrated that impaired cerebral autoregulation measured by NIRS is an independent risk factor for postoperative delirium. We also found consistently lower rSO$_2$ levels in patients with postoperative delirium, which has been shown as an independent predictor for postoperative delirium after cardiac surgery before.[25,26] Although the relation between blood flow velocities and rSO$_2$ was poor, slower recovery of CA-CBFV and lower rSO$_2$ levels may be signs for cerebral hypoperfusion. However, both – cerebral hypo- and hyper-perfusion – are discussed as triggers for neurological deterioration after cardiac surgery.[27,28]
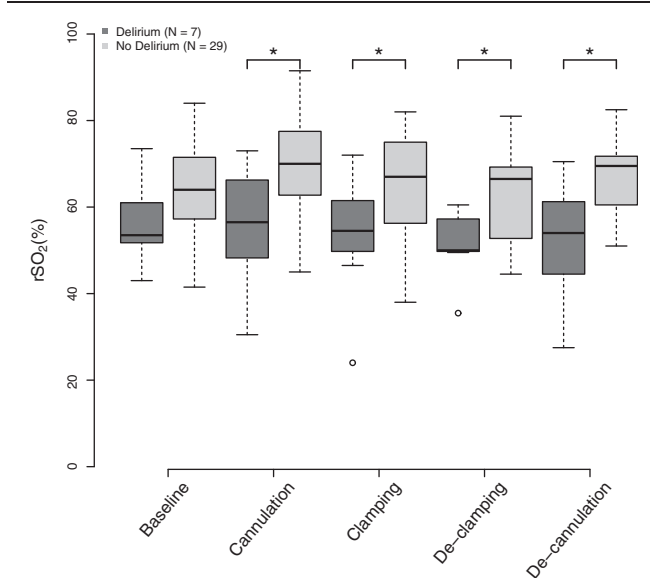
Weaning from CPB and the post-CPB course are the most vulnerable phases during cardiac surgery that encompasses re-establishing stable hemodynamics aligned with an appropriate fluid and pharmacologic management of vascular resistance as well as an optimized ventilation strategy.[29] We deliberately hyperventilated 4 of 7 delirious patients after CPB due to
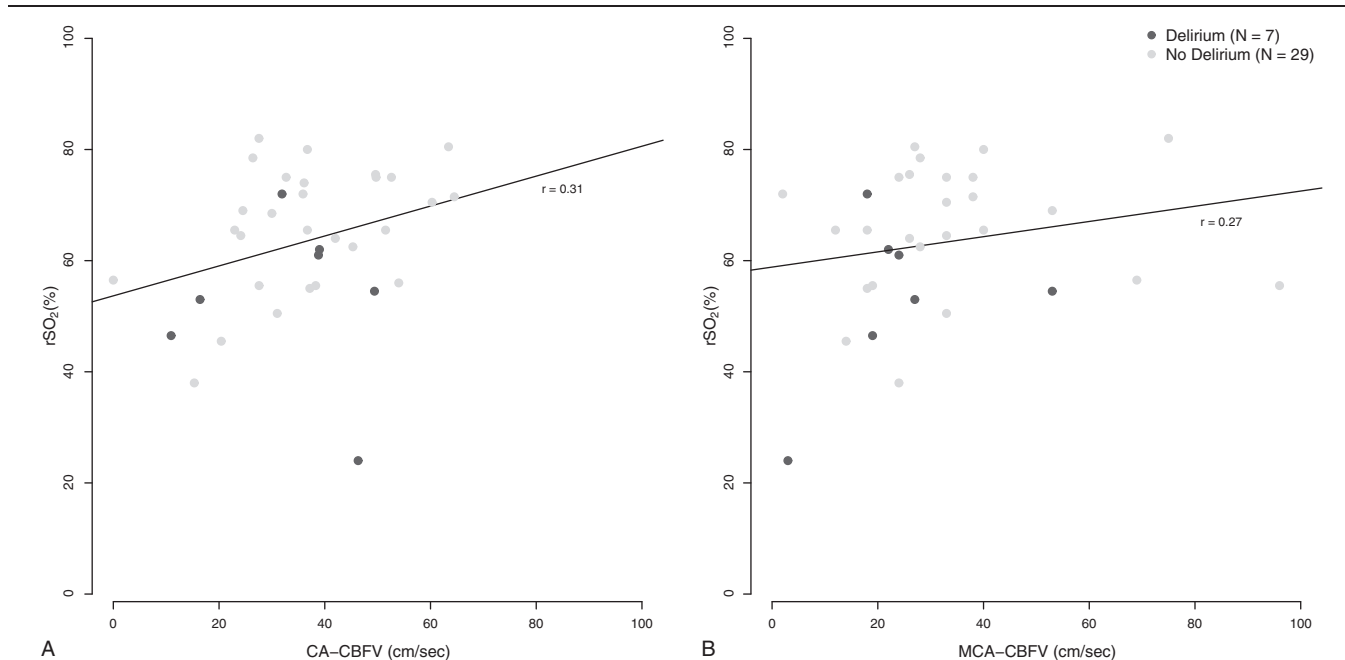

Figure 3. Correlation of (a) carotid artery blood flow velocity (CA-CBFV) and correlation of (b) median cerebral artery flow velocity (MCA-CBFV) with regional oxygen saturation (rSO$_2$) during cardiopulmonary bypass. Dark gray dots indicate patients with postoperative delirium, light gray dots indicate patients without postoperative delirium. The respective Spearman's rank correlation coefficient is indicated within the graph.

