Associations between mean arterial pressure during cardiopulmonary bypass and biomarkers of cerebral injury in patients undergoing cardiac surgery: secondary results from a randomized controlled trial

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Declarations of interest: none

Acknowledgements

The study was funded by the Danish Heart Foundation (24-R97-A5179-22868 and 15-R99-A6034-22905), the Research Foundations at Rigshospitalet (E-22329-01), University of Copenhagen, Denmark, the Lundbeck Foundation (R186-2015-2132), the Swedish Research Council (#2017-00915; #2018-02532), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016615; #201809-2016862), the European Research Council (#681712), the Swedish Alzheimer Foundation (#AF-742881), Hjärnfonden, Sweden (#FO2017-0243), and the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (#ALFGBG-715986; #ALFGBG-720931). HZ is a Wallenberg Scholar. JK is supported by NovoNordisk Foundation Grant number NNF17OC0028706.

Abstract

Objectives: Cardiac surgery is associated with risk of cerebral injury and mean arterial pressure (MAP) during cardiopulmonary bypass (CPB) is suggested to be associated with cerebral injury. The 'Perfusion Pressure Cerebral Infarcts' (PPCI) trial randomized patients undergoing coronary artery bypass grafting (CABG) and/or aortic valve replacement to a MAP of 40-50 or 70-80 mmHg during CPB and found no difference in clinical or imaging outcomes between the groups. We here present PPCI trial predefined secondary end points, consisting of biomarkers of brain injury.

Methods: Blood was collected from PPCI trial patients at baseline, 24 and 48 h after induction of anaesthesia and at discharge from the surgical ward. Blood was analysed for neuron-specific enolase, tau, neurofilament light and the glial marker glial fibrillary acidic protein. Linear mixed models were used to analyse differences in biomarker value changes from baseline between the 2 MAP allocation groups.

Results: A total of 193 (98%) patients were included. We found no differences in biomarker levels over time from baseline to discharge between the 2 MAP allocation groups (PNSE = 0.14, PTau = 0.46, PNFL = 0.21, PGFAP = 0.13) and the result did not change after adjustment for age, sex and type of surgery.

Conclusions: We found no significant differences in levels of biomarkers of neurological injury in patients undergoing elective or subacute CABG and/or aortic valve replacement randomized to either a target MAP of 40-50 mmHg or a target MAP of 70-80 mmHg during CBP.

Keywords: Aortic valve replacement; Biomarkers; Coronary artery bypass grafting; Neurological injury.

Introduction

Cardiac surgery, including coronary artery bypass grafting (CABG) and aortic valve replacement (AVR), is associated with a considerable risk of cerebral injury, including silent stroke, overt stroke, and post-operative cognitive dysfunction (POCD)[1–3]. The pathophysiology of cerebral injury

remains poorly understood, but cerebral perfusion pressure, which can be approximated as the difference between mean arterial pressure (MAP) and jugular venous pressure (JVP), may affect the risk. During on-pump cardiac surgery, cardiopulmonary bypass (CPB) is applied to deliver oxygenated blood to all tissues, and the MAP can be targeted by regulating pump flow or by using vasopressors. The knowledge regarding the optimal MAP during CPB is sparse as previous randomized trials have yielded conflicting results[4–6], and contemporary guidelines recommend a relative wide MAP interval from 50 to 80 mmHg during CPB[7].

Accordingly, the 'Perfusion Pressure Cerebral Infarcts' (PPCI) trial was conducted at our institution, in which patients undergoing CABG and/or AVR were randomized to a target MAP of 40-50 mmHg versus 70-80 mmHg during CPB[8]. The study found no difference in the primary endpoint consisting of total volume of cerebral infarcts at day three to six after surgery, detected by diffusion weighted magnetic resonance imaging (DWI), nor in a secondary outcome, defined as the occurrence of POCD at discharge[9]. In addition, the PPCI trial defined a number of biomarkers of cerebral injury as secondary endpoints with a potential higher sensitivity compared to clinical endpoints.

We here present PPCI trial pre-defined secondary endpoints, consisting of biomarkers of cerebral injury, including the neuronal proteins neuron-specific enolase (NSE), tau, neurofilament light (NFL) and the glial marker glial fibrillary acidic protein (GFAP), measured before and after surgery. We hypothesized that the high target MAP group would have lower release of circulating brain injury biomarkers after cardiac surgery, reflecting minimized neurological injury.

