Cardiac surgery and the brain
- studies on cerebral blood flow autoregulation and mechanisms of cerebral injury

Björn Reinsfelt

Department of Anaesthesiology and Intensive Care
Institute of Clinical Sciences
Sahlgrenska Academy

UNIVERSITY OF
GOTHENBURG

2011

Cardiac surgery and the brain
- studies on cerebral blood flow autoregulation and mechanisms of cerebral injury

ISBN 978-91-628-8369-0 http://hdl.handle.net/2077/27812

Paper I and II are reprinted with permission of the publishers
Printed by Intellecta Infolog AB
Gothenburg, Sweden 2011

Cardiac surgery and the brain - studies on cerebral blood flow autoregulation and mechanisms of cerebral injury

Björn Reinsfelt

Department of Anaesthesiology and Intensive Care, Institute of Clinical Sciences, The Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

Cerebral dysfunction (CD) occurs frequently after cardiac surgery with cardiopulmonary bypass (CPB). The main causes of CD are thought to be cerebral hypoperfusion, cerebral microembolisation , cerebral inflammation or disruption of the blood brain barrier (BBB). Data on the effects of the frequently used anaesthetics, isoflurane and sevoflurane, on the cerebral pressure-flow relationship and cerebral flow-metabolism coupling during CPB are scarce and inconsistent. Furthermore, the effects of cerebral microembolisation on the release of serological or cerebrospinal fluid markers of brain injury and BBB function after transcatheter - (TAVI) or surgical aortic valve replacement (SAVR) have previously not been evaluated.

Patients and methods: The effects of isoflurane and sevoflurane on cerebral blood flow velocity (CBFV), oxygen extraction (COE) and flow autoregulation were performed during cardiac surgery with CPB, using transcranial Doppler (TCD) and a right jugular bulb catheter for measurement of jugular bulb pressure and oxygen saturation. Furthermore, patients undergoing TAVI were studied with TCD for estimation of microembolic signals (MES), and postoperative serum release of S-100B, a marker of glial cell injury. Finally, the effects of SAVR on the BBB function and the release of CSF markers of neuronal and glial-cell injury and two markers of inflammation were analysed. Changes in CSF biomarkers were correlated to the microembolic load.

Results: Isoflurane and sevoflurane both decreased CBFV (27% and 17%, respectively), and COE (13% and 23%, respectively). Both isoflurane and sevoflurane increased the slope of the autoregulation curve, relating cerebral perfusion pressure to CBFV. During the TAVI procedure, 282±169 MES were recorded. Approximately 2/3 appeared during the balloon valvuloplasty of the native valve. Serum S-100B increased sharply within the first hour after the balloon valvuloplasty, and returned toward baseline levels within 4-6 hrs. There was a correlation between MES and the 24hr release of S-100B. In SAVR patients, the two markers of glial cell injury, S-100B and GFAP, increased by 35% and 25%, respectively. The CSF markers of neuronal injury, NSE, Tau and NFL, were not significantly affected postoperatively. The CSF/serum albumin ratio increased by 61%. There was a-12 and-3.5 fold increase in IL-6 and IL-8, respectively. A total of 354±79 MES were detected, but their magnitude correlated neither to the changes in CSF markers of astroglial damage, changes in cytokine levels, nor to the degree of BBB disruption.

Conclusions: Both isoflurane and sevoflurane exert a direct cerebral vasodilatory effect, which impairs the cerebral pressure-flow autoregulation, but improves the cerebral oxygen-supply demand relationship The substantial cerebral microembolic load during TAVI causes a glial cell injury. Cardiac surgery with CPB does not seem to cause neuronal damage but instead induces a substantial cerebral inflammation causing a BBB dysfunction, probably caused by astroglial cell injury. Despite the extensive microembolic load during SAVR, its magnitude does not correlate to the degrees of BBB dysfunction, glial cell injury or cerebral inflammation.

Key words: Cardiac surgery; cerebral dysfunction; cardiopulmonary bypass; anaesthetics; aortic valve replacement; transcranial Doppler; embolism; cerebrospinal fluid; blood-brain barrier.

ISBN 978-91-628-8369-0 http://hdl.handle.net/2077/27812

List of original papers

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. Reinsfelt B, Westerlind A, Houltz E, Ederberg S, Elam M, Ricksten SE
"The Effects of isoflurane-Induced Electroencephalographic Burst Suppression on Cerebral Blood Flow Velocity and Cerebral Oxygen Extraction During Cardiopulmonary Bypass."
Anesthesia & Analgesia 2003;97:1246 –50

II. Reinsfelt B, Westerlind A, Ricksten SE
"The effects of sevoflurane on cerebral blood flow autoregulation and flow-metabolism coupling during cardiopulmonary bypass."
Acta Anaesthesiol Scand 2011; 55: 118–123

III. Reinsfelt B, Westerlind A, Ioanes D, Zetterberg H, Fredén-Lindqvist J, Ricksten SE
"Transcranial Doppler microembolic signals and serum marker evidence of neuronal injury during transcatheter aortic valve implantation."
Acta Anaesthesiol Scand; Accepted for publication Aug 28, 2011.

IV. Reinsfelt B, Westerlind A, Zetterberg H, Blennow K, Fredén-Lindqvist J, Ricksten SE
"Cerebrospinal fluid markers of brain injury, inflammation and blood-brain barrier dysfunction and their relation to cerebral microembolism in cardiac surgery."
Manuscript submitted

Thank You Sven-Erik

Contents

Abbreviations

Abbreviations used in the text

AEP	auditory evoked potential
ANOVA	analysis of variance
AUC_{24hrs}	area under curve for 24 hour release pattern
BBB	blood-brain barrier
CABG	coronary artery bypass grafting
CaO_2	arterial oxygen content
CBF	cerebral blood flow
CBFV	cerebral blood flow velocity
$CjvO_2$	jugular vein oxygen content
CMRgluc	cerebral metabolic rate for glucose
$CMRO_2$	cerebral metabolic rate of oxygen
CNS	central nervous system
COE	cerebral oxygen extraction
CPB	cardiopulmonary bypass
CPP	cerebral perfusion pressure
CSF	cerebrospinal fluid
DO_2	oxygen delivery
EEG	electroencephalography
ELISA	enzyme-linked immunosorbent assay
GFAP	glial fibrillary acidic protein
IL-6/IL-8	interleukin 6/interleukin 8
JVP	jugular vein pressure
MES	microembolic signals
NF-L	neurofilament light chain protein
NSE	neuron specific enolase
PMD	power M-mode Doppler
RMCA	right medial cerebral artery
SaO_2	arterial oxygen saturation
$SjvO_2$	jugular vein oxygen saturation
SAVR	surgical aortic valve replacement
T-tau	total tau
TAVI	transcatheter aortic valve implantation
TCD	transcranial Doppler

Introduction

The problem of central nervous system injury after cardiac surgery

Cerebral dysfunction after cardiac surgery is a complex set of symptoms ranging from discrete cognitive deterioration, noted maybe only by the patients closest relatives, to massive neurological deficits with severe reduction in functional capacity. The less obvious symptoms are probably often under-diagnosed. Reports on the true incidence of cerebral dysfunction after cardiac surgery differs in figures due to the heterogeneous clinical presentation. Definite stroke has an incidence of approximately 2.5% in a modern setting of cardiac surgical patients (1). The incidence of cognitive dysfunction ranges between 50-70% in the early postoperative period and falls to levels of 20-40% within 6 months to 1 year (2). The wide range partly reflects the fact that the tests of cognitive functions used differ between investigating groups. The difficulty in assessing the magnitude of the problem at present is to some extent obscured by changes related to technological and demographic factors. Advances in the peri-operative management aiming to prevent neurological events have been counteracted by the fact that the modern population of patients exposed to cardiac surgery is recognised by higher age and increasingly advanced co-existent diseases. In addition, the emergence of trans-catheter interventions for aortic and mitral valve disease will probably have impact on the amount of high risk patients exposed to open heart surgery in the near future.

The incidence of stroke after various surgical procedures presented in a review by Selim illustrate the particulate position of cardiac surgery (3). General surgery had a risk of stroke ranging from 0.08-0.7%, coronary artery bypass grafting (CABG) surgery 1.4-3.8% and finally open valve surgical procedures with a 4.8-9.7% risk. These figures highlights the use of cardiopulmonary bypass (CPB) in CABG, and the additional exposure of the heart chambers to the atmosphere in valve surgery as contributing factors to the increased risk of stroke. In a risk factor analysis of stroke after cardiac surgery in 16,184 consecutive patients, Bucerius et al. identified 10 variables as independent predictors of stroke (4). Previous history of cerebrovascular disease predicted peri-operative stroke with an odds ratio of 3.55. Among additional predictors were peripheral vascular disease, diabetes, hypertension, prior cardiac surgery and urgent operation - all common co-morbidities in a modern population of cardiac surgical patients. This investigation also documented that patients with stroke had a six-fold increase in mortality compared with patients without stroke (22.2% vs. 3.7%).

Like stroke, postoperative encephalopathy is associated with poor overall outcome (5). Encephalopathy is generally diagnosed as the patient emerges from anaesthesia with persistent agitation or physical combativeness, and its potential for inducing concomitant complications

from other organ systems is obvious. As to cognitive dysfunction, it is often classified as minor or subtle by health care professionals, but might nonetheless have a great impact on the quality of life for the patient and her relatives. In a multi-centre investigation addressing adverse cerebral outcome after CABG surgery, the authors found a 5-10 fold increase in mortality for these patients. They also noted that the duration of intensive care and hospital stay was prolonged (6). In a more recent prospective 1 to 1.5 year follow up of patients diagnosed with early postoperative delirium, Koster et al. found an increased mortality of 12.5%, compared to 4.5% in the group without delirium. They also reported more hospital admissions, memory dysfunctions, concentration problems and sleep disturbances as common concomitant symptoms (7).

Cerebral blood flow and the blood-brain barrier (BBB)

The cerebral blood flow (CBF) constitutes 15% of cardiac output in an awake person at rest. The two internal carotid arteries supply most of the cerebral hemispheres, whereas the vertebral arteries supply the brain stem and the cerebellum. These arteries lie within the cranial cavity and are mostly devoid of anastomoses with extracranial arteries. The brain vessels receive their sensory innervations from the trigeminal nerve. Sympathetic fibres innervate brain vessels and release vasoactive substances. Nonetheless the smaller vessels can still constrict and dilate in response to local control (8).

On the capillary level, the central nervous system exerts a strict control of the constituents of its interstitial fluid by the use of the blood brain barrier (BBB). The BBB is a functional neurovascular unit illustrated in figure 1 (9) .

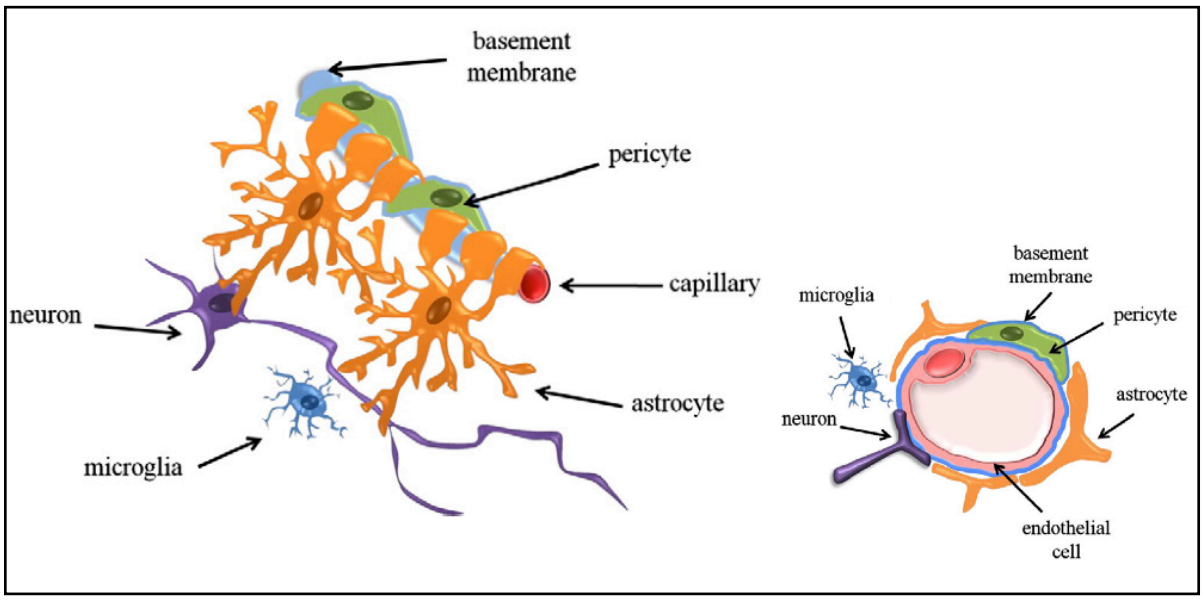

Figure 1: The cellular structure of the blood-brain barrier (BBB) in 3D and cross section (adapted from Cardoso et al).

The layer of endothelial cells is held together with tight junctions regulated in response to signals from astrocytes. This results in a relatively impermeable barrier to water soluble molecules larger than 200-400 Daltons in size (10). Water itself is freely permeable cross the BBB, and the volume of water transport is related to the hydrostatic pressure difference as well as the colloid osmotic pressure. Size, lipid solubility, specific transporters and electrical charge are otherwise the properties that determine the passage of substances through the BBB.

An important feature of the cerebral anatomy and physiology is the role of the cerebrospinal fluid (CSF). The volume of CSF in the cerebral ventricles and subarachnoid space is 130-140 mL. In addition, approximately 75 mL surrounds the spinal cord. The CSF is formed with a rate of 500 mL/day by the choroid plexus, implicating that the total amount is renewed more than twice every 24 hours. The brain almost floats in CSF, and the theoretical buoyancy effect reduces the weight of the brain to less than 100g - a very important mechanical protection function. In addition, water and soluble substances are freely exchangeable between CSF and the interstitial fluid of the nervous tissue. Examination of the CSF composition gives information of the extracellular fluid of the brain. Normally the concentration of sodium, potassium, and other ions is about the same in CSF as in the blood. However the concentration of glucose is about 2/3 of that in the blood, and the CSF protein concentration is less than 0.5% compared to plasma. The distribution and flow of CSF is driven by vascular pulsations mediated by the larger cerebral arteries (11). Accordingly the circulation of CSF inside the CNS ceases during cardiopulmonary bypass (CPB).

Regulation of cerebral blood flow (CBF)

The CBF exhibits a high degree of autoregulation in the sense that conditions in the brain itself determine the blood flow. Thus the autonomic circulatory control plays a minor part in the brain in contrast to most other organs.

Metabolic control

CBF is regionally heterogeneous, and its random distribution is not dependent of the anatomic vascular organization or the innervation pattern of the vessels. There is instead a coupling between the regional cerebral metabolic demand for oxygen and glucose generated by neuronal activity and the volume of blood flowing to that tissue (12,13). To some extent this metabolic hypothesis has been challenged by the fact that it has been shown that the regional CBF response to functional activation increases in excess of the actual increase in oxygen consumption. The uncoupling of flow and oxidative metabolism with a relative "luxury" perfusion under normal conditions has yet to be fully explained (12,14).

Pressure-flow autoregulation

The CBF is independent of changes in mean arterial blood pressure (MAP) within the range of ≈60 to 160 mmHg. Below the MAP level of 60 mmHg the CBF falls steeply. Conversely, it increases steeply at MAP levels above 160 mmHg. Figure 2 shows the illustration of CBF

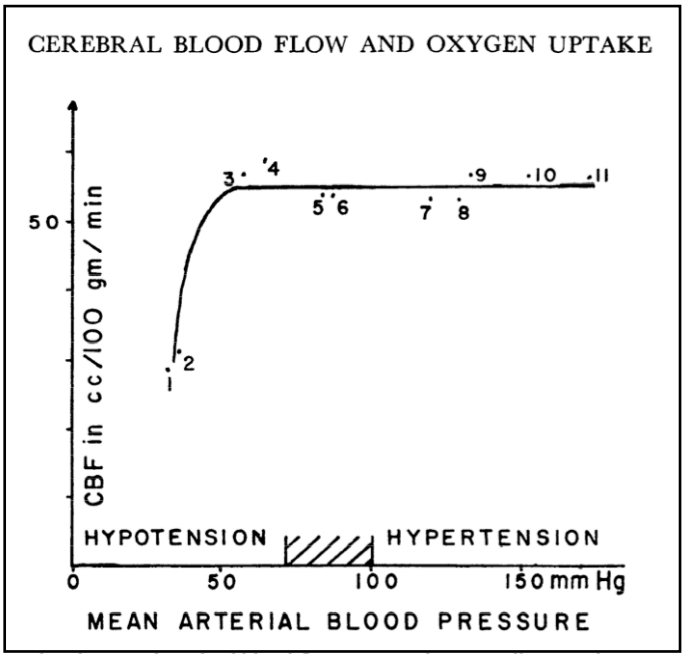

Figure 2: The plateau of cerebral blood flow autoregulation (adapted from Lassen, 1959).

autoregulation from the original paper of Lassen (15). The traditional view of the horizontal profile of the CBF autoregulation curve in the 60 to 160 mmHg MAP range has, however, recently been challenged (Lucas et al) (see Discussion)(16).

