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ORIGINAL ARTICLE

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Perioperative cerebral perfusion in aortic arch surgery: a potential link with neurological outcome

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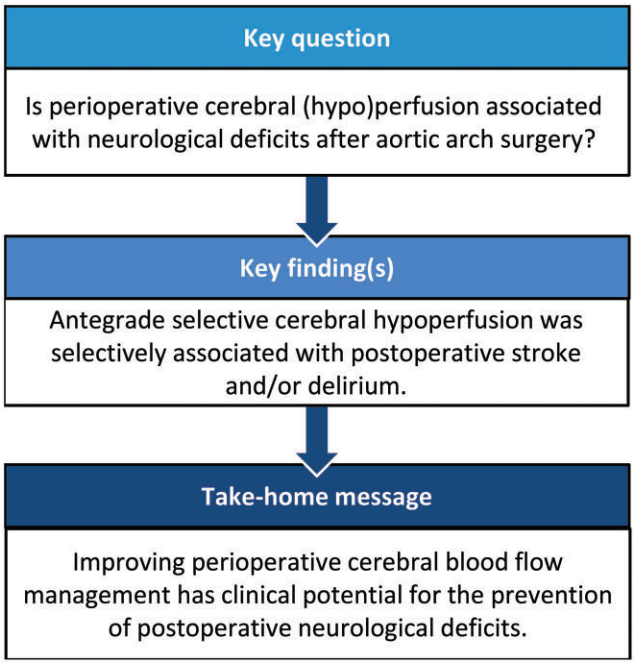

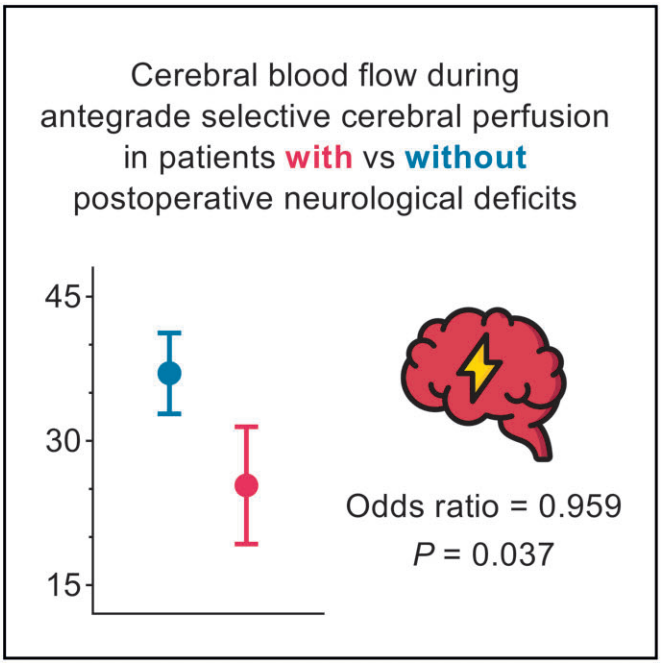

Abstract

OBJECTIVES: The aim of this study was to examine whether perioperative changes in cerebral blood flow (CBF) relate to postoperative neurological deficits in patients undergoing aortic arch surgery involving antegrade selective cerebral perfusion (ASCP).

METHODS: We retrospectively analysed data from patients who underwent aortic arch surgery involving ASCP and perioperative transcranial Doppler assessments. Linear mixed-model analyses were performed to examine perioperative changes in mean bilateral blood

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velocity in the middle cerebral arteries, reflecting changes in CBF, and their relation with neurological deficits, i.e. ischaemic stroke and/or delirium. Logistic regression analyses were performed to explore possible risk factors for postoperative neurological deficits.

RESULTS: In our study population ($N = 102$), intraoperative blood velocities were lower compared to preoperative levels, and lowest during ASCP. Thirty-six (35%) patients with postoperative neurological deficits (ischaemic stroke, $n = 9$; delirium, $n = 25$; both, $n = 2$) had lower blood velocity during ASCP compared to patients without (25.4 vs 37.0 cm/s; $P = 0.002$). Logistic regression analyses revealed lower blood velocity during ASCP as an independent risk factor for postoperative neurological deficits (odds ratio = 0.959; 95% confidence interval: 0.923, 0.997; $P = 0.037$).

CONCLUSIONS: Lower intraoperative CBF during ASCP seems independently related to postoperative neurological deficits in patients undergoing aortic arch surgery. Because CBF is a modifiable factor during ASCP, our observation has significant potential to improve clinical management and prevent neurological deficits.

Keywords: Aortic surgery • Antegrade selective cerebral perfusion • Cerebral circulation • Perioperative management • Postoperative complication • Thoracic aorta

ABBREVIATIONS

ASCP	Antegrade selective cerebral perfusion
CA	Circulatory arrest
CBF	Cerebral blood flow
CI	Confidence interval
CO_2	Carbon dioxide
$EtCO_2$	End-tidal carbon dioxide
IQR	Interquartile range
MAP	Mean arterial pressure
MCA	Middle cerebral artery
MCAv	Mean bilateral middle cerebral artery blood velocity
MEC-U	Medical Research Ethics Committees United
NYHA	New York Heart Association
OR	Odds ratio
ROC	Receiver operating characteristic
RPM	Revolutions per minute
SD	Standard deviation
TCD	Transcranial Doppler