Methods

The present study presents the analysis of a pre-defined secondary endpoint of the investigator-initiated, assessor-blinded, randomized, controlled PPCI trial. The trial protocol and primary results have previously been published[8,9]. In brief, the study included adult patients scheduled for elective or subacute CABG and/or AVR. Exclusion criteria included previous stroke, transient ischemic attack, as well as progressive neurodegenerative disease. Patients were randomized to a low MAP target of 40-50 mmHg or a high MAP target of 70-80 mmHg during CPB. Assigned MAP targets were achieved by boluses of phenylephrine up to a maximum of 2.0 mg, which could be followed by continuous infusion of norepinephrine up to 0.4 μg per kg per min. CPB pump flow was fixed at a flow rate of 2.4 liters per minute per square meter body surface area plus 10-20% in both groups. Vasodilators were not administered. Other perioperative treatment was at the discretion of the treating physician[8].

Biomarker measurements

Blood samples were collected preoperatively prior to initiation of CPB, 24 hours after anaesthesia induction, 48 hours after anaesthesia induction, and at discharge from the surgical department or no later than 7 days after surgery. The first blood sample was drawn from a radial artery catheter, whereas other blood samples were drawn from either a radial artery catheter, a central venous line or a cubital vein. In all cases, a total of 9 mL blood was drawn and divided in ethylenediamine-tetraacetate (EDTA), citrate-coated and heparin-coated tubes. Samples were centrifuged at 3000 rpm for 10 minutes at 4°C, where after plasma was transferred to polypropylene test tubes and stored at − 80 °C until assaying.

T-tau, GFAP and NFL concentrations were measured with commercially available Simoa kits (Quanterix, Billerica, MA). For all biomarker assays, calibrators were run in duplicates, and obvious

outlier calibrator replicates were masked before curve fitting. Samples were diluted four-fold and run in singlicate. Two quality control (QC) levels were run in duplicates in the beginning and the end of each run.

For tau, a QC sample with a concentration of 4.9 pg/mL achieved a repeatability of 4.2% with an intermediate precision of 4.4%, while a QC sample with a concentration of 21.3 pg/mL achieved a repeatability of 5.5% with an intermediate precision of 8.5%. The validated measurement interval for tau was 1.22 – 317 pg/mL with a lower limit of quantification (LLoQ) of 1.22 pg/mL. For GFAP, a QC sample with a concentration of 82.4 pg/mL achieved a repeatability of 4.5% with an intermediate precision of 5.9%, while a QC sample with a concentration of 223 pg/mL achieved a repeatability of 8.2% with an intermediate precision of 8.2%. The dynamic range for GFAP was 5.48 – 4000 pg/mL with an LLoQ of 0.69 pg/mL. For NFL, a QC sample with a concentration of 6.3 pg/mL achieved a repeatability of 8.3% with an intermediate precision of 9%, while a QC sample with a concentration of 48.5 pg/mL achieved a repeatability of 8.1% with an intermediate precision of 8.2%. The dynamic range for neurofilament was 1.9 – 1800 pg/mL with an LLoQ of 1.9 pg/mL. NSE concentrations were measured using standard clinical chemistry assays on a Cobas platform (Roche Diagnostics, Penzberg, Germany).

Statistical analysis

All analyses were conducted on the population of PPCI patients who had biomarker levels measured at baseline. Crude median biomarker values with range from 25th percentile to 75th percentile (Interquartile range, IQR) were presented at each sampling time point after stratification for MAP allocation (Figure 1).

For analyses of the development of biomarker levels over time, due to the randomized, longitudinal design, we applied constrained (i.e. baseline corrected) linear mixed models (CLMM) of covariance, including the individual biomarker as the dependent outcome variable and the time of biomarker sampling and MAP allocation group as the two independent exposure variables. The primary results were the 'time*MAP allocation'-interaction, as a marker of different biomarker development over time in each allocation group. We prespecified to apply an unstructured covariance structure for the analyses. In case the distribution of a biomarker was right skewed, we prespecified to apply logarithmic transformation as appropriate, to approximate normal distribution prior to statistical analysis.