Alterations in arterial $PaCO_2$ and O_2

Hypercapnia and hypoxia both result in vasodilatation as the arterioles and precapillary sphincters relax which increases CBF. Within a PCO_2 range of 25 to 60 mmHg there is an exponential relationship between $PaCO_2$ and CBF, with a change of ≈4% change in CBF for each mmHg change in PCO_2. The exact mechanism is not fully understood, but is believed to depend on changes in the pH in the vicinity of the vascular smooth muscle cells (17). The partial pressure of oxygen (PaO_2) has little effect on global CBF until it falls below 50 mm Hg. At this point, a dramatic increase in blood flow with further reductions in PaO_2 occurs.

Neural control

Efferent nerves travel along and innervate the cerebral vessels; sympathetic, parasympathetic and sensory nerves originate from the superior cervical ganglion, sphenopalatine and otic ganglia, and trigeminal ganglion, respectively. The majority of these fibres are sympathetic, and function by reducing CBF under conditions where it has been increased by metabolic demand.

Cerebral oxygen supply versus demand

The cerebral metabolic rate ($CMRO_2$) of awake adults is 3.5 mL O_2/100 g/minute and glucose uptake is 5.5 mg glucose/100 g/minute. An assessment of the global hemispheric cerebral oxygen supply/demand is possible by the traditional analysis of differences in the arterial and venous oxygen content. The venous sinuses drain the cerebral venous blood through the jugular foramina and into the internal jugular veins. The jugular bulb venous oxygen content reflects the overall balance between cerebral oxygen supply and demand. This value is accessible by analysis of the arterial and jugular bulb oxygen saturation

Oxygen supply = CBF x arterial O_2 content

Oxygen demand ($CMRO_2$) = CBF x (arterial O_2 - venous O_2 content)

Jugular bulb vein saturation ($SjvO_2$) is dependent on CBF, $CMRO_2$, SaO_2 and haemoglobin (Hgb). The normal value is 55-75%. A decrease of $SjvO_2$ < 55%

indicates that the oxygen supply is insufficient to meet the metabolic demands. An increased SjvO2 > 75% indicates that the oxygen supply to the brain is elevated in relation to the metabolic demands ("luxury perfusion")

As previously mentioned CBF and $CMRO_2$ are normally coupled in the normal resting brain, an increase in metabolic demand will lead to an increase in flow. However, during functional activation, regional CBF and regional glucose metabolism (CMRglc) are coupled as they increase in proportion, whereas oxygen metabolism , $CMRO_2$, only increases to a minor degree - the so-called uncoupling of CBF and oxidative metabolism (12). The mechanism for this coupling is unlikely to be the change in CMRglc itself. These findings indicate a compartmentalization of brain metabolism into a basal component in which CBF is coupled to oxygen metabolism and an activation component in which CBF is controlled by another and yet unknown mechanism (18,19).

Pathophysiology of cerebral dysfunction after cardiac surgery with cardiopulmonary bypass (CPB)

In reviews addressing this issue the major theories proposed regarding the aetiology centre on the following issues (5,20):

- Cerebral oxygen supply/demand mismatch during CPB
- Cerebral embolization of both particulate and gaseous material
- Possible blood-brain barrier dysfunction
- Inflammation, both systemic and within the brain itself
- Cerebral oedema
- Temperature perturbations, particularly hyperthermia
- The influence of genetics regarding susceptibility for injury, and repair once it has occurred

Cerebral oxygen supply/demand mismatch

Previous data on the cerebral pressure-flow autoregulatory capacity during CPB are scarce and controversial. In previous studies on this topic, the measurements of CBF have been performed with static methods, Kety-Schmidt or ^{133}Xenon clearance techniques. The disadvantage of these techniques is that they are static, allowing only few measurements during CPB. Using the ^{133}Xenon clearance technique, both Govier and Murkin (21,22) found that cerebral pressure-flow autoregulation was intact during CPB. In contrast Newman, also using the ^{133}Xenon technique, found that CBF was pressure-dependent during CPB (23). These investigations were performed with a basic opioid and bensodiazepine anaesthesia. Ederberg et al used the more dynamic transcranial Doppler (TCD) technique and suggested that the CBF was pressure-dependent during CPB in fentanyl and droperidol anaesthetised patients (24).

Other factors, in addition to CBF, that affects the oxygen supply demand balance during CPB are anaesthetics, temperature, haemodilution and acid base management (25) . Sevoflurane or isoflurane are commonly used anaesthetics during CPB. Both are known to decrease cerebral metabolism and in

lower doses to decrease and at higher doses to increase CBF, in non-cardiac surgery (26). Data on the effects of volatile anaesthetics on cerebral pressure-flow autoregulation during cardiac surgery with CPB, on the other hand, are scarce and controversial, and have not been evaluated with dynamic methodology such as TCD. Aladj et al. (27) studied the effects of isoflurane on pressure-flow cerebral autoregulation during hypothermic (27°C) CPB using the ^{133}Xenon clearance technique. When isoflurane was added to a basal anaesthesia of fentanyl and midazolam, CBF decreased by 35%. However, autoregulation appeared to be preserved during isoflurane anaesthesia, as a phenylephrine-induced increase in the mean arterial blood pressure (MAP) ≥ 25% caused no change in CBF.

Studies on the effects of volatile anaesthetics on cerebral flow-metabolism coupling are scarce. Investigators have found that electroencephalographic (EEG) burst-suppression concentrations of isoflurane induce a partial loss of the coupling between CBF and metabolism (28,29). These studies were performed in hypothermia (28°C) and studies on the effects of volatile anaesthetics during mild to moderate hypothermia are lacking.

Low temperature affects the oxygen demand-supply effectively by decreasing the $CMRO_2$, which decreases by 6-7% per degree Celsius reduction in temperature, implicating a decrease in oxygen demand. In addition to the effects on metabolism, hypothermia induces suppression of the generation of free radicals, inhibition of destructive enzymatic reactions and reduced metabolic requirements in low-flow regions. As a total, hypothermia provides a favourable balance between oxygen supply and demand (30,31). Fast rewarming rates and uncontrolled cerebral hyperthermia during CPB and in the early post-CPB period have the potential to induce worse neurologic outcome (32).

Haemodilution decreases blood viscosity which will increase CBF (25). On the other hand, the delivery of oxygen to the brain is defined by the product of CBF and the arterial O_2 content, implicating that haemodilution may potentially reduce O_2 delivery. Low haematocrit during CPB has been associated with in-hospital mortality, adverse events including renal injury and in a recent review it is stated the efforts should be made to reduce haemodilution to avoid subsequent allogenic blood transfusion (32).

Cerebral embolization of both particulate and gaseous material

Numerous studies have shown that the use of CPB is associated with cerebral microemboli (2,33). Both MRI investigations and convincing post-mortem examinations of patients who underwent cardiac surgery reveals evidence of cerebral microemboli (2,34). In clinical practice, TCD insonating intracerebral vessels can detect high intensity signals representing microembolic signals (35,36). A major limitation of the TCD method for microembolic detection is the inability of most devices to discern between gaseous and particulate microembolic signals (20). Gaseous emboli are caused by air that is introduced into the CPB circuit or into cardiac chambers during open-heart procedures. The two main sources of

particulate emboli are: 1) atherosclerotic and calcified debris originating from aorta and great arteries and 2) particles from fat, marrow and other sources in the mediastinum and pericardial wall that are aspirated into the CPB circuit via the cardiotomy suction (37,38). Similar to particulate emboli, the cerebral arterial gas emboli involve migration of gas to small arteries which causes a reduction in perfusion distal to the obstruction and an inflammatory response to the damaged tissue (37). The distribution of microembolic signals related to intra-operative events during open-heart surgery has previously been described by van der Linden et al (39).

Blood brain barrier (BBB) dysfunction

BBB ensures an optimally controlled homeostasis of the brain's internal environment. Surprisingly little information is known about the function and integrity of the BBB in the setting of cardiac surgery, probably due to the difficulties in assessing BBB in a clinical setting. Most reviewers assume that there is a disruption of the BBB integrity associated with cardiac surgery with CPB (20,40). Changes in the BBB could explain cerebral oedema that has been demonstrated in patients undergoing cardiac surgery (41).

Systemic and cerebral inflammation

The systemic inflammation reaction to cardiac surgery is well described (42,43), but its exact role in the genesis of cerebral dysfunction is not established (20). Data addressing the specific cerebral inflammatory response to CPB is scarce. Mielck et al investigated the arterio-venous difference of inflammatory markers on CABG patients without any findings of gradients indicating cerebral release of inflammatory markers reaching the circulation (44). On the other hand, Kalman et al found that the inflammatory marker IL-6 in CSF was significantly increased in patients 1 week after CABG (45).

Cerebral oedema, temperature perturbations and genetic susceptibility

All are explanatory factors which to some extent interacts with the four previously discussed mechanisms, and it is difficult to extract their individual role in the pathophysiology of cerebral dysfunction after cardiac surgery (20).

As shown above, the possible aetiologies to cerebral dysfunction after cardiac surgery are very heterogeneous and interact with each other. Although all are plausible theories, there is a lack of firm evidence connecting them to clinical outcome.

Risk factors for cerebral dysfunction after cardiac surgery

Well validated risk factors associated with development of stroke after cardiac surgery are history of cerebrovascular disease, peripheral vascular disease, diabetes, hypertension, previous cardiac surgery, preoperative infection, urgent operation, CPB time more than 2 hours, need for intraoperative haemofiltration, high transfusion requirement and pulmonary hypertension (1,4). As to risk factors for pure cognitive function, older age, diabetes mellitus, renal failure and preoperative cognitive decline are most important (46,47).

Prevention/treatment of cerebral dysfunction after cardiac surgery

Due to the obvious heterogeneous and to some extent undefined exact aetiology of cerebral dysfunction after cardiac surgery, the options for prophylaxis and treatment are equally dispersed, and dependent on the pathophysiological target meant to be addressed. The main approaches are related to the practical conduct of CPB, and to pharmacologic neuroprotection (48). A definition of cardiac surgery also includes CABG surgery without the use of CPB ("off-pump" CABG), and transcatheter based valve procedures. In both of these sub-groups there is a particular focus on the role of embolic events as part of the pathophysiology of cerebral dysfunction (49-51).

In an evidence-based review of the practice of CPB in adults, focusing on neurologic injury, published in 2006, the authors defined 8 recommendations with sufficient level of evidence in the literature regarding the conduct of CPB to avoid cerebral injury (52): 1) α-stat pH management; 2) avoidance of hyperthermia 3); avoidance of direct re-infusion to the CPB circuit of unprocessed blood exposed to pericardial and mediastinal surfaces; 4) performance of intra-operative TEE or epiaortic ultrasonographic scanning of the aorta in patients at increased risk of neurological events; 5) incorporation arterial line filters in the CPB circuit; 6) maintainance of perioperative euglycemia; 7) reduction of haemodilution to avoid allogenic blood transfusion; and 8) reduction of circuit surface area and the use of biocompatible surface-modified circuits to attenuate the systemic inflammatory response. In a similar review, Hogue et al also highlighted the potential effect of a patient-specific anticoagulation protocol in order to decrease coagulation factor consumption and platelet activation during CPB, which, in turn, could conceivably influence platelet-thrombus microemboli formation (48). These authors also address the potential advantage of surgical field CO_2 insufflation and its supposed reduction of intracardiac and aortic microemboli (48,53). This technique is in frequent clinical use but the potential benefit in preventing neurocognitive complications has still not been proven (54).

Finally the topic of systemic flow during CPB and its effect on CBF needs consideration. Data on autoregulation of CBF during CPB are controversial (see above). A mean arterial blood pressure of 50 mm Hg is commonly viewed as the minimal acceptable arterial blood pressure during CPB (25). This level, however, fails to consider the wide individual variation in the capacity of cerebral autoregulation (48). In addition to the CPB pump flow, the effect of anaesthetics on CBF and their effects on cerebral pressure-flow autoregulation and flow-metabolism coupling have to be taken into consideration.

As to pharmacological prophylaxis/ treatment, the anaesthetic drugs have been in focus based on the hypothesis that anaesthesia induces reduction in cerebral metabolic rate ($CMRO_2$), which could increase tolerance to cerebral ischemia (55). However previous investigations regarding thiopental (56,57), propofol (24,58) and isoflurane (27,28) all provide controversial results, both regarding effects on cerebral haemodynamics and neurological

outcome. The strategy of anaesthetics as a mean for cerebral protection during cardiac surgery has not yet been proven (48). Similarly, pharmacological investigations addressing among other anti-inflammatory, anti- oxidant, and membrane stabilisation drugs have failed to show any effect on neurological outcome (48).

Aims

- To study cerebral pressure-flow autoregulation during cardiopulmonary bypass (CPB) directly, using the transcranial Doppler technique, and indirectly by continuous measurements of jugular bulb oxygen saturation.

- To evaluate the effects of isoflurane and sevoflurane on pressure-flow autoregulation, as well as flow-metabolism coupling during non-pulsatile CPB and mild hypothermia.

- To quantify the cerebral embolic load and its intra-procedural distribution during trans-catheter aortic valve implantation, and also to evaluate the association between the cerebral embolic load and post-procedural release of S-100B, a serum marker of cerebral injury.

- To study the effects of surgical aortic valve replacement on cerebral microembolism, and its relation to cerebrospinal fluid markers of blood-brain barrier dysfunction, neuronal and glial cell injury, as well as cerebral inflammation.

Patients and methods

Patients

The Human Ethics Committee of the University of Gothenburg approved the study protocols and the patients were included after written informed consent was obtained.

The effect of isoflurane (Paper I) and sevoflurane (Paper II) on the auoregulation of CBF during CPB

A total of 34 patients (16 in paper I and 18 in paper II) were included. They were studied in the operation theatre during elective cardiac surgery using mild hypothermic CPB - 32°C in paper I and 34°C in paper II. Demographic data are illustrated in table 1.

Exclusion criteria in both studies were diabetes mellitus, uncontrolled hypertension, and cerebrovascular disease. Two patients in paper II were excluded because of failure to obtain an acceptable TCD registration after anaesthetic induction, thus the statistics were based on calculations on n=16.

Cerebral microembolic signals during transcatheter aortic valve replacement (TAVI) (Paper III)

Twenty-one consecutive patients scheduled for TAVI were included into this prospective, observational study. All patients were considered unsuitable for open-heart surgery due to unacceptable risks related to co-morbidity. There were no exclusion criteria for recruitment to the study, and all patients scheduled for TAVI at our centre between May 2009 and December 2010 were invited to participate. Baseline patient characteristics and co-morbidities are presented in table 1

Cerebral microembolism and cerebrospinal biomarkers after surgical aortic valve replacement (SAVR) patients (Paper IV)

Ten patients with the following inclusion criteria were recruited: a) elective isolated open aortic valve replacement surgery (SAVR) with a biological valve prosthesis, b) normal preoperative coagulation tests (i.e. partial thromboplastin time < 45 s and prothrombin time [international normalized ratio] < 1.5 and a platelet count > 80,000), c) absence of recent (< 1 week) treatment with thrombolytic or potent anti-platelet drugs and d) preoperative left ventricular ejection fraction ≥ 50%. Patients were excluded if coagulation tests or thrombelastograms were abnormal in the morning the day after surgery. Baseline patient characteristics are presented in table 1.