INTRODUCTION

Patients with aortic arch disease, primarily involving aneurysms and dissections, ultimately require open thoracic surgery to reduce the risk of life-threatening complications [1, 2]. Open aortic arch surgery is a technically demanding procedure that necessitates a period of circulatory arrest, placing a significant burden on the body, especially on the brain due to its high metabolic rate [3]. Hypothermic circulatory arrest and anaesthetic agents primarily protect organs against ischaemia by lowering body temperature and metabolism [4, 5]. In addition, cerebral perfusion strategies, such as antegrade selective cerebral perfusion (ASCP), contribute to maintenance of sufficient cerebral blood flow (CBF) during circulatory arrest [6]. Despite these evolving preventive measures for cerebral protection [7], rates of postoperative neurological deficits, including ischaemic stroke, embolic stroke and delirium, remain high [6]. Specifically, whilst different cerebral perfusion techniques provide similar cerebral protection [8, 9], large meta-analyses report rates ranging from 4.7% up to 7.3% and 10.3% for permanent and temporary neurological deficits, respectively, when using cerebral perfusion techniques together with deep or moderate hypothermic circulatory arrest [9, 10].

Several studies have demonstrated the importance of CBF for brain health and function [3]. For example, cerebral hypoperfusion is an established cause of stroke [11]. This highlights the importance of optimal intraoperative cerebral perfusion. However, the relationship between intraoperative CBF and postoperative neurological deficits has not yet been explored. Therefore, the primary objective of this retrospective study is to examine pre- and intraoperative changes in mean bilateral blood velocity in the middle cerebral arteries (MCAv), a close proxy for changes in CBF, and their association with postoperative neurological deficits, specifically ischaemic stroke and/or delirium, in patients undergoing aortic arch surgery involving ASCP. As a secondary objective, we explored possible (other) risk factors for postoperative neurological deficits that could be accounted for when exploring the association between changes in CBF and postoperative neurological deficits. We hypothesised that lower intraoperative MCAv is independently associated with postoperative neurological deficits. Confirming this hypothesis is clinically relevant, because MCAv, and thus CBF, can be modified during ASCP, making CBF during aortic arch surgery a potential target to prevent postoperative neurological deficits.

MATERIALS AND METHODS

Ethics statement

This study (Z20.052/PREPAIR) was approved on 15 May 2020 by the medical ethical committee Medical Research Ethics Committees United (MEC-U). Given the retrospective nature of this study and because all data were collected as part of routine medical care, they waived the need to obtain informed consent. All procedures were performed in accordance with the ethical standards of the MEC-U and with the Helsinki Declaration of 1975.

Study design and population

In this retrospective, single-centre, observational, cohort study, peri- and postoperative data were included from patients that underwent aortic arch surgery involving bilateral ASCP in the St. Antonius Hospital (Nieuwegein, Netherlands) in 2017–2020. To meet standardization of perioperative procedures, only patients that underwent scheduled, i.e. elective and urgent, surgery were included, whereas emergency cases were excluded. In case a patient underwent aortic arch surgery more than once within this period, only data pertaining to the first surgical intervention were

included to prevent bias resulting from analyses on the same individuals. Furthermore, we only included individuals who had at least 1 successful perioperative transcranial Doppler (TCD) assessment.

Antegrade selective cerebral perfusion procedures

All patients underwent elective or urgent aortic arch surgery involving bilateral ASCP. Preoperatively, a functional and anatomical assessment of the circle of Willis was performed using transcranial colour Doppler sonography. However, outcomes of this assessment did not impact ASCP, as ASCP was consistently applied bilaterally. According to guidelines, patients were cooled to a central (rectal) temperature of 25°C, resulting in a nasal temperature of 17–18°C. ASCP is taken of the arterial line and via a y-connector separated in left and right cerebral perfusion line, both monitored with a separate flow probe. The French size of the cannula used for the left carotid artery is 15. Flow rates are set according to minimal flow rates of 8–10 ml/min/kg of bodyweight [7], right and left radial artery pressure, TCD and NIRS measurements. To increase flow rates, the RPM of the centrifugal pump is increased, and gas flow is decreased to increase partial pressure of carbon dioxide to vasodilate cerebral vessels. A multimodal approach using TCD combined with near-infrared spectroscopy and electroencephalography were continuously used for intraoperative neuromonitoring, and were acted on by adjusting ASCP settings (e.g. perfusion pressure) by a clinical perfusionist if deemed necessary and possible, for example in case of marked MCAv drops or MCAv left-to-right asymmetry. These modalities, in particular TCD, were also used to confirm successful positioning of the cannulas for ASCP. Near-infrared spectroscopy and electroencephalography data were not captured and stored. As the time of cerebral perfusion falls within the time period of hypothermic circulatory arrest, and bilateral cannulation for ASCP only takes a few min, we assume that the ASCP duration approximates the duration of hypothermic circulatory arrest.

Data collection

Patient and procedural characteristics. Data pertaining to cardiovascular treatment are registered in the Dutch National Heart Registry (in Dutch: Nederlandse Hart Registratie) by default. From this registry, relevant data were extracted on patient characteristics, surgical procedures, perioperative measures and postoperative outcome.