As secondary analyses, we repeated the CLMM models adjusting for suspected confounding factors, including age (included as continuous variable), sex, and type of surgery (CABG versus valve replacement). In case of greater than 5% missing biomarker values, we prespecified to conduct the following sensitivity analyses: Repetition of the primary analysis with imputation of missing biomarker values in a 'best-and-worst' case scenario: In one analysis, missing biomarker values were replaced with the lowest measured biomarker value for the given MAP allocation group at the given time point (i.e. a best case scenario), and in another analysis, missing biomarker values were replaces with highest measured biomarker value for the given MAP allocation group at the given time point (i.e. a worst case scenario). A significance level of 0.01 was applied throughout in accordance with the trial protocol[8], and SAS software, version 9.4 (SAS institute, Cary, North Carolina, USA) was used for all statistical analysis.

Results

A total of 197 patients were included in the PPCI trial, with 98 patients being randomized to the high MAP allocation group and 99 patients being randomized to the low MAP allocation group. [9]. At baseline, 95 (97%) patients in the high MAP allocation group and 98 (99%) patients in the low MAP allocation group had blood analyzed for all four biomarkers. Patients allocated to the high MAP group were significantly older than patients allocated to the low MAP group (69 ± 8.5 years vs. 65 ± 11 years, p = 0.002). Otherwise, the groups were well balanced (Table 1), and further analyses were conducted on the presented population of a total of 193 (98%) patients.

After 24 and 48 hours, between 2% and 5% of patients had missing biomarker measurements, depending on the biomarker and MAP allocation group. At discharge, between 13% and 15% had missing biomarker measurements (Table 2).

We did not find any significant differences in the development of biomarker levels over time from baseline between the two MAP allocation groups (Figure 1).

In models adjusted for age, sex, and type of surgery, we did not find any significant differences in the development of biomarker levels over time from baseline between the two MAP allocation groups for neither NSE (p =0.14), tau (p = 0.47), NFL (p = 0.22), or GFAP (p = 0.14) (Table 3). Increasing age was found to be significantly associated with higher levels of NFL (p < 0.0001) and GFAP (p < 0.0001), whereas female sex was associated with higher levels of tau (p = 0.0005, Table 3). Excluding 10 (1.3%) NSE samples with a positive hemolysis index (i.e. Roche Hemolysis index greater than 20) did not change these results.

In a 'best case' sensitivity analysis, where missing biomarker levels were replaced with the lowest recorded value in the MAP allocation group at the given timepoint, we did not find any significant differences in the development of biomarker levels over time from baseline between the two MAP allocation groups for NSE (p = 0.29), tau (p = 0.59), NFL (p = 0.33), or GFAP (p = 0.13).

In a ‘worst case’ sensitivity analysis, where missing biomarker levels were replaced with the highest recorded value in the MAP allocation group at the given timepoint, we did not find any significant differences in the development of biomarker levels over time from baseline between the two MAP allocation groups for NSE ($p = 0.15$), tau ($p = 0.02$), NFL ($p = 0.13$). We found a significantly different development of GFAP levels over time between MAP allocation groups in the ‘worst case’ scenario ($p = 0.006$) with GFAP levels being higher in the high MAP allocation group at 48 and 72 hours after induction. This difference was driven by a single patient in the high MAP allocation group with a GFAP level of 2,673 pg/mL 48 hours after induction and a GFAP level of 4,765 pg/mL 72 hours after induction. This patient had a complicated postoperative course with cognitive impairment postoperatively. The second highest levels of GFAP in the cohort were 982 pg/mL 48 hours after induction and 786 pg/mL 72 hours after induction. If the outlier (patient no. 115) was excluded, we fund no differences in GFAP levels over time between the two MAP allocation groups ($p = 0.18$) in the sensitivity analysis.

Discussion

In this secondary endpoint analysis of the PPCI trial, we discovered no significant differences in biomarkers of neurological injury in cardiac surgery patients being randomized to a low MAP target of 40 – 50 mmHg versus a high MAP target of 70 – 80 mmHg during CPB. This corresponds well with previously published primary and secondary endpoint analyses, in which no differences were found in volume and number of new cerebral infarcts[9], domain-specific patterns of POCD[10], or long-term mortality or occurrence of POCD[11] between the two MAP allocation groups.