Table 4

Perioperative pCO$_2$ levels [mm Hg].

	No delirium (N=29)	Delirium (N=7)	P-value
Preoperative	36.9 [34.7;38.2]	38.6 [36.5;41.5]	.176
Before CPB	41.0 [39.3;43.8]	38.8 [37.6;43.7]	.409
During AoCC	41.5 [39.2;43.1]	39.4 [38.8;41.0]	.246
After CPB	40.3 [38.0;42.3]	31.9 [30.0;.3]	.006

Values are presented as median [inter-quartile range]. The listed P values of statistical tests were calculated by using the Mann–Whitney U-test.
AoCC = aortic cross-clamp, CPB = cardiopulmonary bypass, POD = postoperative day.

preoperatively diagnosed right ventricular dysfunction to reduce pulmonary vascular resistance. Hyperventilation, however, may impair cerebral blood flow.[30] The different MCA-CBFV after CPB in our study may be influenced by this hyperventilation.

Despite the association between hyperventilation and postoperative delirium,[31] there are further contributing factors.[23] Other potential factors are increased cerebral metabolic demand, excessive cerebral microembolic load, endothelial damage, and a disrupted blood–brain barrier.[28] These aberrations expose patients to neuro-inflammation, which has been suggested to contribute to delirium susceptibility.[32] In our study intraoperative microemboli occurred and postoperative levels of IL-6 were elevated but there were no differences between the 2 groups. However, history of PAOD was more common in delirious patients. Due to the low number of affected patients (N=2) the significant difference could also be achieved by chance. Nevertheless, the presence of PAOD would also favor the hypothesis of an impaired cerebral blood supply, being more distinct in PAOD.[33] Obviously cerebral micro-angiopathy is already present in patients with a history of PAOD but without concomitant severe carotid artery stenosis.

Furthermore, intraoperative hematocrit levels were different between the 2 groups possibly resulting from slightly lower preoperative hematocrit levels in delirious patients. Previous studies produced conflicting results on low hemoglobin levels and

postoperative delirium.[34–36] To date it is not clear if preoperative anemia in cardiac surgery is predictive or preventive for postoperative delirium.[36,37] Though our study seems to support the notion that increased cerebral oxygen delivery is associated with higher rSO$_2$ that might eventually protect from delirium.

Our finding that one-fifth of cardiac surgery patients developed postoperative delirium is in accordance with recently published data,[37,38] although higher incidences have also been reported.[1–3] Delirium in our patients was associated with a prolonged LOS, which was also shown before.[39]

There are some limitations concerning our trial that require mentioning. Delirium is a clinical diagnosis based on observations made by nurses and physicians. Therefore, it is likely that we underestimated the true frequency of delirium since assessment was done using a structured evaluation by a trained psychiatrist.[28,32,40] Also, we did not distinguish between hyperactive, hypoactive, and mixed forms of delirium. Hypoactive forms are frequently missed leading to a relative over-reporting of hyperactive delirium.[41] To reduce detection bias we used 2 different delirium-screening tools, a one-time assessment (CAM-ICU) and a continuous observation tool (ICDSC).

We cannot rule out further impacts of additional, undetected confounding factors for delirium despite having included the most relevant risk indicators. For instance, we did not screen our patients for preoperative depression, although an association between pre-existing depression and risk for delirium after cardiac surgery has been shown.[3]