Methods

Anaesthesia/CPB management paper I and II

The patients were premedicated with flunitrazepam 0.015 mg/kg orally and morphine 0.15 mg/kg and scopolamine 0.006 mg/kg IM. Before the induction of anaesthesia, a catheter was placed in the radial or femoral artery for blood sampling and continuous monitoring of mean arterial blood pressure (MAP). Anaesthesia was induced with fentanyl 10 µg/kg, and thiopental sodium (2–3 mg/kg, paperI) or propofol (0.5mg/kg,

Table 1 **Demographic data, paper I, II, III and IV**	**I** **isoflurane** **(n = 16)**	**II** **sevoflurane** **(n = 18)**	**III** **TAVI** **(n = 21)**	**IV** **SAVR** **(n = 10)**
Age (yr)	71±2.6 *	72±1.9 *	81±6 °	73±6 *
Sex Male Female	 14 2	 13 5	 11 10	 8 2
Body Surface area (m^2)	1.89±0.0 *	1.89±0.04 *		
Body Mass Index			24±2.7 °	30±3 *
Logistic Euroscore, %			19.2±8 °	
NYHA class I / II / III / IV			0/0/16/5	4/2/3/1
Aortic stenosis gradient, mmHg			56±19 ° (mean)	92±14* (max.)
NT-pro-BNP level, ng/L			5070 (291-35000)#	
Creatinine, µmol/L			106±38 °	88±11 *
Co-Morbidities Hypertension Diabetes Previous stroke or TIA Atrial fibrillation Previous cardiac surgery	 3	 11	 9 5 2 3 10	 3 5 1 1 0
Procedure CABG§ Valve Combined Maze Ascending aortic aneurysm	 4 3 8 1 0	 1 4 11 0 2		 10
LVEF† (%)	54±3.3 *	55±2 *	52±13 °	59±9 *
CPB‡ time (min)	128±9.5 *	109±6 *		93 ± 25 *
Cross-clamp time (min)	84±8.6 *	81±5 *		74 ± 24 *

Data are mean±SEM*, mean±SD° or median (range)#. CABG§: Coronary artery bypass grafting. LVEF†: left ventricular ejection fraction. CPB‡:Cardiopulmonary bypass.

paper II) sufficient to abolish the eyelash reflex, and droperidol (0.05mg/kg) in addition to fentanyl. Neuromuscular block was obtained with a bolus dose of pancuronium 0.1 mg/kg. In the prebypass period, anaesthesia was maintained with 50% N_2O in oxygen and fentanyl (2.5–5μg/kg, paper I). In paper II an infusion of fentanyl (200-250μg/h), and supplemental doses of droperidol up to a total of dose of 0.1 mg/kg was used in the pre-bypass period. During CPB, fentanyl was administered intermittently (2.5–5 μg/kg, paper I) or as a continuous infusion (200-250μg/h, paper II). After CPB, anaesthesia was maintained with isoflurane at an inspiratory concentration of 1.5%–2.5% in paper I, and with sevoflurane 1.5-2.5% in paper II. An additional feature of paper II was that the anaesthetic depth was monitored by an auditory evoked potential monitor (AEP Monitor/2, Danmeter, Odense, Denmark) and adjusted to an AAI index of 15–25. The AEP monitor uses a two-lead right-sided fronto-temporal EEG to analyse the electrophysiological response to a repetitive acoustic stimulus delivered by bilateral earphones (59). This method is suitable for surgery during CPB, as the electrophysiological signal is not obscured by hypothermia.

The perfusion system consisted of a hollow fibre, membrane oxygenator, and a Sarns 9000 max pump (Sarns; Ann Arbor, MI/Sorin Group, Mirandola, Italy). Non-pulsatile perfusion of 2.4 L/min/m^2 was maintained during the experimental procedure. The pump was primed with acetated Ringer's solution and mannitol, with the haematocrit maintained between 20%-25%. $PaCO_2$, PaO_2, and pH measurements were performed online. $PaCO_2$ was maintained at 4.7- 5.3kPa (35– 40 mm Hg) and was uncorrected for body temperature. PaO_2 was maintained at 15 - 20 kPa (113– 150 mm Hg). The study was performed during CPB with stable hypothermia at a nasopharyngeal temperature of 32°C (paper I) or 34°C in (paper II).

Anaesthesia management paper III (TAVI patients)

On arrival at operation room, standard perioperative monitoring was established, including an AEP monitor for anaesthetic depth measurements and radial arterial and central venous lines. General anaesthesia was induced with propofol 0.5-1 mg/kg and fentanyl 100-150 μg. Tracheal intubation was facilitated using atracurium 0,5 mg/kg. A propofol infusion was used to maintain an anaesthetic depth adjusted to an AAI index of 15-30 as recorded by the AEP monitor. Haemodynamic stability was obtained by the use of colloidal solution administration, guided by the use of intra-operative transoesophageal echocardiography, and norephineprine to maintain a mean arterial pressure above 75 mmHg.

Anaesthesia/CPB management paper IV (SAVR)

Premedication consisted of flunitrazepam 0.015 mg/kg orally in addition to morphine 0.15 mg/kg and scopolamine 0.006 mg/kg intramuscularly. A catheter was placed in the radial artery before the induction of anaesthesia for blood sampling and continuous monitoring of mean arterial blood pressure (MAP). Anaesthesia was induced with fentanyl (10 μg/kg) followed by a bolus of propofol (0.5 mg/kg). Rocuronium (0.6 mg/kg) was used for neuromuscular blockade. Before and

after cardiopulmonary bypass (CPB), anaesthesia was maintained with inhalation of sevoflurane 0.5-2.5% in a 50% O_2/air mixture. During CPB, anaesthesia was maintained with an intravenous infusion of propofol at a rate of 2-4 mg/kg/hr. Anaesthetic depth was monitored as described above. Norepinephrine was used to maintain a MAP within the range 70-80 in the pre- and post-CPB period, and a MAP within the range of 60-80 mm Hg during CPB. Management of CPB was performed as described above. During CPB, the body temperature was maintained at 36ºC in all patients. A standard neurological examination and assessment of focal neurological impairment was performed the day before and the day after the operation. PaO_2 was maintained at 180-195 mmHg (24-26 kPa). During CPB, the body temperature was maintained at 36ºC in all patients.

Measurement of cerebral hemodynamic variables

Cerebral blood flow velocity (CBFV) by transcranial Doppler (TCD)

TCD is based on the use of a range-gated, pulsed-Doppler ultrasonic beam of 2 MHz frequency (60). The ultrasonic beam crosses the intact skull at points known as 'windows' and is reflected back from the moving erythrocytes in its path. The difference between the transmitted signal and the received signal is called the Doppler shift, and can be expressed by the formula:

$$\text{Doppler frequency shift} = 2 \cdot V \cdot Ft \cdot \cos u / C$$

V is the velocity of the reflector (red cells), Ft is the transmitted frequency, C is the speed of sound in soft tissue, and cosu is the correction factor based on the angle of insonation (u). In TCD, Ft (2 MHz) and C (1540 m/s) remain constant; therefore, frequency shift depends mainly on the blood flow velocity and the angle of insonation of the TCD probe (61). TCD ultrasound is pulsed. This means that a pulse of ultrasound is sent out and then there is a period of 'listening'. The time interval from pulse emission to receiving will determine the depth from which any Doppler frequency shift is detected. Thus, the depth of insonated structures can be adjusted by altering the interval between emitting and receiving the TCD signal. TCD is performed through ultrasonic windows where ultrasounds can reach the cerebral arteries. In papers I-IV the right-sided trans-temporal window found above the zygomatic arch was used. The identification of the medial cerebral artery is established by sample depth, flow direction, angle between beam and skin surface, and the response of the TCD signal to compression of the ipsilateral internal carotid on the neck (62-65). (Table2).

Within a vessel, different erythrocytes move at different speeds, thus the Doppler signal obtained is a mixture of different frequency components. A TCD machine uses spectral analysis to display the three-dimensional Doppler data in a two-dimensional format; time is represented on the horizontal scale, frequency shift (e.g. flow velocity) on the vertical scale and signal intensity as the relative colour. Figure 3A illustrates a TCD output during the pre-bypass period with pulsatile cerebral blood flow velocity (CBFV), and figure 3B, a TCD signal during CPB with non-pulsatile flow velocity. The upper part of the displays shows the depth of the velocity signal

Table 2 Patterns for TCD identification of cerebral arteries

Vessel direction	Probe direction	Depth of flow (mm)	Direction of flow	Ipsilateral carotid compression	Contralateral carotid compression
Anterior cerebral artery	Anterior	55-75	Away	Flow reversal	Increased velocity
Medial cerebral artery	Perpendicular	35-60	Toward	Reduced velocity	No change
Posterior cerebral artery	Posterior	65-70	Toward	No change	No change

registered. It is important to remember that TCD gives information only about vascular blood flow velocity and not blood flow. CBFV ≈ Blood flow volume/ blood vessel diameter (66,67). Assumptions about changes in CBFV will only be valid if the vascular diameter ie. area is constant. Validation studies have shown that the absolute values of CBFV correlates poorly to CBF (68). However several investigators have found that *changes* in CBFV reliably correlates with *changes* in CBF (69-71).

In paper I we used the Doppler device "Multidop X" (DWL, Sipplingen, Germany). In papers II-IV, we used a "PowerM-mode TCD" (Spencer technology, Seattle, WA). The right medial cerebral artery (RMCA) was insonated by the transtemporal approach at a depth of approximately 50 mm using standard criteria, and the probe was secured with a headband. The time-mean flow velocity, considered the most physiologic measure of flow velocity, was continuously recorded.

Cerebral perfusion pressure (CPP) and cerebral oxygen extraction (COE) using jugular bulb oximetry catheter

The venous sinuses of the brain drain blood out of the skull through the jugular foramina and into the internal jugular vein. Immediately distal to the jugular foramen, the vein dilates, forming the jugular venous bulb. Although blood in the jugular bulb is derived from both cerebral hemispheres, it is generally accepted that most patients have a dominant side of venous drainage, usually the right (72). Jugular bulb venous pressure (JVP) represents the cerebral venous pressure, and the cerebral perfusion pressure (CPP) can be expressed as:

$$CPP = MAP - JVP$$

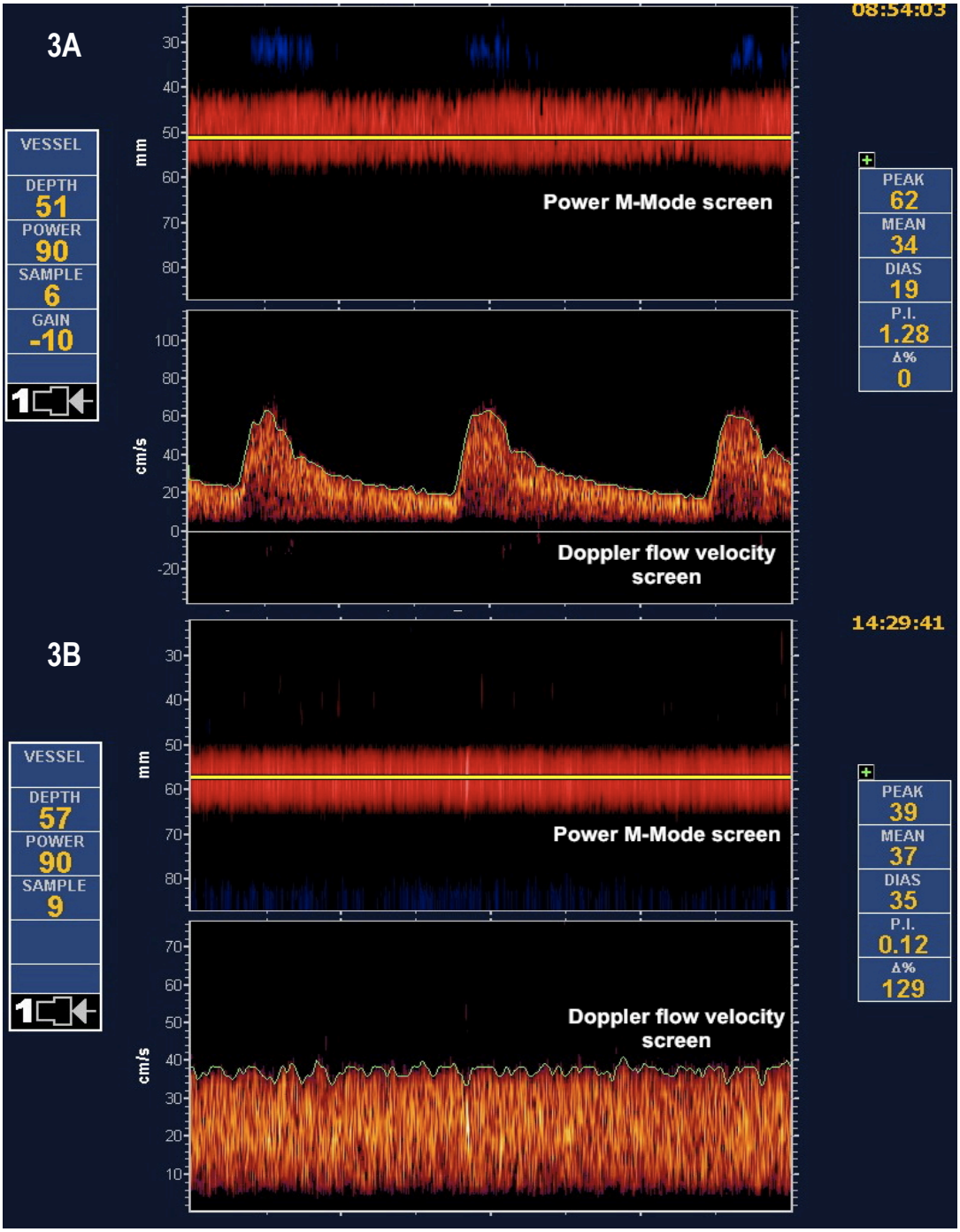

Figure 3A: Transcranial Doppler (TCD) recording in pre-bypass period during cardiac surgery. **Figure 3B:** TCD recording during cardiopulmonary bypass (CPB).

The jugular bulb venous oxygen saturation ($SjvO_2$) reflects the overall balance between cerebral oxygen supply and demand (73,74). Cerebral oxygen demand ($CMRO_2$) is the product of CBF and difference in arterial O_2 content (CaO_2) and cerebral venous content ($C_{jv}O_2$);

$$CMRO_2 = CBF \times (CaO_2 - C_{jv}O_2)$$

Cerebral oxygen delivery is the product of CBF and CaO_2;

$$DO_2 = CBF \times CaO_2$$

The balance between cerebral oxygen demand ($CMRO_2$)and, supply DO_2, can thus be expressed as;

$SaO_2 - SjvO_2/SaO_2$,

i.e cerebral oxygen extraction (COE). The mathematics behind the extraction of this equation is depicted in figure 4.

In papers I and II, we measured CPP and COE using a jugular bulb vein catheter. During anaesthesia, before surgery, a 4F, 3-wavelength oximetry catheter (Opticath©; Abbott Laboratories, North Chicago, IL) was placed in the right jugular bulb, using a retrograde internal jugular vein approach, for continues monitoring of jugular venous pressure (JVP) and jugular bulb saturation ($SjvO_2$) by a dosimeter (Oximetrix3, Abbott Laboratories). The correct position of the catheter tip was verified by fluoroscopy (figure 5). The oximeter was calibrated in vitro before insertion. Accurate fiberoptic saturation values were verified by analysis of blood samples drawn from the catheter and measurement of oxygen saturation (ABL 510; Radiometer, Copenhagen, Denmark). The fiberoptic catheter was re-calibrated in vivo when there was a discrepancy between fiberoptic and blood oxygen saturation ≥ 5% units. The catheter SjvO2 data were used for COE calculation. There is a good correlation between laboratory oximeter measurements and in vivo oximetry during CPB and hypothermia (73).

Electroencephalographic measurements

Electrical activity of the brain results from ionic currents generated by

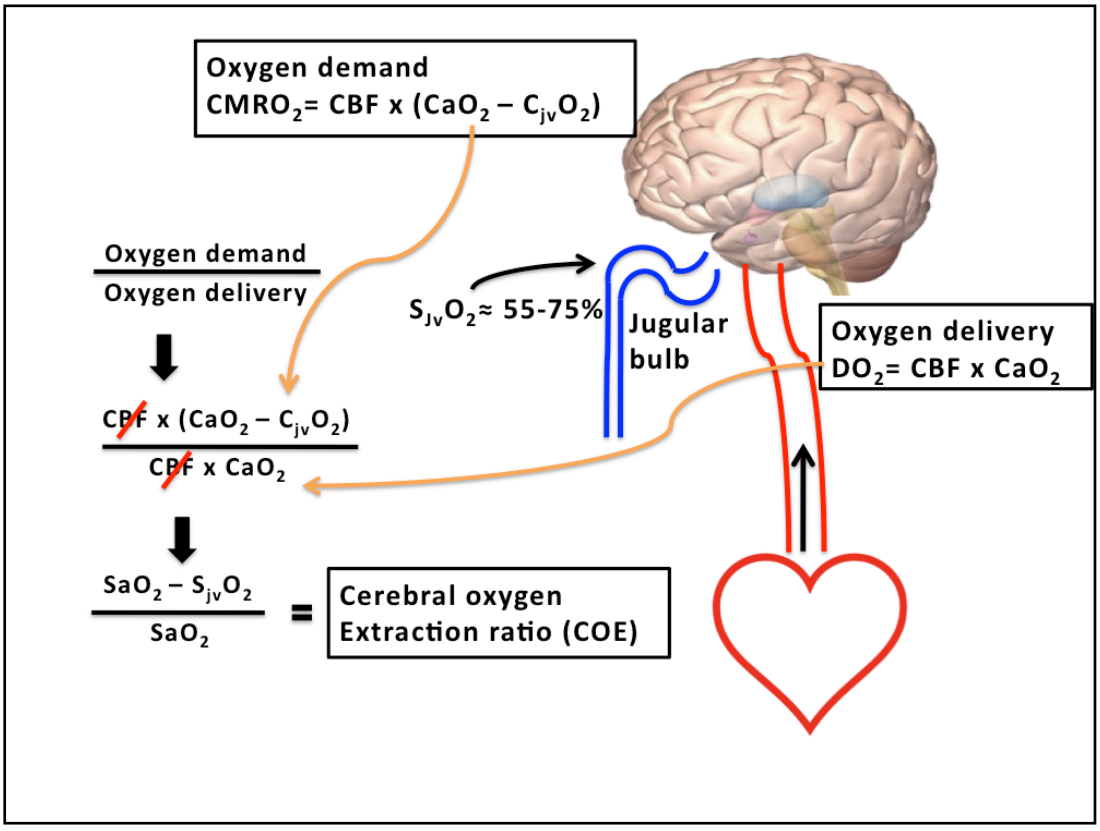

Figure 4: Mathematical calculation leading to the formula for cerebral oxygen extraction ratio (COE).