The past decade, several novel biomarkers of cerebral injury have emerged. Neuron-specific enolase (NSE) is a dimeric glycoprotein present in cells of neuroectodermic origin. In out-of-hospital cardiac arrest, NSE is a specific marker of neurological outcome[12–14], and it has been shown as a marker of brain injury after CPB[15]. Tau protein originates from the axonal cytoskeleton, and serum levels of tau have been associated with poor clinical outcome after cardiac arrest[16] and with neurocognitive deficits after CPB[15]. Glial fibrillary acidic protein (GFAP) originating from the astroglia cell cytoskeleton has been associated with diseases of acute brain injury, including hypoxic brain injury, stroke, traumatic brain injury, and subarachnoid hemorrhage[17–19], and it has been suggested that GFAP may be a marker of acute brain injury after cardiac surgery[20]. Neurofilaments are a group of proteins integrated in the neuronal and axonal cytoskeleton[21]. Blood (plasma or serum) concentration of neurofilament light (NFL) is a sensitive, but disease-unspecific, biomarker for both neurodegeneration and acute neuronal injury[21,22]. Blood NFL has been suggested to serve as a potential biomarker for subtle neuronal injury after circulatory arrest[23], as higher levels after cardiac arrest accurately predict poor clinical outcome[24]. Importantly, a study specifically including patients operated with or without CPB during cardiac surgery found more pronounced increases in blood tau and NFL levels in patients with CPB than in those without[25]. Consistent with previous studies, levels of tau and GFAP reached peak concentrations rapidly following CABG, whereas NFL levels were steadily increasing in the days after CABG[20,25]. Accordingly, it is possible that NFL levels could separate at a later timepoint than at discharge.

While our primary and secondary analyses were neutral between the two MAP allocation groups, one sensitivity analysis, in which missing biomarker values were replaced with the highest recorded value in the same MAP allocation group at the same time point, suggested a significantly

higher level of GFAP in the high MAP allocation group. One weakness of this pre-specified sensitivity analysis is that a single outlier can inflate the results to a great degree. In accordance, replacing the missing GFAP levels with the second highest recorded GFAP level resulted in no significant differences between groups, and our results suggest that the difference in the sensitivity analysis was caused by this single outlier.

The presented results should be interpreted in light of some limitations. In the PPCI trial protocol, in addition to the included biomarkers, we defined the matrix metallopeptidase 9 (MMP-9) and ubiquitin C-terminal hydrolase 1 (UCH-L1) as secondary endpoints[8], however, we have not been able to complete those analyses at present. We also chose to analyze tau although this was not prespecified in the original trial protocol. The reason for this was the promising results of tau as a marker of neurologic injury[26], as well as feasibility, since tau was analyzed using the same assay as GFAP and NFL. We saw a relatively high frequency of missing blood samples at discharge (13-15%), but a low frequency of missing blood samples at earlier sampling timepoints (1-5%). The higher frequency of missingness at discharge was primarily caused by logistic difficulties in obtaining blood samples prior to patient discharge. As NSE originate from cells of neuroectodermic origin, it is present in erythrocytes and platelets. Accordingly, hemolysis occurring during CPB can result in falsely elevated NSE levels, however, removing patients with a positive hemolysis index did not alter the results. For all biomarkers of cerebral injury, preexisting cerebral disease may result in elevated levels, however we found no differences in biomarker levels at baseline, and our results should be unaffected by this. While any neutral results could be caused by a lack of power, we saw no tendencies to higher biomarker values in one of the two randomized MAP allocation groups and it is difficult to clearly define what a clinically important difference would be..

Conclusions

In this secondary endpoint analysis of the PPCI trial, we found no significant differences in daily recorded levels of biomarkers of neurological injury in patients undergoing elective or subacute CABG and/or AVR being randomized to a target MAP of 40 – 50 mmHg versus a target MAP of 70 – 80 mmHg during CBP.

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Table 1. Characteristics of cardiac surgery patients randomized to a mean arterial blood pressure of either 40-50 mmHg (low) or 70-80 mmHg (high).