Transcranial Doppler assessments. As part of usual care, pre- and intraoperative TCD assessments were performed using pulsed Doppler transducers (2 MHz, Delica, type EMS-9UA, Shenzhen Delica Electron) placed over the temporal bone, that were fixed with a headframe. These assessments, performed by a trained sonographer and evaluated by a clinical neurophysiologist, allow estimates of CBF by measuring mean blood velocities in the left and right middle cerebral artery (MCA) [3, 12]. Under the condition that there are no significant changes in diameter of the MCA, mean bilateral changes in MCA velocities (MCAv), i.e. the primary parameter in this study, equal changes in CBF [13]. To insonate the main stem of the ipsilateral MCA, the transducers were gated at a focal depth of 45–60 mm. MCAv signal identification was based on MCAv-specific waveform and flow direction. A preoperative assessment is performed to obtain a patient-specific reference value. Intraoperatively, TCD is used for continuously monitoring changes in MCAv. Since complete storage of the continuous data was not available due to technological difficulties, only real-time single values were recorded in the patient medical files at pre-determined timepoints during surgical procedures. Simultaneously measured values of mean arterial pressure (MAP) and end-tidal carbon dioxide ($EtCO_2$) were also recorded. By default, these data were collected for the following consecutive surgical procedures after: (i) patient intubation; (ii) initiation of extracorporeal circulation; (iii) initiation of ASCP under hypothermic circulatory arrest with aortic clamping; (iv) termination of ASCP; (v) termination of aortic clamping; and (vi) termination of extracorporeal circulation upon cardioversion. Preoperatively, $EtCO_2$ was not measured.

To account for possible interactions between MAP and CBF during surgery, we calculated the cerebrovascular conductance index as MCAv/MAP. We also derived an MCAv-to-bodyweight ratio to take bodyweight-guided settings for CBF during ASCP into account.

Postoperative neurological deficits. The primary end point in this study was postoperative neurological deficits, i.e. the occurrence of ischaemic stroke, transient ischaemic attack or delirium during postoperative hospitalization following aortic surgery. Ischaemic stroke was defined as neurological dysfunction due to cerebral ischaemia (including retinal focal ischaemia), caused by an acute infarction as a result of thrombosis, embolism, systemic hypoperfusion or systemic haemorrhage. Ischaemic stroke and transient ischaemic attack were diagnosed by a neurologist following international guidelines [14], and recorded in the Dutch National Heart Registry. Delirium events were not reported in this registry, hence this outcome was obtained from patient records. Presence of delirium during postoperative hospitalization was defined when patients were prescribed antipsychotic agents (e.g. haloperidol) and/or benzodiazepines (e.g. oxazepam), as prescription of these drugs are strong clinical indicators of delirium presence. In addition, we confirmed the presence of delirium by screening postoperative notes from medical and nursing staff in the patient medical files for the presence of 1 or more delirium symptoms, i.e. hallucination, anxiety, restlessness, agitation or confusion [15]. This process was supervised by a geriatrician specialized in delirium care (Jurgen A.H.R. Claassen).

Data processing

Variables with >50% missing values and binary variables with event rates <10% or >90% were not used for analyses, except in case such a variable was assumed to be strongly related to postoperative neurological deficits as the primary outcome of interest.

In case an MAP value was missing but the systolic and diastolic blood pressure values were available for a certain assessment, the MAP was calculated. If MCAv values for both the right and left middle cerebral arteries were available for a certain assessment, MCAv left-to-right ratio, i.e. (a)symmetry, was calculated, and the mean bilateral MCAv was calculated for each timepoint of assessment. In case the MCAv was available for only 1 side, that value was taken as the mean bilateral MCAv under the assumption that the MCAv is symmetrical between the left and right sides.

To deal with incomplete data across multiple variables in the original dataset, missing values were imputed for variables with ≤30% missing values, using multiple data imputation with predictive mean matching, after patterns of missing data were checked to follow the assumption that data were missing at random. The number of imputations was assimilated to the percentage of incomplete cases. The maximum number of iterations was set at 20. By visually inspecting the iteration plots for each imputed variable, healthy imputed distribution and convergence were verified.

After multiple data imputation, the body mass index, EuroSCORE II [16], cerebrovascular conductance index (=MCAv/MAP) and MCAv-to-bodyweight ratio were calculated for the original dataset and each imputed dataset. Ultimately, pooled estimates were derived from each imputed dataset for all variables included for analysis.

Statistical analyses

All statistical analyses were performed using SPSS (version 25.0). Recommendations from the STROBE Statement [17] and guidelines from the *European Journal of Cardio-Thoracic Surgery* [18] were followed for reporting our research. Shapiro–Wilk tests were used to assess distributions of continuous variables. Normally distributed variables are presented as mean with standard deviation, and non-normally distributed variables are presented as median with interquartile range. Dichotomous variables are presented as frequency number with percentage. Univariable logistic regression analyses were performed to calculate odds ratios for each covariate separately with the primary end point, i.e. postoperative neurological deficits, as independent variable. Linear mixed-model analyses were performed using a random intercept with the assessment timepoint as a fixed effect (timepoint) to evaluate changes in primary and secondary parameters across perioperative repeated assessments. Subsequently, linear mixed-model analyses with an additional fixed timepoint-by-deficits interaction effect (timepoint × deficits) allowed to examine whether changes across timepoints interacted between patients with *versus* without postoperative neurological deficits. As linear mixed-model analyses allow extrapolation of missing data, these analyses were only performed using the original data. *Post hoc* analyses were performed for group comparisons for each assessment timepoint. After performing linear mixed-model analyses, we further explored possible risk factors associated with postoperative neurological deficits using multivariable logistic regression analyses. Complete cases analyses were performed on the original data, and repeated on the imputed datasets. Through univariable logistic regression analyses with postoperative neurological deficits as the dependent variable, candidate variables were selected based on a significance level $P \leq 0.1$, and used for multivariable analyses. Possible risk factors for postoperative neurological deficits were identified using hierarchical blocks with stepwise backward elimination. To assess potential collinearity of the final multivariable models, variance inflation factors were calculated. *Post hoc* power analyses were performed in G*Power (version 3.1) to check the probability of finding true significance in each logistic regression model. Eventually, receiver operating characteristic (ROC) and calibration analyses were performed to, respectively, explore the discriminative accuracy and reliability of MCAv changes during ASCP relative to baseline for estimating the risk for developing postoperative neurological deficits.