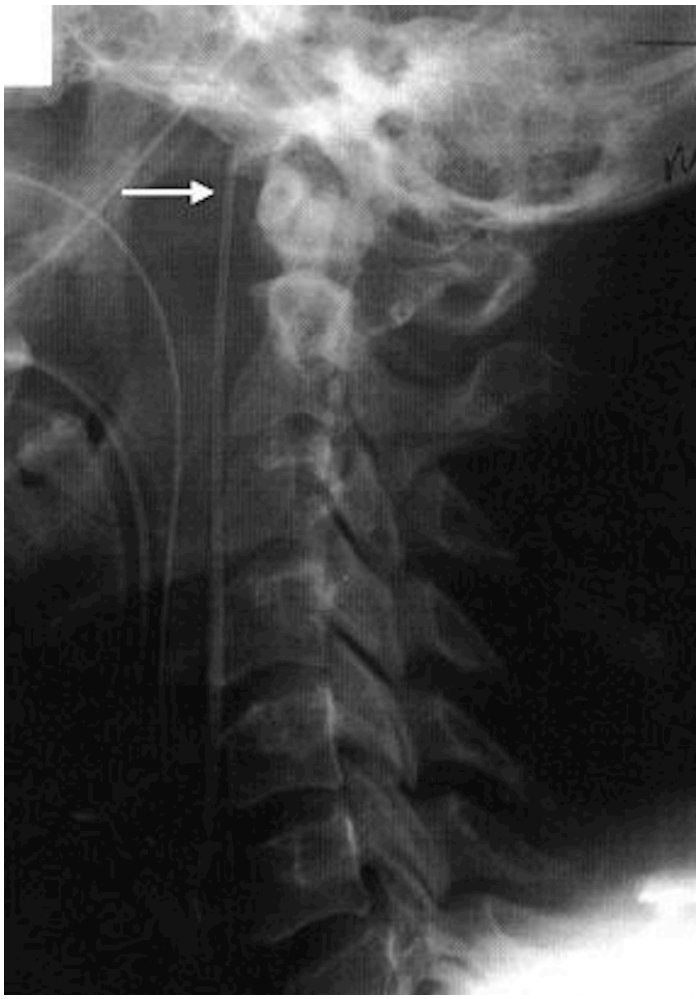

Figure 5: Lateral fluoroscopic view of oximetry catheter in jugular bulb (white arrow).

biochemical processes at the cellular level. These ionic currents generates the electroencephalographic signal (EEG) registered by cranial electrodes (75). The characteristic EEG burst-suppression pattern seen when the brain is exposed to anaesthetic drugs consists of transient sequences of high voltage slow waves intermingled with sharp waves, altering with periods of depressed background activity (figure 6). In anaesthesia induced burst- suppression, almost all cortical neurons become electrically silent during the "flat" EEG periods. Nonetheless, thalamic cells continue to "fire" while the cortex is silent, and accounts for the cyclic EEG bursts (76). With increasing doses of anaesthetics, there is a progressive reduction from early burst suppression, late burst-suppression towards an EEG devoid of any activity (75).

In papers I and II we used the characteristic EEG burst-suppression pattern to secure an equal anaesthetic depth for all the patients. In paper I, the initial concentration of isoflurane in the interventional part during CPB was 1.5%. Isoflurane concentration was increased in a stepwise manner, guided by the EEG response, to induce an EEG burst-suppression pattern of 6 –9/min using a modified version of full diagnostic EEG equipment.

In paper II, we monitored anaesthetic depth by an auditory evoked potential monitor (AEP Monitor/2, Danmeter, Odense, Denmark) and adjusted to an AAI index of 15–25%. The AEP monitor uses a two-lead right-sided fronto- temporal EEG to analyse the electrophysiological response to a repetitive acoustic stimulus delivered by bilateral earphones (59). To obtain a standardized anaesthetic depth

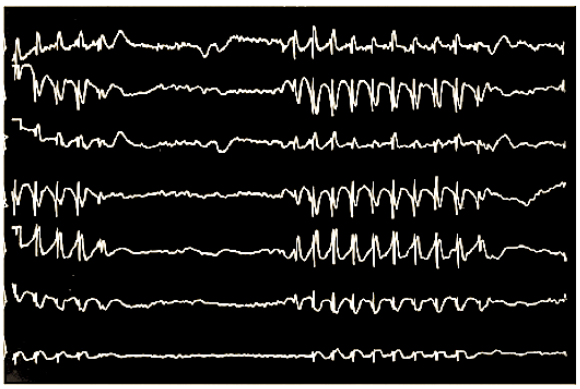

Figure 6: Electroencephalographic (EEG) signal with burst-suppression pattern during anaesthesia.

with sevoflurane during the intervention on CPB, the concentration of sevoflurane was changed in a stepwise manner, to induce an EEG burst- suppression pattern of 4–6 bursts/min as recorded by the raw EEG signal from the AEP monitor.

In papers III (TAVI) and IV (SAVR) the AEP monitor was used to secure an equi-anaesthetic depth for the patients during the recording period in general anaesthesia.

Measurement of microembolic signals (MES) by TCD

Microembolic signals (MES) appear as signals of high intensity and short duration within the transcranial Doppler (TCD) frequency spectrum, resulting from the different acoustic properties of the underlying microemboli (ME) compared with the circulating blood (36,77). We used the TCD device "PowerM-mode TCD" (Spencer technology, Seattle, WA). This device collects: 1) the traditional 2 MHz spectral singe-gate TCD information at a specific depth and 2) the power M-mode (PMD) information from 33 sample volumes placed at 2 mm intervals from 24 to 88 mm depth of insonation. The PMD display was configured with red or blue colours for directionality. The PMD display embolus count was based on "embolic signature" criteria defined in the

Table 3 Criteria for counting Emboli signals on spectral vs. PMD TCD

Spectral TCD criteria	PMD criteria
Transient, lasting <300ms	Embolic signature visible at least 3 dB higher than the highest spontaneous PMD display of background blood flow signal
At least 3 dB higher signal intensity than that of the highest background blood flow signal	Embolic signature reflects motion in one direction at a minimal spatial extent of 7.5 mm and a minimal temporal extent of 30 ms. An MCA embolic signal is required to move towards the probe.
Unidirectional	The embolic signal must traverse a specific depth determined by the highest intensity of the insonated artery in order to avoid repeated counting of the same embolus-depth defined by the optimal spectrogram waveform
Accompanied by snap, chip or moan on the audible output.	NA

PMD: Power M-mode Doppler. TCD: Transcranial Doppler.

literature (78,79), and illustrated in table 3. In papers III and IV, we used these PMD criteria for microembolic detection.

A typical TCD trace illustrating the features of 3 microembolic signals detected both with spectral and PMD criteria is shown in figure 7.

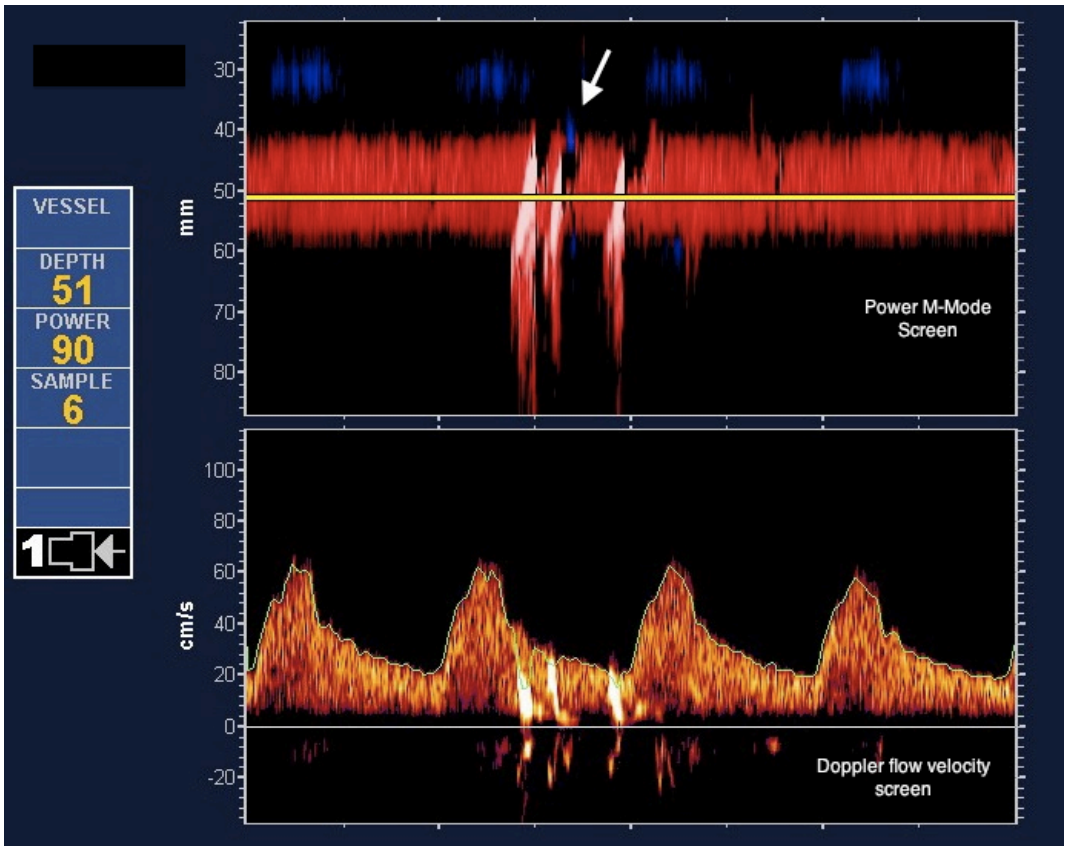

Figure 7: TCD recording showing 3 microembolic signals (white arrow) detected during catheter manipulation in aortic arch in patient receiving transcatheter aortic valve implantation (TAVI).

Serum and cerebrospinal fluid (CSF) biochemical analysis (Paper III and IV)

In paper III, we analysed the levels of serum S-100B as a marker of injury to central nervous system cells. S-100B is a Ca^{2+}-binding protein with a low molecular weight found mainly in the astroglial and Schwann cells in the CNS (80). Serum was prepared from blood that was allowed to clot for 30 min followed by centrifugation at 2300 G for 10 min. Samples were immediately aliqouted and stored at -80°C pending biochemical analyses. Serum levels of S-100B were determined by an electrochemoluminescence immunoassay using the Modular system and the S-100B reagent kit (Roche Diagnostics, Basel, Switzerland).

In paper IV, we analyzed biomarkers from CSF prior to, and 24 hrs after open aortic valve (SAVR) surgery. A CSF sample volume of 2.5 ml and a 4 ml blood sample were collected at both time points. We used a 27 G Whitacre spinal needle (Becton Dickinson S.A. S. Agustin del Guadalix, Madrid, Spain) for lateral approach at L3-4 level in the sitting position.

Serum and CSF levels of S-100B were determined as described above. Serum

and CSF levels of neuron specific enolase (NSE) were analysed using an immunofluorescent assay with time-resolved amplified cryptate emission (TRACE) technology (Kryptor-NSE; BRAHMS, Hennigsdorf, Germany). Albumin levels in CSF were measured by immunonephelometry on an Immage immunochemistry system (Beckman Coulter Inc, Fullerton, Calif.). CSF total tau (T-tau) concentration was determined using a sandwich enzyme-linked immunosorbent assay (ELISA) (Innotest hTAU-Ag; Innogenetics, Gent, Belgium) specifically constructed to measure all tau isoforms irrespective of phosphorylation status. Glial fibrillary acidic protein (GFAP) concentrations in CSF were analysed using a previously described ELISA method (81). Neurofilament light chain protein levels (NF-L) were determined using a commercial assay as described by the manufacturer (Uman Diagnostics AB, Umeå, Sweden). CSF and serum levels of IL-6 and IL-8 were determined using the Human Proinflammatory II 4-Plex Assay, Ultra-Sensitive Kit, with electrochemiluminescent detection according to the instructions from the manufacturer (Meso Scale Discovery®, Gaithersburg, MD, USA). IL-6 and IL-8 were readily measurable above the limit of quantification in all CSF samples.

Intra- and inter-assay coefficients of variation (CVs) were well below 10% for all analyses except for CSF albumin that had an inter-assay CV of 11%. Inter-assay CV is, however, of little relevance to the current investigation as all measurements were performed in a single round of analyses.

Experimental procedures

Paper I

Sixteen patients were studied during elective cardiac surgery when on stable CPB at 32°C. Phenylephrine and sodium nitroprusside was used to induce stepwise increase or decrease in MAP within the range of 80-40 mmHg (first part of experimental procedure = control). MAP, JVP, CBFV from RMCA and $SjvO_2$ were continuously monitored. Stepwise changes in MAP induce a cerebral autoregulatory response, which develops during approximately 20–30 s (69). Values of the different variables were therefore obtained after a 30-s stabilization period at each blood pressure level. Isoflurane was then administered directly to the CPB circuit by an overflow vaporizer. The initial concentration of isoflurane was 1.5%, which was increased in a stepwise manner, guided by the EEG response, to induce an EEG burst-suppression pattern

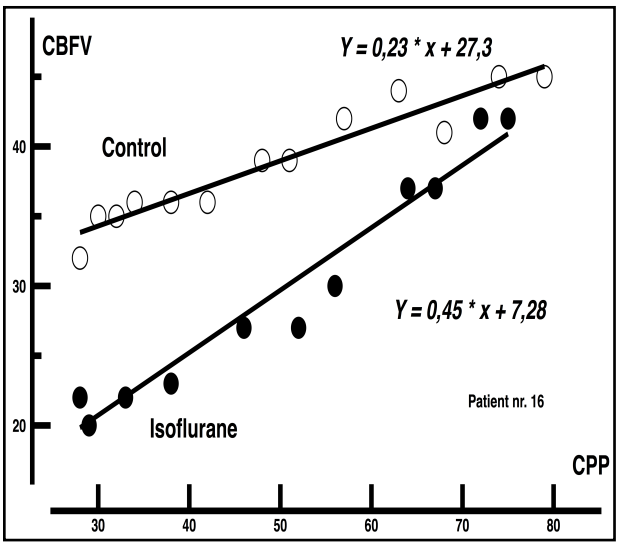

Figure 8: Relationship between cerebral perfusion pressure (CPP) and cerebral blood flow velocity (CBFV) during cardiopulmonary bypass (CPB). Plot during control and with isoflurane added to CPB circuit in one patient.

of 6 –9/min. During isoflurane administration, MAP was again changed in a stepwise manner, using sodium-nitroprusside or phenylephrine, recording the same variables as described above. For each patient, the relationship between CPP (MAP-JVP) and CBFV (figure 8), as well as the relationship between CPP and COE (COE =(SaO_2 - SjO_2)/SaO_2), before and during isoflurane administration was subjected to a linear regression analysis. The slope (regression coefficient) of the relationship between CPP and CBFV was defined as cerebral pressure-flow autoregulation. CBFV and COE values fitted to each regression line were obtained at CPP values of 30, 40, 50, 60, and 70 mm Hg.

Paper II

Sixteen patients were studied with a protocol similar to paper I, but with some modifications; CPB was conducted at a stable temperature of 34°C. Norepinephrine was used to increase MAP instead of phenylephrine. MAP was manipulated between 40-90 mmHg. EEG burst suppression was set to 4-6 bursts/min.

The experimental procedures for paper I and II are illustrated in figure 9.