		Low MAP[1] allocation n = 98	High MAP[1] allocation n = 95
Demographics			
Age, years	Mean ± SD	65 ± 11	69 ± 8.5

Male sex	n (%)	92 (94)	81 (85)
Actively working	n (%)	61 (62)	69 (73)
Medical History			
Recent myocardial infarction	n (%)	31 (32)	23 (24)
Hypertension	n (%)	82 (84)	84 (88)
Diabetes mellitus	n (%)	24 (24)	24 (25)
Current smoker	n (%)	18 (18)	15 (16)
Current alcohol abuse	n (%)	7 (7.1)	7 (7.4)
Symptoms			
CCS[2] score above 1	n (%)	63 (64)	46 (48)
NYHA[3] class			
I	n (%)	32 (33)	20 (21)
II	n (%)	34 (35)	44 (46)
III	n (%)	28 (29)	25 (26)
IV	n (%)	4 (4.1)	6 (6.3)
Objective Findings			
BMI, kg per m2	mean ± SD	27 ± 3.8	27 ± 3.9
Heart rate, beats per minute	mean ± SD	67 ± 14	69 ± 11
Left ventricular ejection fraction	median (IQR)	55 (45 - 60)	55 (45 - 60)
P-creatinine, micromol/L	mean ± SD	92 ± 28	88 ± 17
EuroSCORE II, percent	median (IQR)	1.6 (0.97 - 2.9)	2.0 (1.3 - 3.1)
Surgical Procedure			
CABG[4]	n (%)	67 (68)	71 (75)
No. of grafts	median (IQR)	2 (0 - 3)	2 (0 - 3)
AVR[5]	n (%)	27 (28)	29 (31)
MVR[6]	n (%)	4 (4.1)	6 (6.3)
MAP during bypass, mmHg	mean ± SD	45 ± 4.7	67 ± 4.7
Surgery time, minutes	mean ± SD	185 ± 49	190 ± 57
CPB[7] time, minutes	mean ± SD	94 ± 32	103 ± 72
Cross clamp time, minutes	mean ± SD	63 ± 27	64 ± 29

1) Mean arterial pressure
2) Canadian Cardiovascular Society
3) New York Heart Association
4) Cardiopulmonary bypass
5) Aortic valve replacement
6) Mitral valve replacement
7) Cardiopulmonary bypass

Table 2. Number of analyzed blood samples at different time points, stratified by biomarker in cardiac surgery patients randomized to a mean arterial blood pressure of either 40-50 mmHg (low) or 70-80 mmHg (high).

	Sampling time	Neuron-specific enolase	Tau	Neurofilament light	Glial fibrillary acidic protein
		n (%)	n (%)	n (%)	n (%)
High MAP allocation n = 98	Baseline	95 (97)	96 (98)	96 (98)	96 (98)
	24 hours after induction	93 (95)	93 (95)	93 (95)	93 (95)
	48 hours after induction	93 (95)	93 (95)	93 (95)	93 (95)
	At discharge[1]	83 (85)	83 (85)	83 (85)	83 (85)
Low MAP allocation n = 99	Baseline	98 (99)	98 (99)	98 (99)	98 (99)
	24 hours after induction	97 (98)	96 (97)	97 (98)	97 (98)
	48 hours after induction	97 (98)	95 (96)	97 (98)	97 (98)
	At discharge[1]	86 (87)	86 (87)	86 (87)	86 (87)