RESULTS

Study population

Data from 102 unique patients were included for analyses (Fig. 1). The number of missing values for each incomplete variable is presented in Supplementary Material, Table S1. During postoperative hospitalization, 9 (8.8%) patients developed ischaemic stroke, 25 (24.5%) patients had a delirium and 2 (2.0%) had both. Accordingly, 36 (35.3%) patients were identified with postoperative neurological deficits. Pre- and intraoperative data on patient and procedural characteristics for the total study population and for both groups, i.e. patients with and without postoperative neurological deficits, are presented in Table 1.

Perioperative cerebral haemodynamics

Linear mixed-model analyses (Fig. 2 and Supplementary Material, Tables S2 and S3) revealed significant changes in MCAv, representing proportional changes in CBF, across the various timepoints. Compared to preoperative baseline, a reduction in MCAv was noted immediately upon intubation, with a further decline during extracorporeal circulation. Subsequently, MCAv remained stable across all timepoints during extracorporeal circulation, followed by an increase upon completion of extracorporeal circulation at the end of surgery. Patients with postoperative neurological deficits had a lower MCAv during ASCP compared to those without [25.4; 95% confidence interval (CI): 19.3, 31.5 vs 37.0; 95% CI: 32.8, 41.2; $P = 0.002$]. Changes in MAP or in $EtCO_2$ are known to affect CBF, and therefore also MCAv, through cerebral autoregulation and CO_2 reactivity, respectively [3]. Both MAP and $EtCO_2$ demonstrated marked reductions during surgery, however, there were no differences between groups during ASCP for MAP and $EtCO_2$. Cerebrovascular conductance index increased during surgery but was significantly lower during ASCP in patients with postoperative neurological deficits compared to those without. The MCAv-to-bodyweight ratio was significantly lower in patients with postoperative neurological deficits during ASCP specifically. Finally, more MCAv left asymmetry was seen during ASCP compared to preoperative baseline, but we found no group differences for MCAv left-to-right ratio.

Risk factors for postoperative neurological deficits

Uni- and multivariable logistic regression analyses were performed on 85 cases with complete data for factors included in these analyses from the original dataset and repeated on 102 cases in the imputed datasets (Supplementary Material, Table S4). We created 63 imputed datasets by multiple imputation to impute 422 missing datapoints (out of 6528 datapoints, i.e. 6%) across variables used for multiple imputation, of which the pooled results are presented. Univariable logistic regression analyses identified several factors that were associated with the development of postoperative neurological deficits, including male sex [odds ratio (OR) = 2.566; 95% CI: 1.088, 6.053; $P = 0.031$), intraoperative thrombocytes administration in litres (OR = 1.002; 95% CI: 1.000, 1.004; $P = 0.015$), intraoperative use of vasodilatory agents (OR = 2.765; 95% CI: 1.118, 6.837; $P = 0.028$) and lower

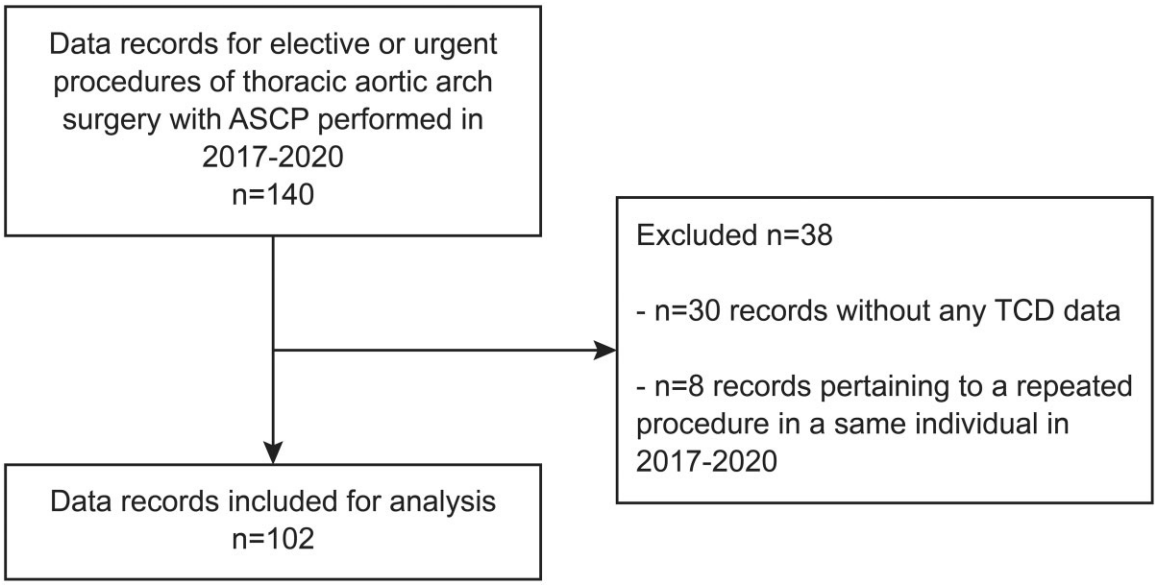

Figure 1: Data record CONSORT flow diagram. Flow of available data records that were screened for eligibility and subsequently excluded (with reasons for exclusion) or included for analysis.