Paper III

Twenty-one patients were studied during, and 24 hours after, the TAVI procedure in this descriptive investigation. During the procedure, TCD data from RMCA were continuously monitored and saved to hard drive for offline analysis of MES and CBFV. In order to elucidate the main mechanisms of cerebral microembolism during TAVI, the following intra-procedural events were defined with respect to the appearance of

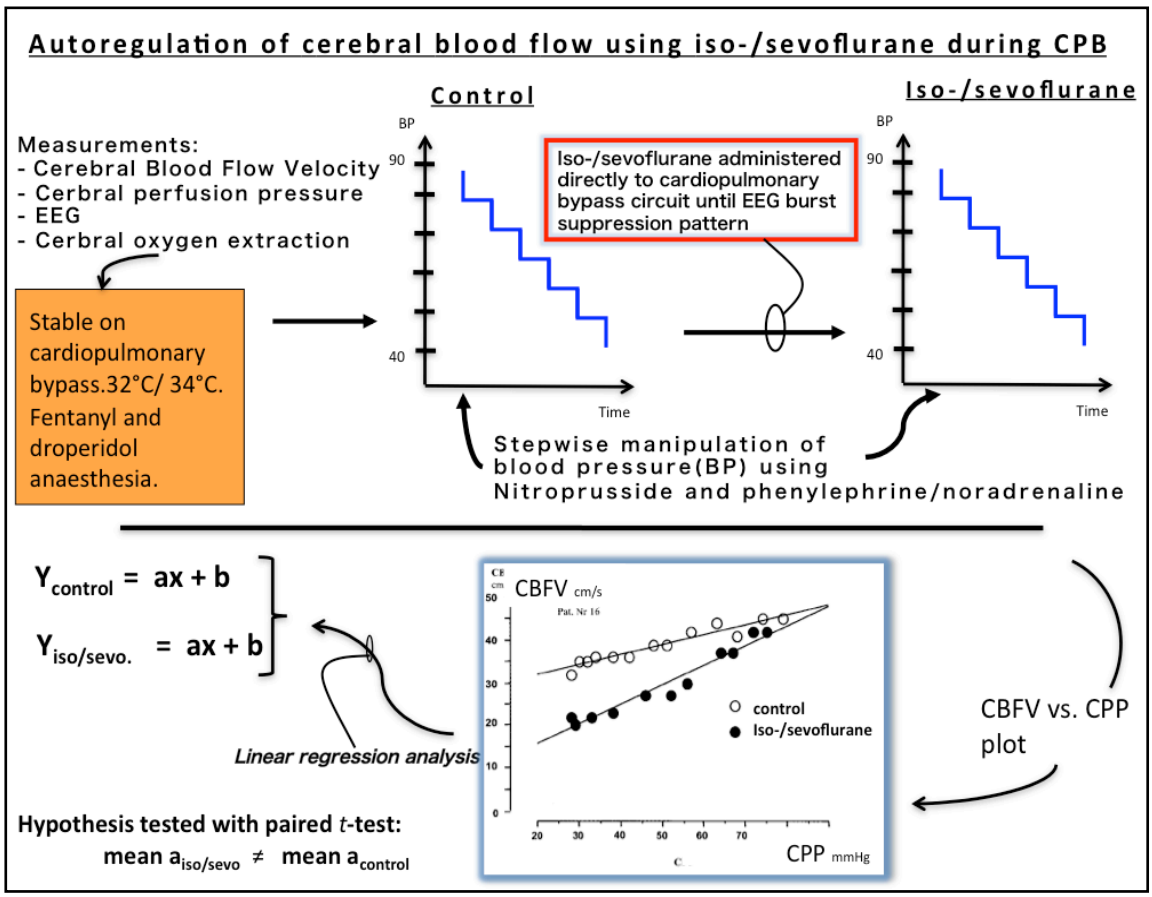

Figure 9: Graphic presentation of study design in paper I and II.

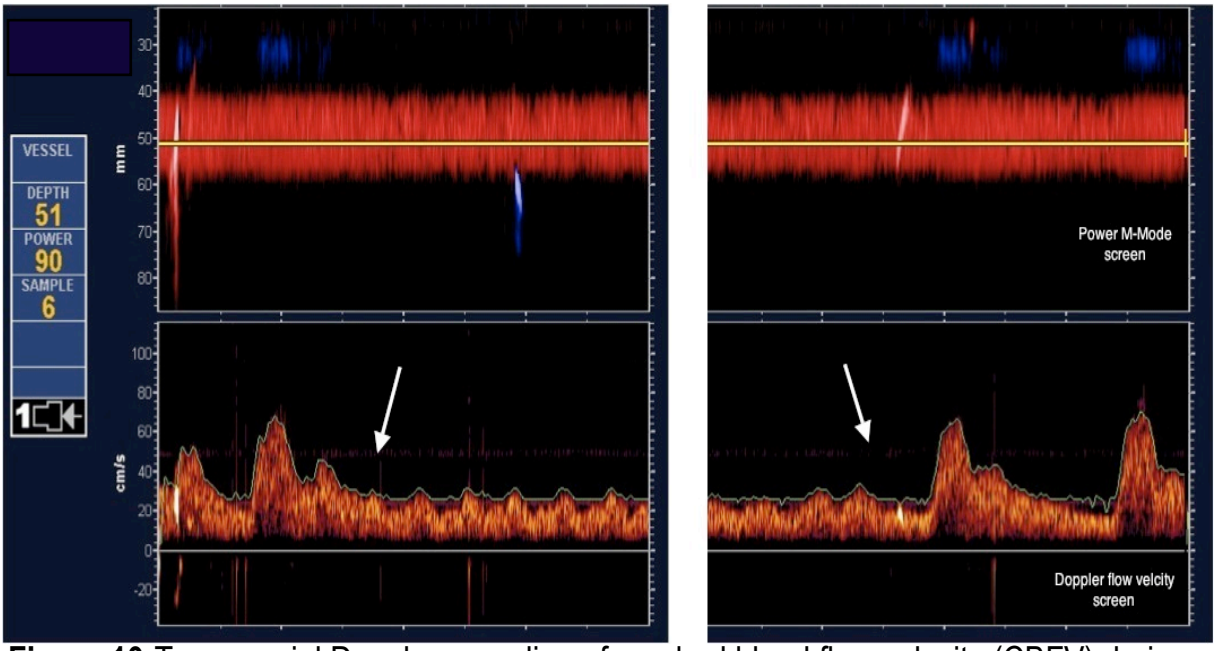

Figure 10: Transcranial Doppler recording of cerebral blood flow velocity (CBFV) during start and end (white arrows) of rapid pacing with balloon expansion of native aortic valve during transcatheter aortic valve implantation (TAVI).

MES: 1) aortic arch/root/valve instrumentation, including scraping of the aortic arch/root, manipulation and passage of the native aortic valve with catheters/guide-wires, 2) valvuloplasty of the native aortic valve, i.e. the time period from balloon expansion of the native aortic valve to the positioning of the prosthetic valve and 3) frame expansion of the valve prosthesis, i.e. the time period from frame expansion to the end of the procedure. The duration of each of these three events was also recorded in each patient.

By analysis of the TCD flow velocity signals, we determined the exact duration (sec.) of systemic hypotension during rapid pacing and balloon expansion of the native aortic valve (Figure 10). The values of cerebral flow velocities prior to, and during the balloon expansion were also registered.

Blood samples were obtained after the anaesthesia induction serving as the baseline value (T_0). Thereafter, blood samples for serum measurements of S-100B were taken 1, 2, 4, 6,12, and 24 hours after the balloon dilatation of the native aortic valve. The area under curve (AUC) relating the S-100B serum level to time was calculated using the value at T_0 as baseline. The experimental procedure is illustrated in figure 11.

Paper IV

Ten patients undergoing isolated open aortic valve replacement were included in an exploratory investigation. CSF was obtained the day before and 24 hours after surgery for assessment of cerebral inflammation (IL-6 and IL-8), neuronal damage (NSE, T-tau and NF-L), glial cell injury (S-100B, GFAP) and BBB integrity (CSF/serum albumin ratio).

The intra-operative extent and distribution of microemboli were described using the transcranial Doppler technique. The following intra-procedural events were defined with respect to the appearance of cerebral microembolic signals in RMCA: 1) aortic cannulation before start of CPB, 2) CPB

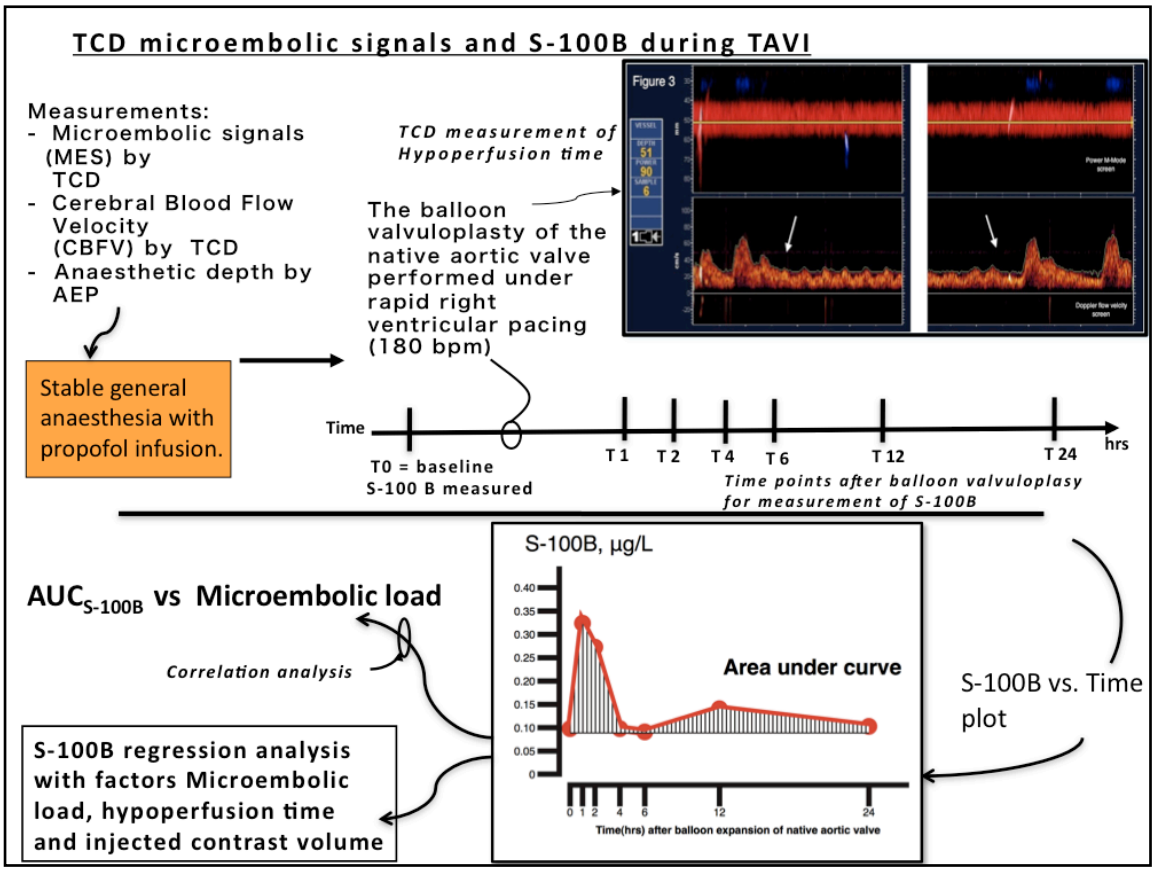

Figure 11: Graphic presentation of study design in paper III.

before aortic cross-clamp, 3) during aortic cross-clamp, 4) de-clamping of aorta to end of CPB 5) end of CPB to aortic de-cannulation and 6) aortic de-cannulation to sternum closure. The duration of each of these events was recorded in each patient.

Statistical Analyses

In paper I, statistical analysis was made by StatView 4.0, and in papers II-IV statistical analyses were made by PASWStatistics 18.0 and GraphPad Prism version 5.0c for Mac OS X. Values are presented as mean ± SEM in paper I, II and IV, and as mean ± SD in paper III due to instructions from publishing journal. A probability level (p-value) of less than 0.05 was considered statistically significant.

Data management

Pre-drug control periods in paper I and II were compared to the interventional drug (isoflurane and sevoflurane, respectively) regarding cerebral autoregulation. There were no post drug control evaluations of cerebral autoregulation performed neither in paper I nor II.

In paper III, the TCD data were prospectively collected during the procedure. A measurement of serum S-100B was collected before start of procedure, and served as baseline level for each patient. The subsequent 6 Serum S-100B measurements were used to create a 24 hours release pattern curve, of which the area under the curve served as a marker of total S-100B release for each patient.

In paper IV, all TCD data were prospectively collected during the

surgical procedure. The levels of neurobiochemical markers and albumin in CSF preoperatively were compared to the subsequent CSF levels the day after surgery.

Shapiro-Wilks test

Shapiro-Wilks test for goodness of fit to normal (Gaussean) distribution was performed on all data variables. In paper I and II, values for CBFV, COE, and the slopes (regression coefficients) relating CBFV and COE to CPP did not violate the assumption of normal distribution.

In paper III, the total amount of microembolic signals, the measurements of S-100B, and the CBFV in RMCA during balloon expansion of the native aortic valve also respected the assumptions of normal distribution.

In paper IV, values for microembolic signals and neurobiochemical markers were normally distributed, with the exception of total-Tau in CSF prior to surgery.

Paired t-test

Paired t-test was used in papers I and II to compare the slopes (regression coefficients) of the relationship between CPP and CBFV, as well as CPP and COE, in the control situation and when isoflurane, or sevoflurane, respectively, was added.

In paper III, the peak levels of s-100B were compared to baseline by paired t-test. The difference between the mean CBFV in RMCA prior to and during balloon expansion of the native valve was also analysed by a paired t-test.

In paper IV, differences between pre- and postoperative concentrations of the various cerebrospinal proteins were tested using a paired *t*-test.

Repeated measures ANOVA

In papers I and II, repeated measures ANOVA (PASW18.0; General linear model-repeated measures) were used. We tested the effect of the two independent factors CPP and the study drug (isoflurane or sevoflurane respectively) on the dependent value CBFV, and also the interaction effect of the independent factors. The analysis was repeated with COE as dependent value. Assumptions for normal distribution of CBFV and COE were not violated. The assumption of equality of variance between control and treatment groups according to Levene´s test was not violated in paper II. In paper I, Levene´s test indicated equal variance in both groups with the exception of CPP 40 and 50 mmHg in the control group. Thus, it was only the two lower of five CPP levels in the control group who violated the assumption of equal variance. In combination of the fact that there is no non-parametric alternative to this ANOVA test, we chose to rely on the test in the publication of paper I.

Hierarchical multiple regression

In paper III, a hierarchical stepwise multiple regression was used to assess the ability of the total embolic load to predict the level of AUC_{24hrs} for S-100B, after controlling for the confounding influence of the duration of pacing-induced hypotension and the intra-procedural radio-contrast volume injected in the aortic root. Preliminary analyses ensured no violation of the assumption of linearity or homoscedasticity.

Linear regression and correlation

Linear regression analysis of CPP vs. CBFV and CPP vs. COE with curve estimation were performed in papers I and II. In paper III and IV, parametric bivariate correlation analysis (Pearson's) was performed for assessment of correlation between numerical data.

Results

Paper I- Effects of isoflurane

To evaluate the effects of isoflurane-induced EEG burst suppression on CBFV, COE and autoregulation 16 patients undergoing elective cardiac surgery were studied during CPB. Data on the effects of isoflurane on the relationship between CPP and CBFV and the relationship between CPP and COE are shown in Figures 12 and 13.

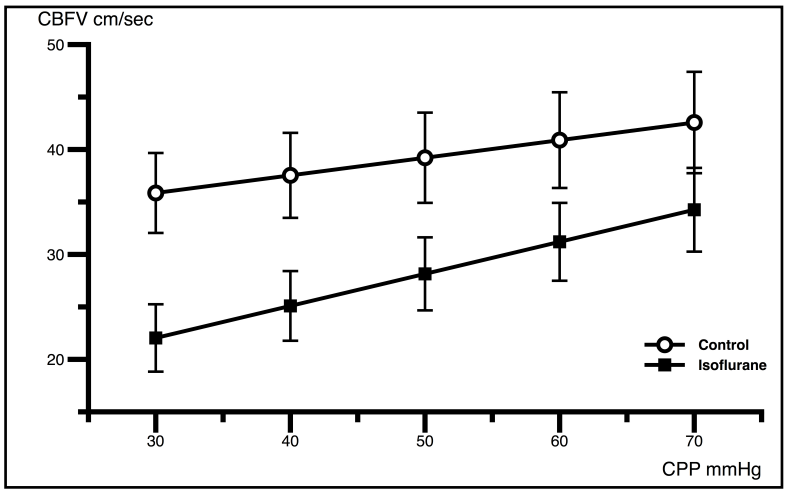

Figure 12: Effects of isoflurane on cerebral blood flow velocity (CBFV) compared with control at 5 different levels of cerebral perfusion pressure (CPP). A 27% decrease in CBFV was found during isoflurane administration ($p<0.05$). The slope of the isoflurane curve was more positive compared with control ($p<0.05$). Values are mean±SEM.