Furthermore, Doppler ultrasound is sensitive to artefact and flow disturbances, especially at higher blood flows, which could create a problem with increasing velocities. Although it is permitted to conclude from blood flow velocities to volumetric blood flow when the diameter of the interrogated vessel remains constant as is the case with the common carotid and the middle cerebral artery, Doppler ultrasound can only quantify blood flow accurately under laminar, not under turbulent flow conditions.[42] Patients with cerebrovascular disease have therefore been excluded from the trial. Also, the assessment of velocities
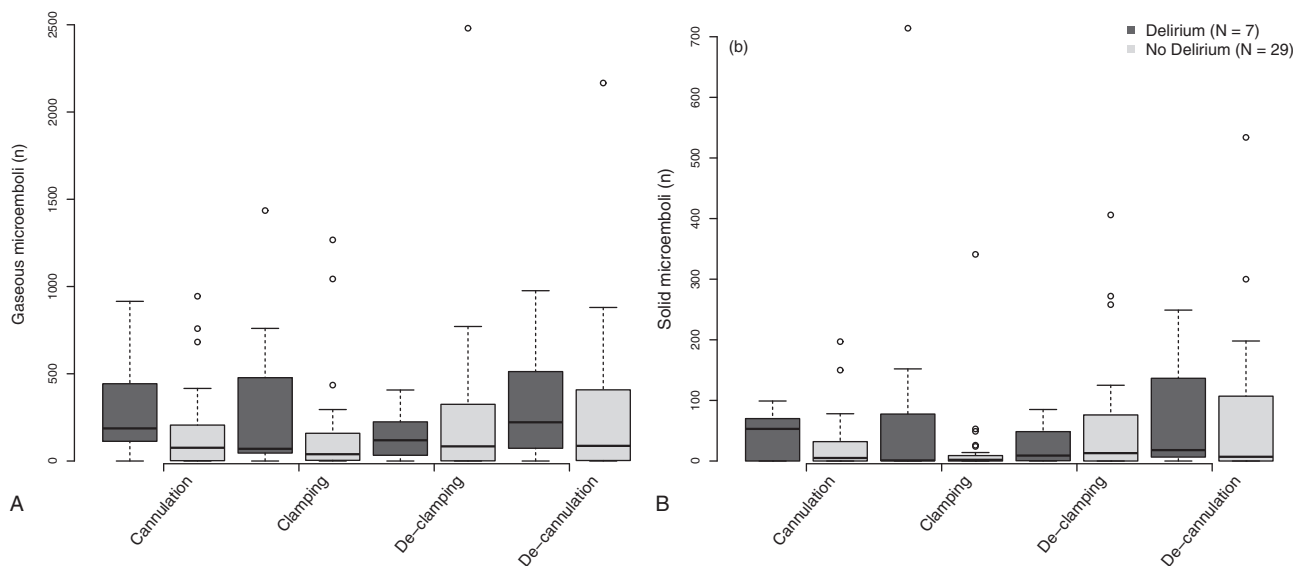

Figure 4. Comparison of the number of gaseous (a) and solid (b) microemboli measured by transcranial Doppler. Dark gray boxes indicate patients with postoperative delirium, light gray boxes indicate patients without postoperative delirium.

has the possibility of inter- and intra-observer variability, which we did not assess.

Lastly, due to the lack of data on the incidence of delirium in our intensive care unit, we had to rely on reported incidences of postoperative delirium for sample size calculation.[1–3] This resulted in a quite low group size after power calculation. However, with the actually observed individuals with delirium, the power is still 60%. The specific findings of this trial may therefore be of value for further larger-scale studies.

In conclusion, this pilot study delineates that slow recovery of CBFV after CPB could be another risk factor for the development of postoperative delirium. Other factors including MCA-CBFV during de-cannulation and low rSO$_2$-values in the course of the procedure may also be accountable for an increased incidence. However, all these factors could potentially just be surrogate parameters for frailty as our patients who developed delirium appeared to be sicker and could have been more susceptible. It remains to be determined if improved cerebral oxygen delivery perioperatively can prevent delirium post cardiac surgery. Therefore, future studies should endeavor to increase the sample size, though only a much larger study would be able to detect the magnitude of potential confounders. However, measurement of intraoperative blood flow velocities in the CA was an easier accessible and available method than the transcranial Doppler sonography and might help identifying patients at risk.

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Author contributions

Conceptualization: Martin Hermann Bernardi, Martin Dworschak, Clemens Kietaibl, Ulrike Weber.
Data curation: Martin Hermann Bernardi, Martin Wahrmann, Maximilian Edlinger-Stanger, Andrea Lassnigg, Ulrike Weber.
Formal analysis: Martin Hermann Bernardi, Martin Wahrmann, Robin Ristl, Ulrike Weber.
Funding acquisition: Martin Hermann Bernardi.
Investigation: Martin Hermann Bernardi, Martin Wahrmann, Maximilian Edlinger-Stanger, Andrea Lassnigg, Ulrike Weber.
Methodology: Martin Hermann Bernardi, Martin Dworschak, Clemens Kietaibl, Michael J Hiesmayr, Ulrike Weber.
Project administration: Martin Hermann Bernardi, Ulrike Weber.
Resources: Martin Hermann Bernardi, Clemens Kietaibl, Michael J Hiesmayr, Ulrike Weber.
Software: Clemens Kietaibl, Robin Ristl.
Validation: Martin Hermann Bernardi, Michael J Hiesmayr, Ulrike Weber.
Visualization: Martin Hermann Bernardi, Robin Ristl.
Writing – original draft: Martin Hermann Bernardi, Ulrike Weber.
Writing – review & editing: Martin Wahrmann, Martin Dworschak, Clemens Kietaibl, Robin Ristl, Maximilian Edlinger-Stanger, Andrea Lassnigg, Michael J Hiesmayr, Ulrike Weber.

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