MCAv during ASCP in cm/s (OR = 0.941; 95% CI: 0.904, 0.980; $P = 0.003$). We repeated the analyses using imputed data, which confirmed the identification of intraoperative use of vasodilatory agents (OR = 2.529; 95% CI: 1.048, 6.106; $P = 0.039$) and lower MCAv during ASCP (OR = 0.957; 95% CI: 0.921, 0.995; $P = 0.027$).

Multivariable analyses identified male sex (OR = 3.535; 95% CI: 1.190, 10.498; $P = 0.023$) and lower intraoperative MCAv during ASCP in cm/s (OR = 0.937; 95% CI: 0.896, 0.979; $P = 0.004$) as independent risk factors for postoperative neurological deficits with 55.8% power. Repeating the analyses on the imputed datasets, we confirmed with 65.1% power that lower intraoperative MCAv during ASCP (OR = 0.959; 95% CI: 0.923, 0.997; $P = 0.037$), but also intraoperative thrombocytes administration in litres (OR = 7.284; 95% CI: 1.165, 45.537; $P = 0.034$), was significantly associated with postoperative neurological deficits. Variance inflation factors pertaining to the final multivariable models were all lower than 1.048 (Supplementary Material, Table S4), indicating the absence of collinearity.

Discriminative accuracy and reliability of lower cerebral perfusion for estimating risk for postoperative neurological deficits

Additional ROC analyses showed that the diagnostic accuracy of the reduction in MCAv during ASCP relative to preoperative MCAv was 71.2% (95% CI: 59.5, 83.0; $P = 0.002$; Fig. 3A). The Youden's index of the ROC curve of 0.43 was identified at the point where the decrease in MCAv during ASCP relative to preoperative MCAv was >37%, with the accompanying sensitivity and specificity of 77.8% and 65.5%. The intercept and slope from calibration curve fitting using linear regression yielded an intercept of -0.21 and a slope of 1.80 (Fig. 3B).

DISCUSSION

The primary aim was to characterize pre- and intraoperative MCAv in patients undergoing aortic arch surgery involving ASCP and to explore correlations with postoperative neurological deficits. In summary, we found that intraoperative MCAv was significantly lower compared to preoperative baseline MCAv, with a further reduction in MCAv after starting extracorporeal circulation. We found that patients who developed postoperative neurological deficits had an ∼30% lower MCAv during ASCP compared to those without neurological deficits. The lower MCAv during ASCP was independently related to the development of postoperative neurological deficits. Taken together, our findings suggest that low MCAv, and therefore low CBF, during ASCP is related to the development of postoperative neurological deficits. This is relevant as CBF is a modifiable factor during ASCP.

Patients undergoing aortic arch surgery with ASCP are subject to proportional changes in MCAv, representing CBF. Compared to preoperative baseline values of 47 cm/s, MCAv reduced by 21–40% to intraoperative values ranging from 28 to 37 cm/s. These intraoperative reductions may relate to the administration of (anaesthetic) pharmacological agents and/or hypothermia, especially since these intraoperative measures reduce cerebral metabolism and neuronal activity [5, 6]. Alternatively, changes in MAP and $EtCO_2$ are known to affect CBF, mediated by cerebral autoregulation and CO_2 reactivity [3], and therefore may contribute to the reductions in MCAv. However, reductions in MAP within the autoregulation plateau, such as in our study, unlikely explain reductions in CBF >10% [3]. The decline in MCAv does not necessarily relate to poor outcomes, as both hypothermia and (anaesthetic) pharmacological agents provide cerebral protection [7], where lower CBF may still match lower neuronal metabolic demand. Importantly, a further intraoperative decrease in MCAv was found after starting extracorporeal circulation, which may be explained by the transition from a physiological pulsatile flow profile to a non-pulsatile, continuous flow profile. However, this decrease was present in those with and without postoperative neurological deficits. This suggests that MCAv levels across extracorporeal circulation, albeit lower, unlikely relate to postoperative neurological deficits. Taken together, our data demonstrate that