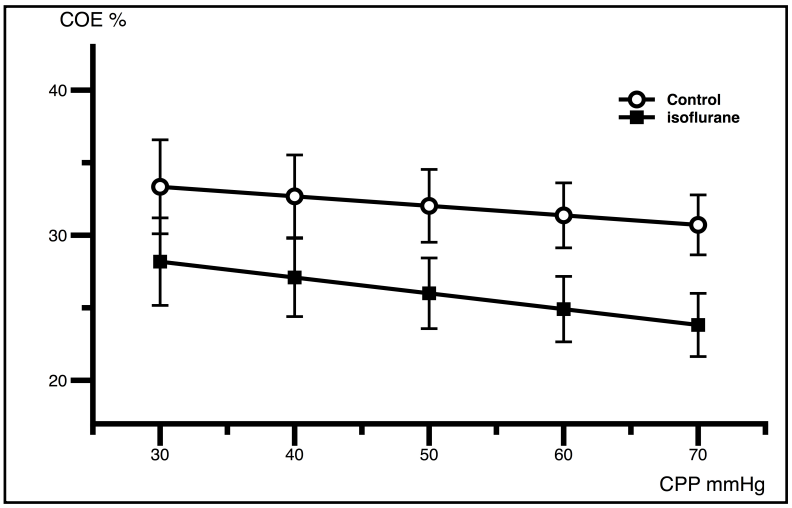

Figure 13: Effects of isoflurane on cerebral oxygen extraction (COE) compared with control at 5 different levels of cerebral perfusion pressure (CPP). A 13% decrease in COE was found during isoflurane administration ($p<0.05$). The slope of the isoflurane curve was more positive compared with control ($p<0.05$). Values are mean±SEM.

Isoflurane decreased mean CBFV from 39.9±2.0 to 29.1±1.6 cm/s (-27%, $p<0.05$). The regression coefficients deviated from zero ($0.0001<p< 0.05$) in 13 and 16 of the 16 patients in the control situation and during isoflurane administration, respectively, indicating a CPP-dependent CBFV. The mean regression coefficient (slope) of the autoregulation curve was more positive with isoflurane compared with control, 0.25±0.04 cm/s/ mm Hg and 0.19±0.04 cm/ s/ mm Hg, respectively ($p<0.05$).

Isoflurane decreased mean COE from 33.6±1.0 to 29.3±1.2 percent units (−13%, $p<0.05$). The slope of the curve relating COE to CPP was more negative with isoflurane compared with control, −0.19±0.02%/mm Hg and

−0.14±0.03%/mm Hg, respectively (p<0.05).

Paper II- Effects of sevoflurane

The study design and measurements of CPP, CBFV and COE were similar to paper I, but instead sevoflurane was added during CPB. Two patients were excluded because of failure to obtain an adequate TCD signal. Data on the effects of sevoflurane on the relationship between CPP and CBFV and the relationship between CPP and COE for the remaining 16 patients are shown in Figs. 14 and 15, respectively. A mean concentration of 3.36±0.03% sevoflurane was added to the CPB circuit to reach an EEG burst-suppression level of 4–6 bursts/min. Sevoflurane decreased the mean CBFV from 39.01±1.02 to 32.57±0.86 cm/s (− 17%, p<0.05). The regression coefficients deviated from zero (0.0001<p<0.05) in 10 patients in the control situation and 14 patients during sevoflurane administration, respectively, indicating a CPP- dependent CBFV in the majority of the patients. The mean regression coefficient (slope) of the autoregulation curve was more positive with sevoflurane compared with control, 0.26 ±0.04 and 0.09±0.03 cm/s/mmHg, respectively (p<0.01).

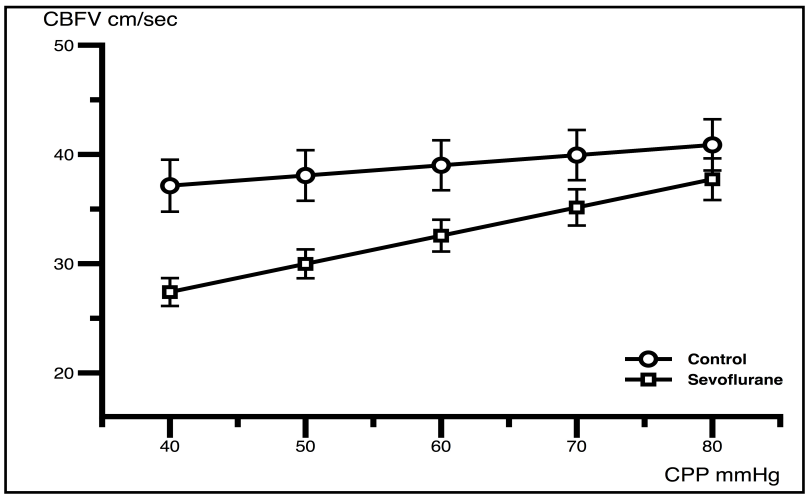

Figure 14: Effects of sevoflurane on cerebral blood flow velocity (CBFV) compared with control at 5 different levels of cerebral perfusion pressure (CPP). A 17% decrease in CBFV was found during sevoflurane administration (p<0.05). The slope of the sevoflurane curve was more

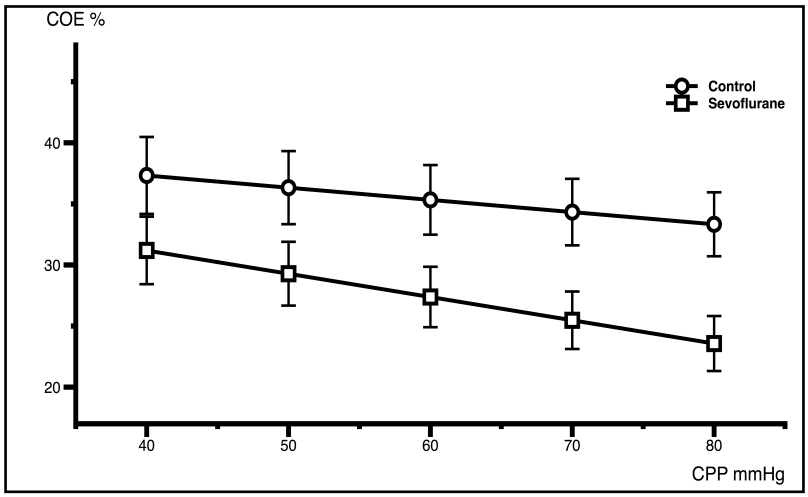

Figure 15: Effects of sevoflurane on cerebral oxygen extraction (COE) compared with control at 5 different levels of cerebral perfusion pressure (CPP). A 23% decrease in COE was found during sevolurane administration (p<0.05). The slope of the sevoflurane curve was more positive compared with control (p<0.05). Values are mean±SEM

Sevoflurane decreased the mean COE from 35.33±1.21 to 27.38±1.12% units

(−23%, p<0.05). The slope of the curve relating COE to CPP was more negative with sevoflurane compared with the control, −0.19±0.02%/mmHg and −0.10±0.03, respectively (p<0.01).

Paper III- TAVI and microembolic load

Successful TCD recordings were obtained in all patients. The TAVI procedure was technically successful in all patients. Four patients needed post-interventional pacemaker implantation. One patient died within 24 hours postoperatively because of retroperitoneal haemorrhage. Data on serum S-100B are therefore missing in this patient. Neurological examination revealed no clinically signs of focal neurological deficit during the 24 hours post-procedural observation time in any of the patients.

Intra-procedural data are presented in Table 4. MES were detected in all patients during aortic arch/root/valve manipulation, during aortic valvuloplasty and finally during expansion of the valve prosthesis. The mean total embolic load was 282±169 MES with an event distribution according to Table 4 and Figure 16. The amount of MES detected during aortic arch/root/valve manipulation was recorded during a relatively long time period (62±33 minutes) when the interventionist established his diagnostic and therapeutic devices in the aorta and left ventricle. Only a few MES appeared during balloon dilation of the native valve. Instead, a "shower" of MES was seen immediately after balloon deflation

Table 4 Intra-procedural data TAVI

Procedure duration, (min)	100±41
Amount of radiocontrast, (ml)	197±96
Fluoroscopy duration, (min)	33±14
Ventricular pacing duration (sec)	14.6±2.24
CoreValve® inserted into previous bioprosthesis valve	3 (14)
Left subclavian artery access	3 (14)
Postoperative need for permanent pacemaker	3 (14)
Transcranial Doppler embolic counts:	
Instrumentation of the aortic arch/root/valve	106±103
Valvuloplasty of the native aorta	62±64
Expansion of the valve prosthesis	115±87
Total embolic load	282±169

Data presented as mean±SD or n (%).

(Figure 17) followed by a falling appearance rate of MES for 12 ± 11 minutes. Finally, a shower of MES also appeared during frame expansion of the valve prosthesis followed by MES detected at a declining appearance rate to the end of the procedure (26 ± 14 minutes).

The S-100B levels increased sharply within the first hour after the balloon expansion of the native aorta, returning towards baseline approximately after 4-6 hours (Figure 18). S-100B increased from a baseline level of 0.061 ± 0.022 µg/l to a peak level of 0.173 ± 0.081 µg/l ($p<0.0001$). There were significant correlations (Pearson) between the total embolic load and AUC_{24hrs} for S-100B, ($r = 0.68$, $p<0.001$, Figure 19) and peak S-100B ($r = 0.63$, $p<0.01$). The mean duration of pacing-induced hypotension was 14.6 ± 2.2 sec. The mean cerebral flow velocity of the RMCA prior to balloon valvuloplasty was 30.2 ± 7.3 cm/s, and during the balloon valvuloplasty 13.4 ± 3.7 cm/s ($p<0.001$). The duration of pacing-induced hypotension and the injected contrast volume were entered at step 1 of the hierarchical multiple regression, explaining only 8% of the variance in AUC_{24hrs} for S-100B (ns). After entry of the total embolic load at step 2, the total variance explained by the model was 53%, ($p<0.01$). In the final model, only total embolic load was significantly ($p<0.01$) associated with the AUC_{24hrs} for S-100B.

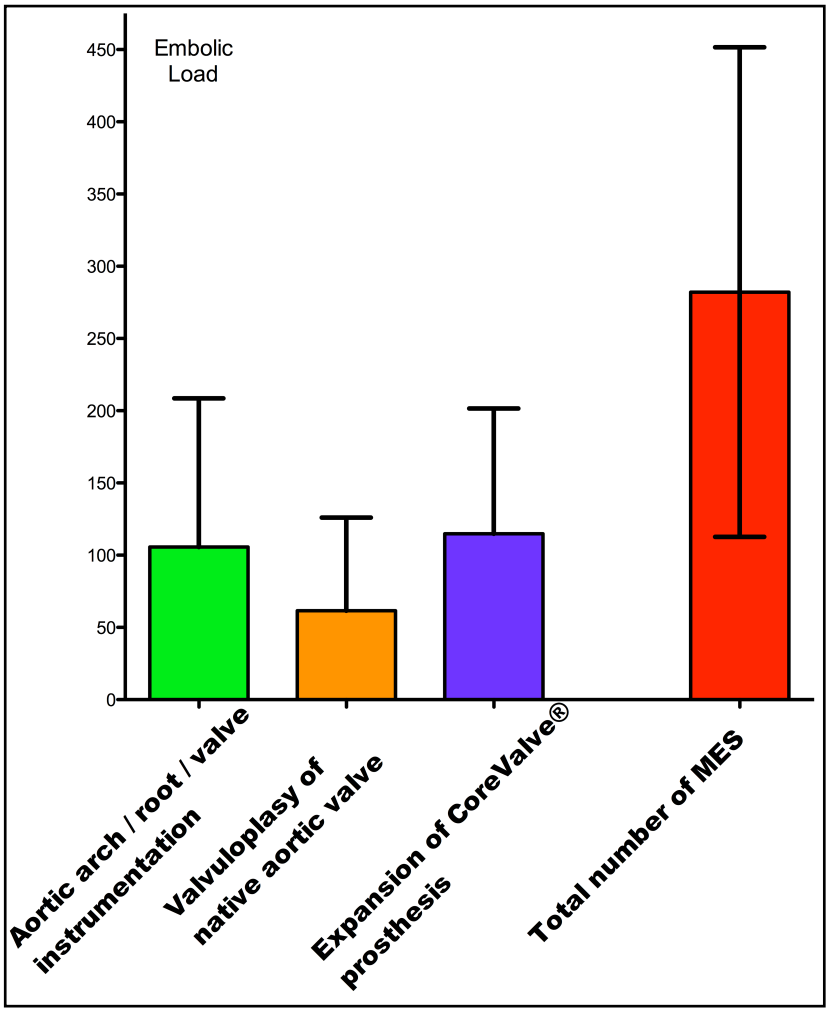

Figure 16: The total number of microembolic signals (MES) related to events during TAVI procedure. (data are presented as means±SD).

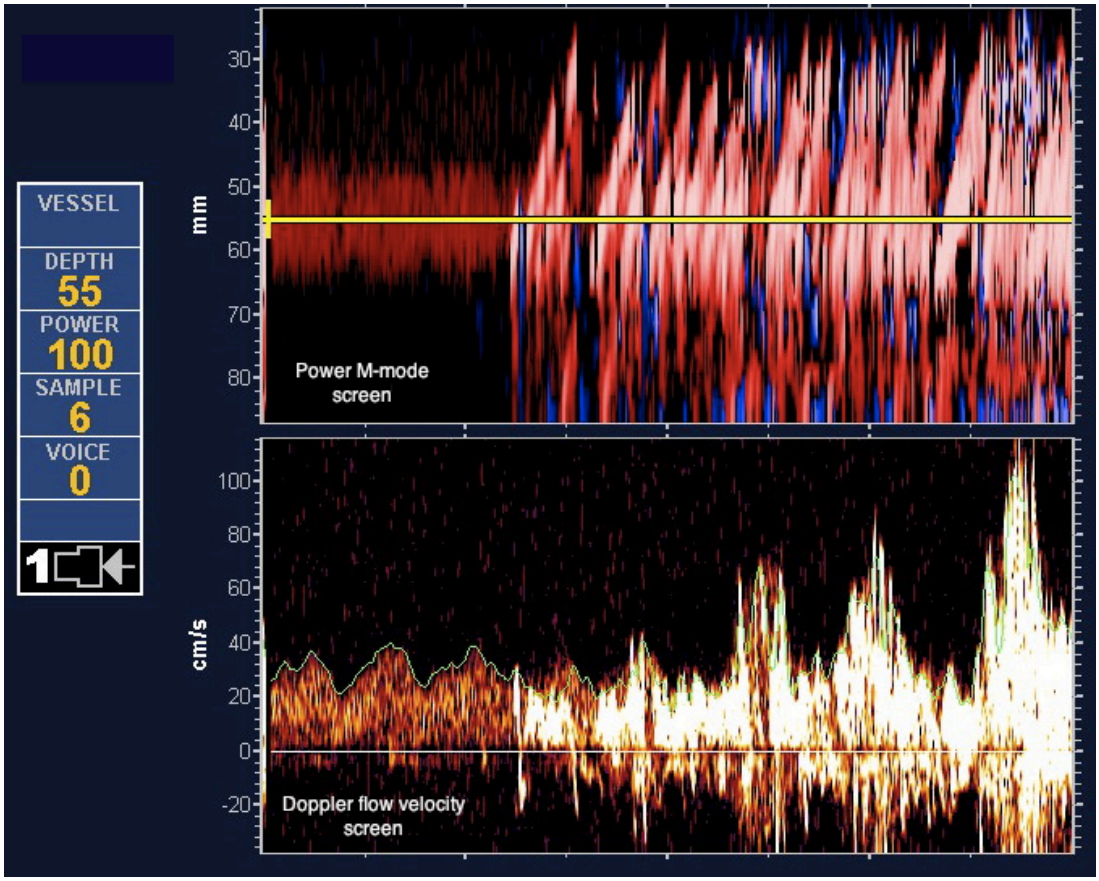

Figure 17: A burst of microembolic signals is recorded as the balloon is deflated, ending the valvuloplasty of the native aortic valve.