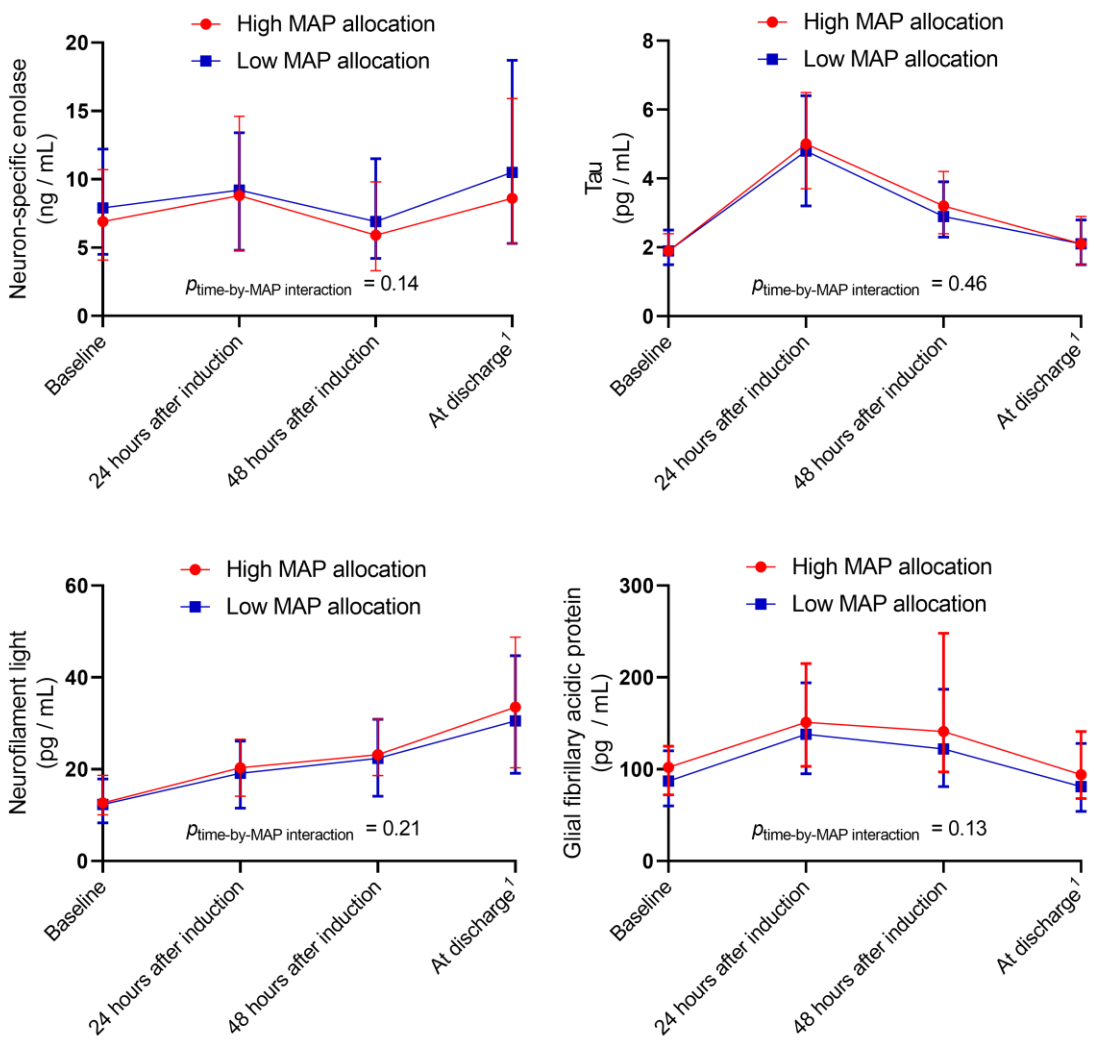
1) at discharge from the surgical department or no later than 7 days postoperatively.

Table 3. Type III Tests of Fixed Effects from Constrained Linear Mixed Models for each biomarker measured in cardiac surgery patients randomized to a mean arterial blood pressure of either 40-50 mmHg (low) or 70-80 mmHg (high).

Covariate	Neuron-specific enolase	Tau	Neurofilament light	Glial fibrillary acidic protein
	p	p	p	p
MAP[1] allocation group	0.86	0.02	0.68	0.20
Age	0.44	0.37	< 0.0001	<0.0001
Sex	0.63	0.0005	0.01	0.04
Type of surgery (CABG[2] versus AVR[3])	0.27	0.27	0.11	0.26
MAP allocation group-by-time interaction	0.14	0.47	0.22	0.14

1) Mean arterial pressure
2) Coronary artery bypass grafting
3) Aortic valve replacement

Figure 1. Median (inter quartile range) biomarker levels from baseline to discharge, stratified by MAP allocation. Cardiac surgery patients randomized to a mean arterial blood pressure of either 40-50 mmHg (low) or 70-80 mmHg (high).



1) At discharge from the surgical ward or no later than 7 days postoperatively