Table 1: Perioperative patient and procedural characteristics

	Grouped, *N* = 102	Postoperative neurological deficits		Odds ratio (95% CI)	*P*-value
		Without, *n* = 66	With, *n* = 36		
Preoperative patient characteristics					
Age (years)	67.0 (58.8–72.3)	66.0 (58.0–70.3)	70.0 (62.8–76.0)	1.044 (0.997, 1.093)	0.069
Male sex, *n* (%)	56 (55)	31 (47)	25 (69)	2.566 (1.088, 6.053)	0.031[a]
Height (m)	1.75 (1.68–1.84)	1.73 (1.67–1.86)	1.78 (1.72–1.83)	1.009 (0.972, 1.048)	0.631
Weight (kg)	78.5 (65.0–97.0)	78.0 (64.0–97.0)	79.0 (68.3–96.3)	1.000 (0.979, 1.021)	0.971
Body mass index (kg/m^2)	25.3 (22.3–29.4)	25.5 (22.6–29.2)	24.4 (21.8–30.2)	0.984 (0.906, 1.069)	0.706
Mean arterial pressure (mmHg)	93.4 ± 12.4[b]	92.3 ± 13.3	95.4 ± 10.4	1.021 (0.988, 1.056)	0.217
Creatinine (μmol/l)	81.5 (71.8–96.3)	79.5 (68.5–93.8)	82.0 (73.0–104.0)	1.008 (0.996, 1.020)	0.185
Haemoglobin (mmol/l)	8.1 ± 1.0	8.1 ± 1.0	8.0 ± 1.0	0.864 (0.575, 1.299)	0.483
Haematocrit (%)	38.8 ± 4.6	39.2 ± 4.7	38.2 ± 4.6	0.010 (0.000, 66.700)	0.304
EuroSCORE II (%)	4.5 (2.9–8.0)[c]	4.0 (2.7–7.5)	6.0 (3.4–10.2)	1.019 (0.963, 1.077)	0.517
NYHA class I/II/III/IV, *n* (%)	57/26/10/0 (61/28/11/0)[d]	35/19/7/0 (57/31/12/0)	22/7/3/0 (69/22/9/0)	0.739 (0.383, 1.427)	0.368
Chronic lung disease, *n* (%)	15 (15)	10 (15)	5 (14)	1.107 (0.347, 3.531)	0.863
Extracardiac arteriopathy, *n* (%)	18 (18)	8 (12)	10 (28)	0.359 (0.127, 1.013)	0.053
Prior cardiac surgery, *n* (%)	37 (36)	23 (35)	14 (39)	0.841 (0.363, 1.947)	0.685
Prior cerebrovascular accident, *n* (%)	8 (8)	4 (6)	4 (11)	0.516 (0.121, 2.200)	0.371
Perioperative procedural characteristics					
Urgent, *n* (%)	19 (19)	9 (14)	10 (28)	0.411 (0.149, 1.130)	0.085
1/2/≥3 major interventions[e]	28/39/35 (27/38/34)	14/26/26 (21/39/39)	14/13/9 (39/36/25)	0.587 (0.344, 1.002)	0.051
Part of thoracic aorta involved for surgery in addition to the arch					
Root, *n* (%)	29 (28)	20 (30)	9 (25)	1.304 (0.520, 3.270)	0.571
Ascending, *n* (%)	93 (91)	60 (91)	33 (92)	0.909 (0.213, 3.874)	0.897
Descending, *n* (%)	40 (39)	22 (33)	18 (50)	0.500 (0.218, 1.147)	0.102
Preoperative use of heparin, *n* (%)	18 (19)[d]	11 (18)	7 (23)	0.739 (0.255, 2.144)	0.578
Preoperative use of platelet antiaggregant, *n* (%)	17 (18)[d]	10 (16)	7 (23)	0.659 (0.224, 1.942)	0.450
Extracorporeal circulation time (min)	226 (194–282)[f]	227 (194–278)	226 (193–309)	1.003 (0.998, 1.008)	0.285
Aortic clamping time (min)	136 (108–165)[c]	139 (112–164)	136 (104–176)	0.999 (0.992, 1.006)	0.818
Hypothermic circulatory arrest time (min)	45 (31–71)[g]	43 (29–74)	46 (37–64)	1.004 (0.992, 1.016)	0.511
Retrograde autologous priming, *n* (%)	18 (19.1)[h]	14 (23)	4 (13)	2.042 (0.612, 6.812)	0.246
Vasodilators, *n* (%)	30 (31.9)[h]	15 (24)	15 (47)	0.362 (0.146, 0.895)	0.028[a]
Haemostasis promoting agents, *n* (%)	11 (11.7)[h]	8 (13)	3 (9)	1.432 (0.353, 5.816)	0.615
Lowest measured blood glucose (mmol/l)	5.6 (5.1–6.2)[d]	5.7 (5.1–6.2)	5.6 (5.3–6.4)	1.345 (0.882, 2.052)	0.169
Lowest measured haemoglobin (mmol/l)	4.7 (4.3–5.2)	4.7 (4.3–5.2)	4.7 (4.2–5.2)	0.917 (0.541, 1.555)	0.748
Lowest measured central body temperature (°C)	24 (22–25)	24 (22–25)	24 (22–24)	1.005 (0.856, 1.180)	0.950
Net intraoperative fluid balance (l)	2430 ± 2249	2301 ± 2218	2665 ± 2318	1.075 (0.896, 1.290)	0.435
Total fluid input (l)	3.4 (2.2–4.7)	3.0 (2.0–4.3)	3.9 (2.5–4.7)	1.093 (0.907, 1.318)	0.351
Blood plasma (l)	0.4 (0.0–0.5)	0.0 (0.0–0.4)	0.4 (0.0–0.6)	3.748 (0.955, 14.714)	0.058
Erythrocytes (l)	0.0 (0.0–0.5)	0.0 (0.0–0.6)	0.3 (0.0–0.8)	1.602 (0.757, 3.391)	0.218
Thrombocytes (l)	0.3 (0.0–0.3)	0.0 (0.0–0.3)	0.3 (0.0–0.3)	8.890 (1.519, 52.008)	0.015[a]
Autologous cell savage (l)	0.8 (0.5–1.3)	0.8 (0.5–1.3)	0.9 (0.5–1.4)	1.188 (0.642, 2.198)	0.583
Other (l)	1.5 (1.0–2.5)	1.8 (1.0–2.5)	1.5 (1.0–2.1)	0.976 (0.706, 1.348)	0.882
Total fluid output (l)	0.5 (0.3–1.5)	0.5 (0.3–1.3)	0.4 (0.2–2.2)	1.021 (0.796, 1.309)	0.872
Urine loss (l)	0.4 (0.2–0.6)	0.4 (0.2–0.7)	0.3 (0.2–0.5)	0.558 (0.221, 1.409)	0.217
Blood loss (l)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.007 (0.628, 1.614)	0.978
Other (l)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.178 (0.816, 1.700)	0.381

Values are mean ± SD, median (IQR) or *n* (%). The *P*-values represent significance levels for odds ratios for developing postoperative neurological deficits from univariable logistic regression analyses.