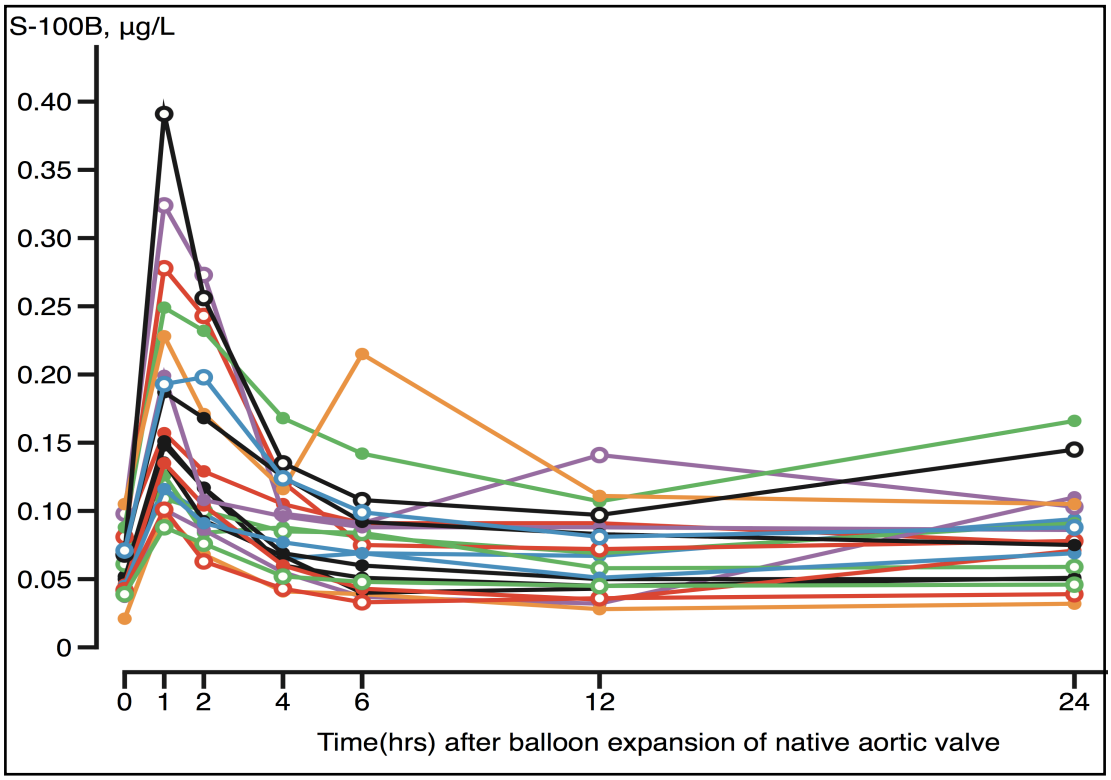

Figure 18: Individual data on serum S-100B after balloon expansion of native

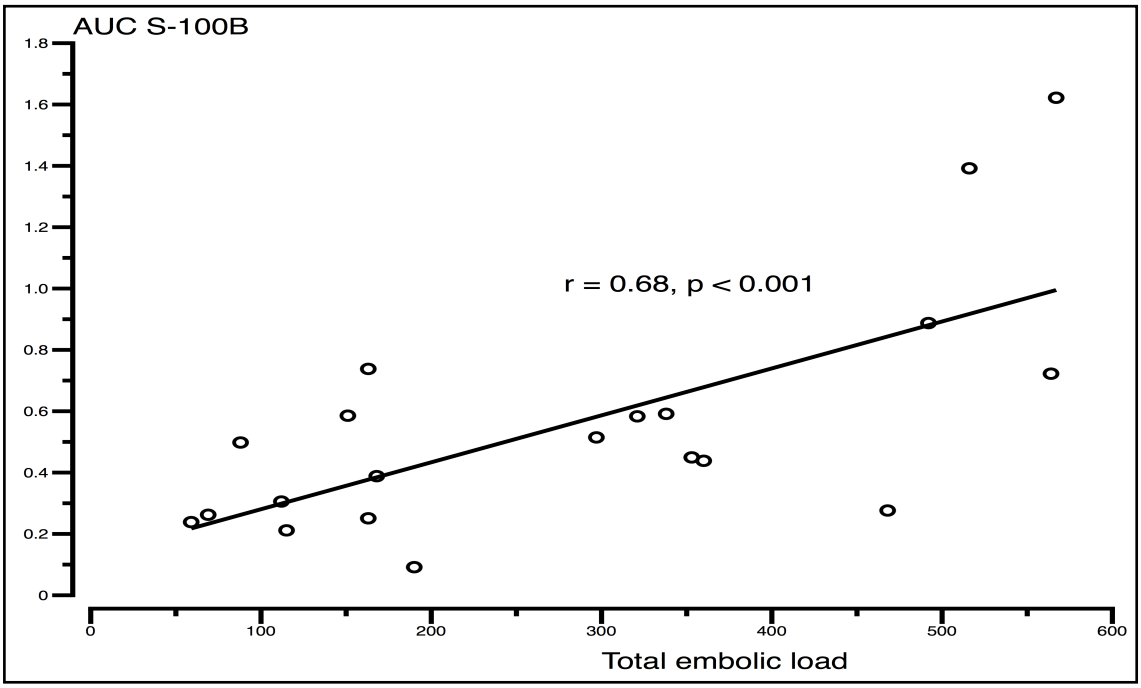

Figure 19: The correlation between total embolic load and the area under curve relating the s-100B serum level to time (AUC S-100B) 24 hrs after the TAVI procedure (r=0.68, p<0.001, n=20).

Paper IV- SAVR and cerebrospinal fluid markers of neuronal injury.

The pre- and postoperative lumbar punctures were uneventful in all patients and in none of the patients was there a bloody tap. Intra-operative transcranial Doppler recordings were successful in all patients. All patients received biological aortic valve prosthesis. One patient suffered from postoperative biventricular heart failure with secondary respiratory failure, and remained in the intensive care unit for 21 days. The remaining 9 patients had an uneventful postoperative period, and postoperative neurological examination at discharge from the intensive care unit the first postoperative day showed no clinical signs of new focal or general neurological deficits. MES were detected with an event distribution according to table 5. Individual data on MES distribution are presented in Figure 20. The mean total MES detected was 354±79. Figure 20 and Table 5 illustrates that the main bulk of 285±75 MES (81%) could be detected during and after weaning from CPB.

The biochemical data from CSF and serum and statistics for differences in pre- and postoperative values are presented in Table 6. Individual data on pre- and postoperative levels of CSF/serum albumin ratio, IL-6, IL-8, S-100B, GFAP are shown in Fig 21 A-E. The two CSF markers of glial cell injury, S-100B and GFAP, increased by 35% (p=0.003) and 25% (p=0.055), respectively. Individual data on T-tau, NF-L and NSE are shown in Fig 22 A-C. Changes in S-100B correlated positively to changes in GFAP (r = 0.74, p=0.014). Serum S-100B increased by 111%. There was no correlation between changes in CSF S-100B and changes in serum S-100B. The three CSF markers of neuronal injury, NSE, T-tau and NF-L, were not significantly affected by the surgical

procedure. CSF albumin increased by 13% (p=0.05), while serum albumin decreased by 27% (p<0.0001). Thus, the CSF/serum albumin ratio increased by 61% (p=0.011). There was a 3.5- and 12-fold increase in CSF IL-8 (p<0.001) and CSF IL-6 (p=0.014), respectively. There was a positive correlation between the change in CSF/serum albumin ratio and the change in CSF IL-6 (r=0.655, p=0.040). There was a 5.3-fold increase in serum IL-6 and a 66% increase in serum IL-8.

The total number of cerebral microemboli did not correlate to changes in CSF markers of glial cell nor neuronal injury. Furthermore, the total number of cerebral emboli did not correlate to changes in the CSF/serum albumin ratio or to changes in CSF levels of IL-6 and IL-8.

Table 5. Intra-procedural data SAVR	
Total procedure duration, (min)	165 ± 54*
CPB time, (min)	93 ± 25
Aortic cross-clamp time, (min)	74 ± 24
Transcranial Doppler embolic counts	
Aortic cannulation before CPB start	17 ± 26
CPB start before aortic cross-clamp	18 ± 20
During aortic cross-clamp	34 ± 38
Aortic de-clamp to end of CPB	226 ± 187
End of CPB to aortic decannulation	39 ± 35
Aortic decannulation to sternal closure	20 ± 39
Total intra-operative embolic count	354 ± 79

CPB: Cardiopulmonary bypass. *Values are mean ±SEM.

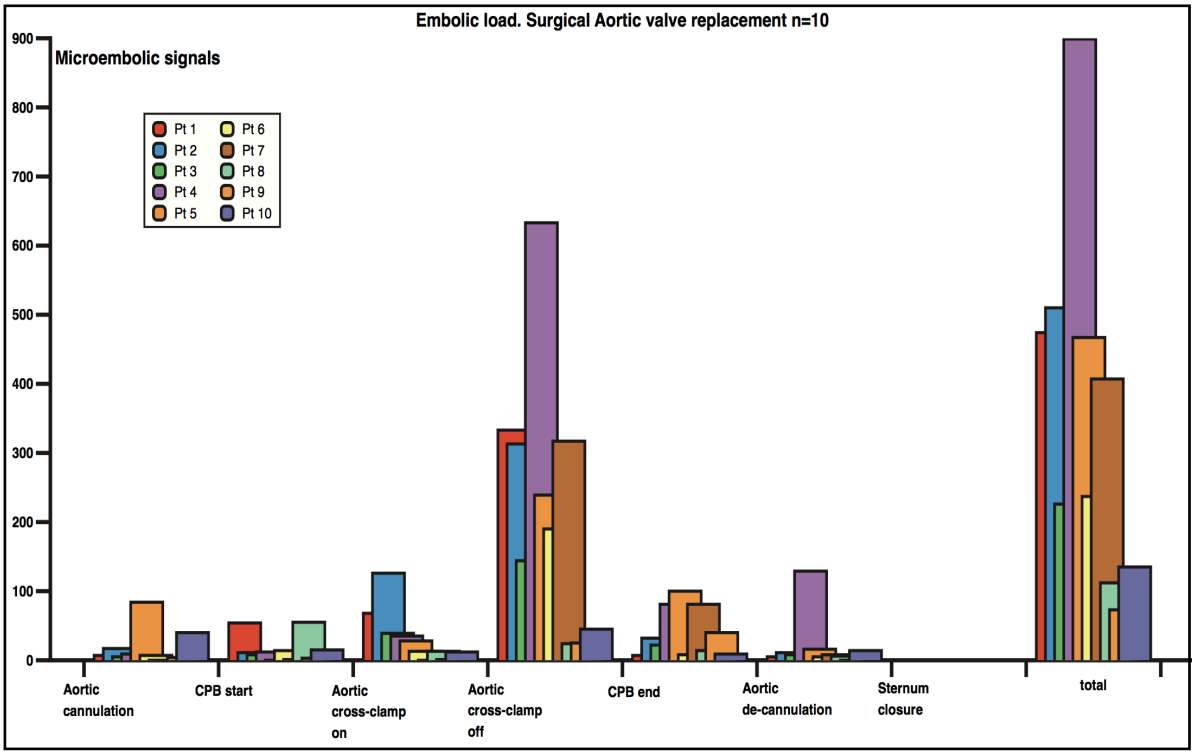

Figure 20: Individual data on the intra-operative distribution of microembolic signals during surgical aortic valve replacement (SAVR).

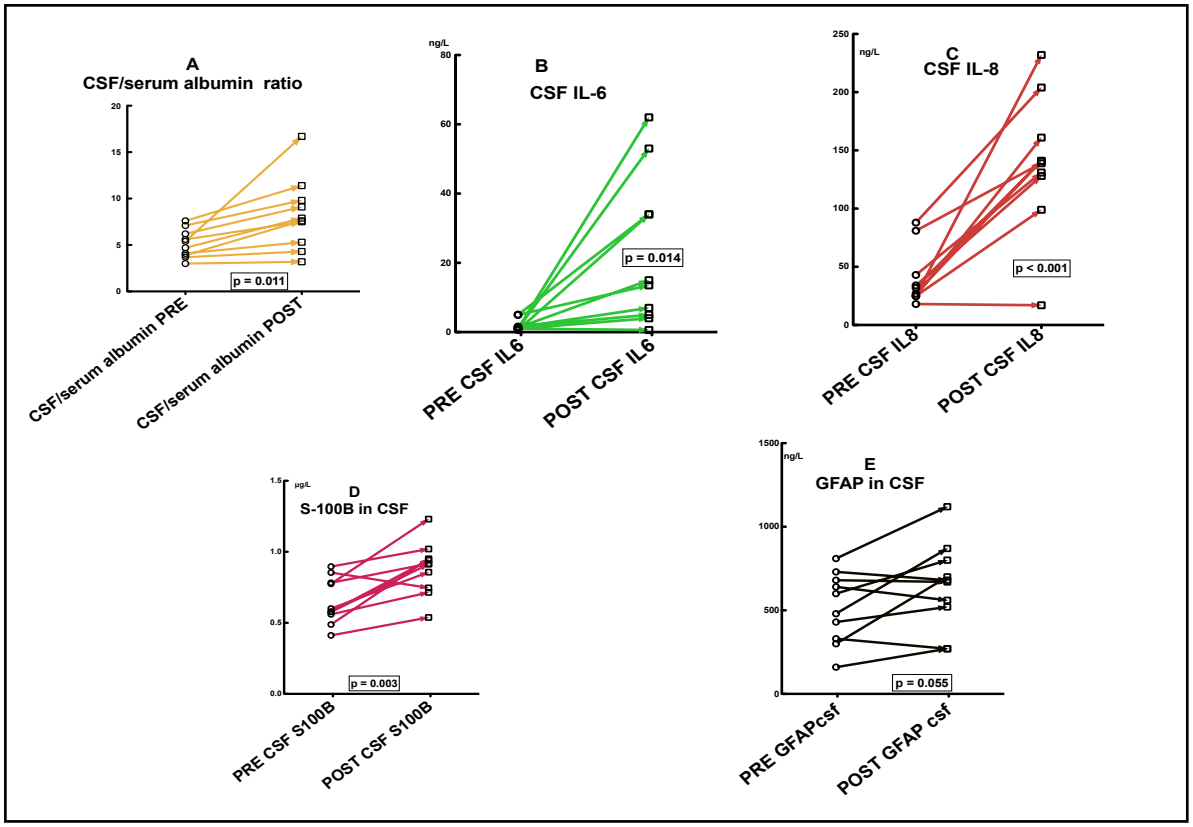

Fig. 21 A-E: Individual data on pre- and postoperative levels of the cerebrospinal fluid (CSF)/serum albumin ratio (A), interleukin-6 (IL-6) (B), interleukin-8 (IL-8) (C), S-100B (D), glial fibrillary acidic protein (GFAP) (E).

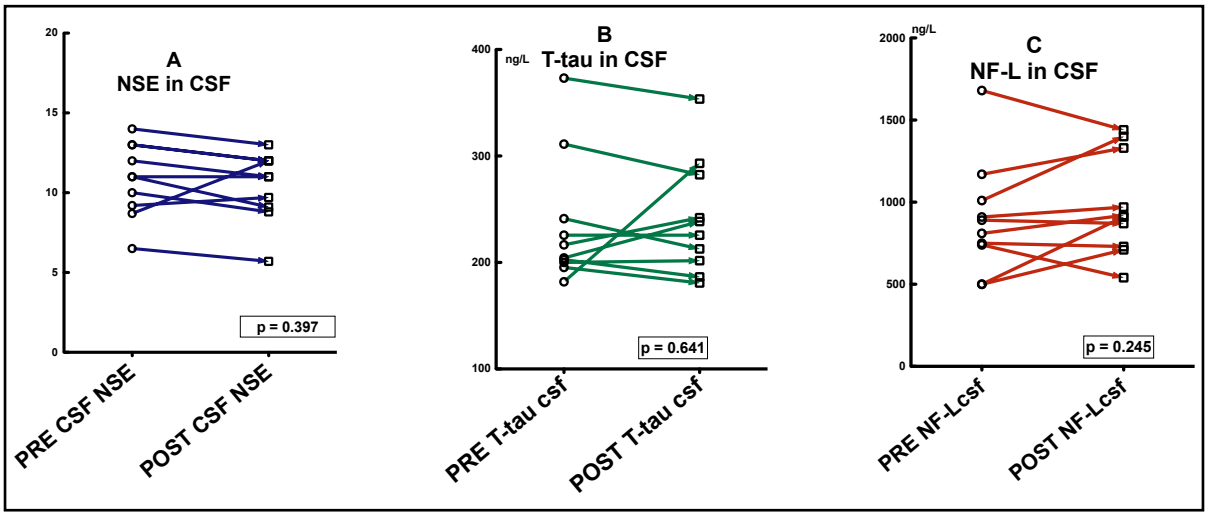

Fig 22 A-C: Individual data on pre- and postoperative levels of the cerebrospinal fluid (CSF) neuron-specific enolase (NSE) (A), total-tau (T-tau) (B), and neurofilament light chain protein (NF-L) (C).