[a]Statistically significant, $P < 0.05$.

[b]One missing.

[c]Eleven missings.

[d]Nine missings.

[e]Did not involve coronary artery bypass grafting in case of 1 major intervention.

[f]Fifteen missings.

[g]Two missings.

[h]Eight missings.

IQR: interquartile range; NYHA: New York Heart Association; SD: standard deviation.

intraoperative reductions in MCAv, thus in CBF, during aortic arch surgery are common.

Whilst pre- and intraoperative courses of MCAv were comparable between patients with *versus* without postoperative neurological deficits, we found marked differences in MCAv during ASCP. Specifically, patients with postoperative neurological deficits had lower (∼25 vs 37 cm/s, i.e. 32%) MCAv when compared to patients without. This suggests a relation between low

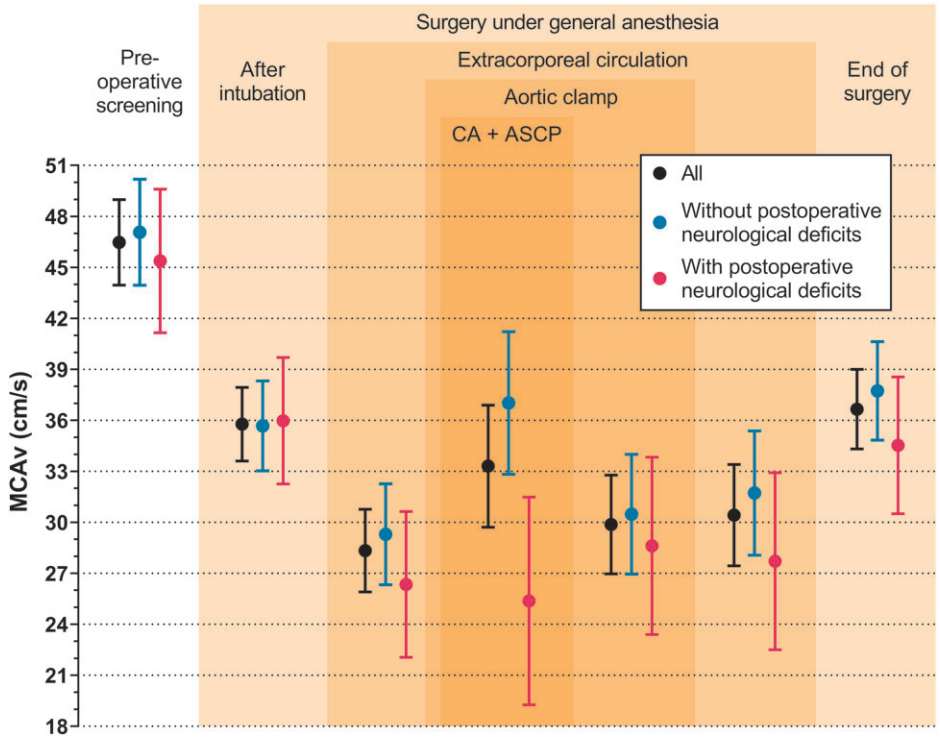

Figure 2: Perioperative mean bilateral middle cerebral artery blood velocities. Courses of MCAv (in cm/s) across perioperative assessment timepoints for all patients (left, black) and for subgroups with (right, pink) and without (middle, blue) postoperative neurological deficits. Values indicate estimated marginal means with 95% confidencce intervals yielded by linear mixed-model analyses. ASCP: antegrade selective cerebral perfusion; CA: circulatory arrest; MCAv: mean bilateral middle cerebral artery blood velocity.

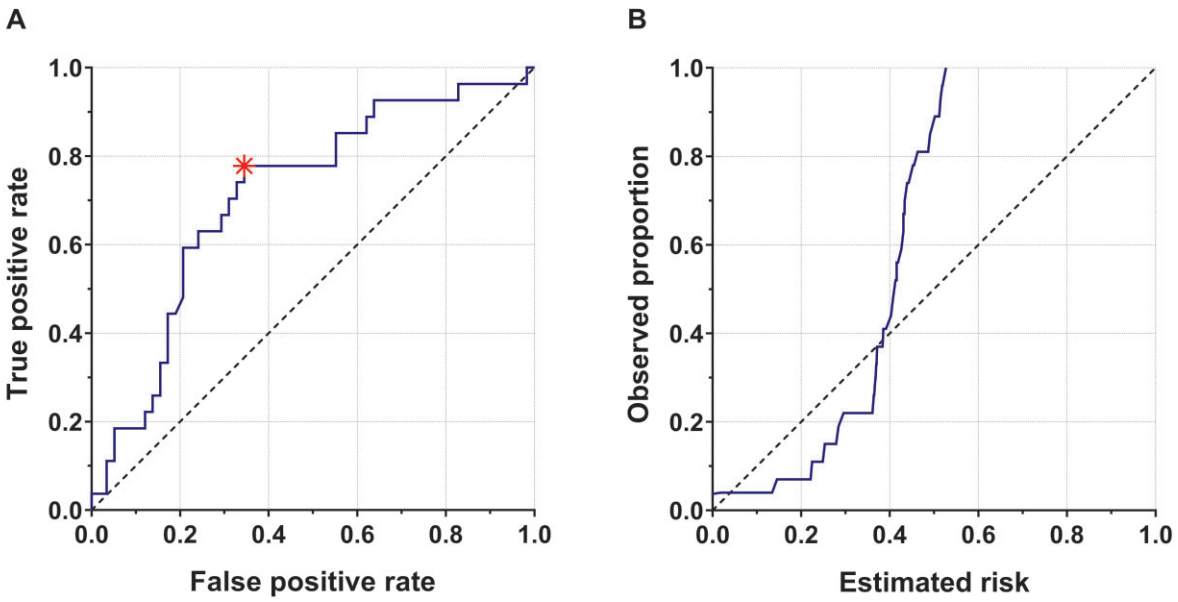

Figure 3: Discriminative accuracy and reliability of lower cerebral perfusion for estimating the risk for developing postoperative neurological deficits. (**A**) Receiver operating characteristic curve showing the discriminative accuracy of MCAv reductions during antegrade selective cerebral perfusion relative to preoperative MCAv for estimating the risk for developing postoperative neurological deficits (blue solid line). The area under the receiver operating characteristic curve is 71.2% (95% confidence interval: 59.5, 83.0; $P = 0.002$). The Youden's index (red asterisk) is 0.43. The black dashed line represents a non-discriminatory test. (**B**) Calibration plot indicating the reliability of MCAv reductions during antegrade selective cerebral perfusion relative to preoperative MCAv for estimating the risk for developing postoperative neurological deficits (blue solid line) with intercept = -0.21 and slope = 1.80. The black dashed line represents the reference line for perfect calibration. MCAv: mean bilateral middle cerebral artery blood velocity.

MCAv, and thus low CBF, during ASCP and the development of postoperative neurological deficits. Although many surgery- and subject-related characteristics affect CBF, our additional regression analyses reinforced that lower MCAv during ASCP was independently related to postoperative neurological deficits. These findings align with previous literature that links cerebral hypoperfusion to neurological disease [3].

The difference in MCAv during ASCP between groups may be a consequence of perioperative management procedures. According to current guidelines, flow rates during ASCP are based on bodyweight and typically set at 8–10 ml/min/kg [7]. Group comparisons in our study revealed no differences in bodyweight or body mass index, whilst MCAv during ASCP remained lower in patients with postoperative neurological deficits after additional correction for bodyweight. Alternatively, the lower MCAv may be caused by cerebral vasoconstriction, although the reasons for this remain speculative, especially since hypocapnia was not present. Finally, the lower MCAv could be explained by technical problems, e.g. problems with the positioning of the ASCP cannula. However, during the procedure, MCAv recordings were used to verify validity of the data collection and, if needed, to correct the position of the cannula.

Neuromonitoring studies suggest a safety threshold for intraoperative CBF of 50% from physiological baseline values, as values below this are indicative for cerebral ischaemia [19, 20]. Indeed, our ROC analyses, although with rather poor discriminative value, confirm that MCAv decreases >50% during ASCP are associated with 48% increased risk of postoperative neurological deficits. However, also those with moderate (37–50%) and even the smallest (<20%) decreases had a 30% and 22% risk of postoperative neurological deficits, respectively. Therefore, whilst our data reinforce that large CBF decreases are associated with elevated risks for neurological deficits, even patients with relatively small CBF decreases may develop neurological deficits.

Limitations

Our findings should be interpreted with some caution, as our study is subject to some limitations. First, given the explorative character of this study, data on a wide variety of possible factors, e.g. related to (technical) procedures and physiology, were not collected for analyses. These factors possibly affect and/or contribute to our main findings. Second, we were unable to distinguish between the potential cause of ischaemic stroke, e.g. hypoperfusion or embolic, as data recorded in the Dutch National Heart Registry were not cross-checked with specific information from the patient medical files. Lastly, we should acknowledge the degree of missing values that could have impacted our findings. We aimed to tackle this through analysis following with and without data imputation. The results from all analyses, either based on the original dataset or the imputed datasets, support our main conclusion that CBF during ASCP seems associated with the development of neurological deficits following aortic arch surgery.

CONCLUSION

In conclusion, our findings suggest that CBF during ASCP may have prognostic value for the development of neurological deficits following aortic arch surgery. Our observation has potential clinical implication, as our work highlights the importance to maintain CBF levels more closely to preoperative baseline levels. This is especially clinically relevant as MCAv during ASCP can be modified, making CBF during aortic arch surgery a potential target to prevent postoperative neurological deficits. Our findings warrant future research to understand the potential causal link between CBF during ASCP and neurological deficits, which may inform future perioperative care to prevent neurological deficits following aortic arch surgery.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: The authors have no conflict of interest to decleare.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Ralf W.J. Weijs: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing—original draft; Writing—review & editing. **Selma C. Tromp:** Conceptualization; Investigation; Methodology; Validation; Writing—review & editing. **Robin H. Heijmen:** Conceptualization; Investigation; Methodology; Project administration; Validation; Writing—review & editing. **Antje A. Seeber:** Investigation; Writing—review & editing. **Nicole J.C.W. van Belle-van Haaren:** Investigation; Writing—review & editing. **Jurgen A.H.R. Claassen:** Conceptualization; Investigation; Methodology; Supervision; Validation; Writing—review & editing. **Dick H.J. Thijssen:** Conceptualization; Investigation; Methodology; Supervision; Validation; Writing—review & editing.

Reviewer information

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