Table 6.	Biochemical data SAVR		
	Preoperative	Postoperative	p-value
CSF S-100B (μg/L)	0.652±0.052	0.882±0.059	p=0.003*
Serum S-100B (μg/L)	0.064±0.007	0.135±0.023	p=0.008*
CSF GFAP (ng/L)	516±66.5	646±82.3	p=0.055
CSF NSE (ng/L)	10.8±0.72	10.4±0.68	p=0.40
CSF T-tau (ng/L)	235.2±19.1	241.7±17.1	p=0.641
CSF NF-L (ng/L)	896±109	982±97.8	p=0.245
CSF-albumin (mg/L)	205±17.4	232±23.4	p=0.05*
Serum albumin (g/L)	41±1.5	30±2	p<0.001*
Albumin CSF/serum ratio	5.13±0.48	8.28±1.22	p=0.011*
CSF IL-6 (ng/L)	1.89±0.5	22.8±6.9	p=0.014*
Serum IL-6 (ng(L)	14.7±12.6	78.6±12.5	p=0.003*
CSF IL-8 (ng/L)	39.8±7.8	139.3±18.3	p<0.001*
Serum IL-8 (ng/L)	13.3±2.0	22.1±2.2	p=0.016*

CSF; cerebrospinal fluid, GFAP; glial fibrillary acidic protein, NSE; neuron-specific enolase,T-tau; total tau, NF-L; neurofilament light chain protein. IL-6; interleukin 6. IL-8; interleukin 8. *Values are mean±SEM.

Discussion

Methodological and experimental considerations

Study population

The populations of patients studied in papers I and II were biased with regards to gender. In paper I (isoflurane) 88% were male, and in paper II (sevoflurane) 72%. The patients were recruited from the list of elective cardiac surgical procedures at our centre, and the question of participating was given at the time of arrival at our hospital the day before the planned procedure. The inclusion was performed consecutively, and ended when the patient number calculated by the power analysis was reached. Thus the sex distribution mirrors the actual willingness of participating in the population exposed for the question. With a larger number asked, the percentage of female participants probably would have increased. The fact that these two papers investigated an intervention during CPB when the patient served as her own control (paired design), reduces the probability that the statistical results and implications were biased by the low percentage of female patients.

The type of cardiac procedures performed in papers I and II show some diversity, but as the technical aspects of CPB did not differ, this was judged to be insignificant. In paper I, published in 2003, the fraction of CABG was 25%. In contrast, in paper II, published in 2011, this fraction was only 6%. This probably reflects the overall reduction in CABG procedures performed at our centre during this period of 8 years.

In paper III (TAVI) the 21 patients recruited were close to the total amount of patients treated with TAVI during 18 months (May 2009-December 2010) at our centre. All patients scheduled for TAVI in the period were asked to participate in the study, and only 2 (both females) declined. Thus, the sex distribution is representative for the actual population treated with TAVI. Comparing patients treated with TAVI with patients treated with open surgical aortic valve replacement is at present not possible at our centre. TAVI is a treatment option offered to patients with aortic stenosis considered unsuitable for open-heart surgery due to an unacceptable high-risk profile, making randomization impossible. The advanced co-morbidity (table 2), and in particular the high mean age (81±6 yrs.), in this population of TAVI patients could be a factor in the susceptibility for neural cell injury in comparison to a low-risk population with an otherwise equal microembolic load. Thus, the study was observational in design.

In paper IV (SAVR) the sample size was planned to be 10. The uneven sex distribution (2 female patients) again mirrors the effect of consecutive inclusion of patients. Eighty-nine patients were asked for participation, reflecting the reluctance in the general population against lumbar punctures for scientific purposes only. With exception for the gender distribution, there are no other demographic signs indicating that this sample of 10 is not representative for the whole population of patients receiving SAVR. The paired design regarding levels

of neurochemical proteins in CSF before and after the SAVR procedure, probably reduces the possible bias of an uneven gender distribution.

Study design

A limitation in the study design of paper I and II was that we were not able to obtain a cerebral autoregulation response curve after the discontinuation of the study drug (isoflurane/ sevoflurane, respectively). Thus there were no postdrug control measurements. This was due to time constraints because rewarming was started soon after the end of the experimental procedure in all patients. Therefore, we cannot eliminate the possibility of time-dependent effects on CBFV and COE.

In paper I, MAP was varied by infusion of phenylephrine (norepinephrine in paper II) or sodium nitroprusside, which could potentially affect CBF. However, neither of these drugs has been shown to have any direct effects on CBF during CPB in humans (82-84).

Paper I and II differs as to temperature management during CPB. In paper I, investigating isoflurane, we used a nasopharyngeal temperature of 32°C, in contrast to paper II, addressing sevoflurane, using a temperature of 34°C on CPB. The reason for the difference is that there has been a trend during the past decade to perform CPB at higher temperatures. A review on this topic published in 2011 states that current evidence suggests that maintaining hypothermia (≤34°C) during cardiopulmonary bypass in adult cardiac surgery is associated with an increased risk of bleeding and allogeneic blood transfusion, but without significant benefits in reducing the risk of postoperative organ complications (85). This advice is respected at our centre, making it impossible to perform a study today with an identical protocol as in paper I. As previously mentioned, the cerebral metabolic rate decreases with 6-7% for each °C reduction in temperature (30). A practical implication in the study design of paper II was that the higher temperature (34°C) also required a deeper anaesthetic level both in the control situation and during intervention, compared to the design in paper I (32°C). The EEG burst suppression in paper II was 4-6 burst/ minute compared to the lighter anaesthetic level of 6-9 bursts/minute in paper I. Different temperature- and anaesthetic management limits general comparisons between paper I and II regarding the effects of isoflurane vs. sevoflurane during cardiac surgery with CPB.

In paper III, the relatively short observation time of 24 hours regarding serum levels of S-100B could affect the interpretation of the assumed connection between S-100B release and brain injury. Previous studies on the release pattern of S-100B in serum after ischemic stroke have shown peak levels 2 to 2.5 days after the ischemic event (86,87). However in both these investigations serum S-100B was measured on admission to hospital due to stroke, and then daily during hospital stay. In paper III, we have captured the early dynamics of S-100B release by measuring immediately before, and with hourly intervals directly after the potential brain injury event (balloon expansion of native aortic valve). It might be possible that we have missed a second peak in serum S-100B that theoretically also could be associated with microembolic load and cerebral hypo perfusion time.

In paper IV, the kinetics of CSF biochemical markers could not be described more than in terms of pre- and postsurgery levels. The obvious limitation is the ethical aspects of repeated lumbar punctures after open cardiac surgical procedures on CPB. The SAVR patients are medicated with subcutaneous heparin and oral warfarin from day 1 after surgery, excluding the possibility of further attempts of lumbar puncture. In fact, studies on stroke and brain trauma suggest that neuronal markers may peak as long as 7-10 days post-insult (88,89), which was impossible to capture using the current study design.

A limitation in the study design of paper III and IV was the lack of a neurogical examination performed by a neurologist. The investigating anaesthesiologist performed the clinical examination. Furthermore no attempt was made to evaluate cognitive dysfunction.

Transcranial Doppler (TCD) measurements of cerebral blood flow velocity CBFV and vasoactive agents

In paper I and II, TCD was used to measure CBFV, assuming that changes in CBFV are proportional to changes in CBF (68-71). One could assume that the manipulation of MAP with vasoactive drugs (norepinephrine, phenylephrine and nitroprusside) themselves, during CPB, could induce an uncoupling of the CBFV/CBF relationship by affecting the cross-sectional area of the middle cerebral artery (MCA). The obvious strong linearity of the CPP vs. CBFV plots in the two papers argues against this assumption . We did not find any patient with a sudden increase or decrease in CBFV, as would be expected if the vasoactive agents changed the tone of the MCA. Furthermore, if the vasoactive agents affected cerebral arterioles, we would have expected a fall in CBF and CBFV at higher, and an increase in CBF and CBFV at lower, MAP levels. The obvious advantage of the TCD technique is that measurements can be performed continuously. Alternative techniques for direct CBF measurements during CPB, such as ^{133}Xenon clearance or Kety-Scmidt (90,91), limit the amount of measurements possible to perform during CPB.

TCD measurements of microembolic signals (MES)

In papers III and IV, we used a TCD device for embolic detection that cannot discriminate between solid and gaseous microemboli. A TCD device able to classify microembolic signals as gas or solid is available, but this technology still has limitations obscuring the accuracy in vivo (92,93). The interpretation of the MES counts related to intraprocedural events and neurobiochemical response during TAVI and SAVR is limited by our lack of differentiation of the microembolic signals into gas vs. solid particles.

Interpretation of results

Pressure-flow autoregulation and flow-metabolism coupling during CPB - effects of volatile anaesthetics (Papers I and II)

During fentanyl/droperidol-based anaesthesia and mildly hypothermic CPB, it was shown that in the majority of patients (72%) the mean regression coefficients of the slopes relating CBFV to

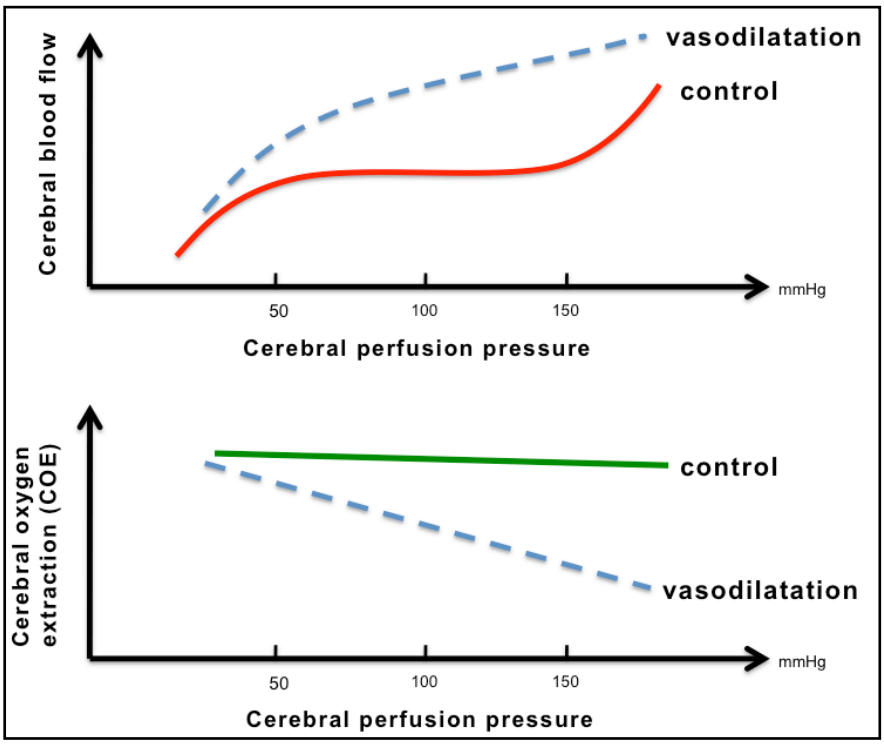

Figure 23: Theoretical illustration of the effect of a vasodilating drug on the CPP-CBFV (above) and CPP-COE (below) relationships.

CPP and COE to CPP were positive and negative, respectively. This indicates an impaired pressure-flow autoregulation, as assessed by two independent methods. One could argue that this impairment was due to anaesthesia and CPB. However, a recent study on conscious healthy volunteers, using the same methodology as in papers I and II, could demonstrate that CBF is indeed pressure-dependent at MAP levels 40-50% above or below baseline (16). In fact that study showed that CBFV changed by 8% for a 10 mmHg change in MAP. Thus, the traditional concept that CBF is perfectly autoregulated at ranges of MAP between 60 and 160 mmHg, as put forward by Lassen et al (15) has to be questioned..

Figure 23 illustrates the theoretical effects of a pure cerebral vasodilator on the CPP-CBFV and CPP-COE relationships. The cerebral vasodilator will impair the pressure-flow relationship, i.e. the slope of the CPP-CBFV will increase (23a). Furthermore, at a certain $CMRO_2$ and CPP, the cerebral vasodilator will decrease COE, i.e. the flow-metabolism coupling is affected and the vasodilator will cause a "luxury perfusion" (23b). In addition, the slope relating COE to CPP will become more negative which is a reflection of the impaired pressure-flow relationship, i.e. a certain fall in CPP causes a more pronounced fall in CBFV, which will be compensated by a greater COE. In other words, the slope of the relationship between CPP and COE, at a constant $CMRO_2$, will indirectly provide information on pressure-flow autoregulation.

Figure 24 similarly illustrates the effects of an isolated decrease in cerebral metabolism, $CMRO_2$, on the relationships between CPP and CBFV or COE. A pure decrease in $CMRO_2$, will decrease CBFV, as a result of the flow-metabolism coupling (24a). If flow-metabolism coupling is perfect, COE will not be affected, as the fall in metabolism will be matched by a proportional decrease in flow (24b). The slopes of the curves should not be affected by a pure decrease in cerebral metabolism.

Burst-suppression doses of isoflurane/ sevoflurane decreased both CBFV and COE during mild hypothermic CPB.

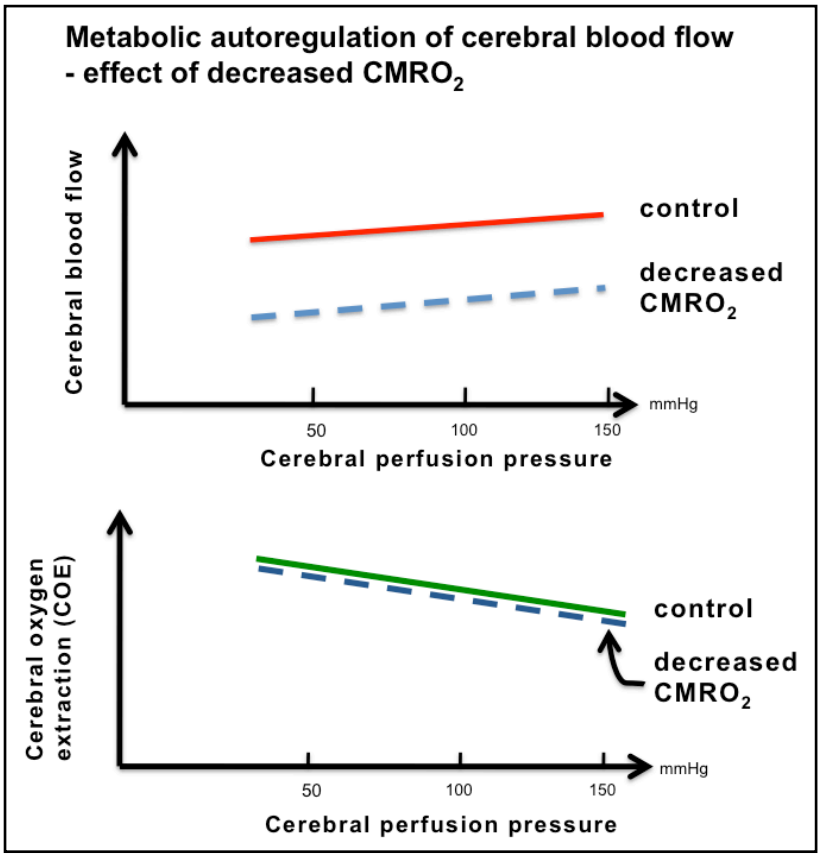

Figure 24: Theoretical illustration of the effect of a decrease in $CMRO_2$ on the CPP-CBFV (above) and CPP-COE (below) relationships.

Despite the decline in CBFV, COE decreased, which suggests that these anaesthetics, in addition to their effect on cerebral metabolism, have a direct intrinsic cerebral vasodilatation effect, causing, at least partially, a loss of flow-metabolism coupling. Furthermore, the slopes of the curves relating CPP to CBFV were more positive with both isoflurane and sevoflurane, indicating disrupted pressure-flow autoregulation. This was supported by the the more pronounced (negative) slopes of the CPP-COE curves, an indirect evidence of an impaired cerebral pressure-flow autoregulation with volatile anaesthetics.

A schematic drawing of the relationships between CPP and CBFV/ COE are shown in figure 25.

Previous studies addressing the influence of volatile anaesthetics on cerebral pressure-flow autoregulation during CPB are scarce. Aladj et al studied the effects of isoflurane (0.6%-1.2%) on pressure flow cerebral autoregulation during hypothermic (27°C) CPB using ^{133}Xenon clearance technique (27). When isoflurane was added to a basal anaesthesia of fentanyl and midazolam, CBF decreased by 35%. However, autoregulation appeared preserved during isoflurane anaesthesia, as a phenylephrine-induced increase of MAP ≥ 25% caused no change in CBF. In this investigation the cerebral vascular response to a change in MAP during isoflurane anaesthesia, CBF was studied only at two MAP levels at a narrow range (35-45 mmHg), making it difficult to draw conclusions on the potential effect of isoflurane on pressure-flow autoregulation during CPB.

The effects of isoflurane on cerebral flow-metabolism coupling (metabolic autoregualation) have previously been studied during hypothermic (25°–28°C) CPB and the results from those studies are somewhat controversial.. Woodcock et al. showed that isoflurane at burst-suppression concentrations (1.1%), when compared with large-dose fentanyl, decreased cerebral metabolic rate with no significant effect on CBF (29), suggesting that isoflurane uncouples flow from metabolism due to a direct vasodilatory effect. Newman et al., however, could not demonstrate an

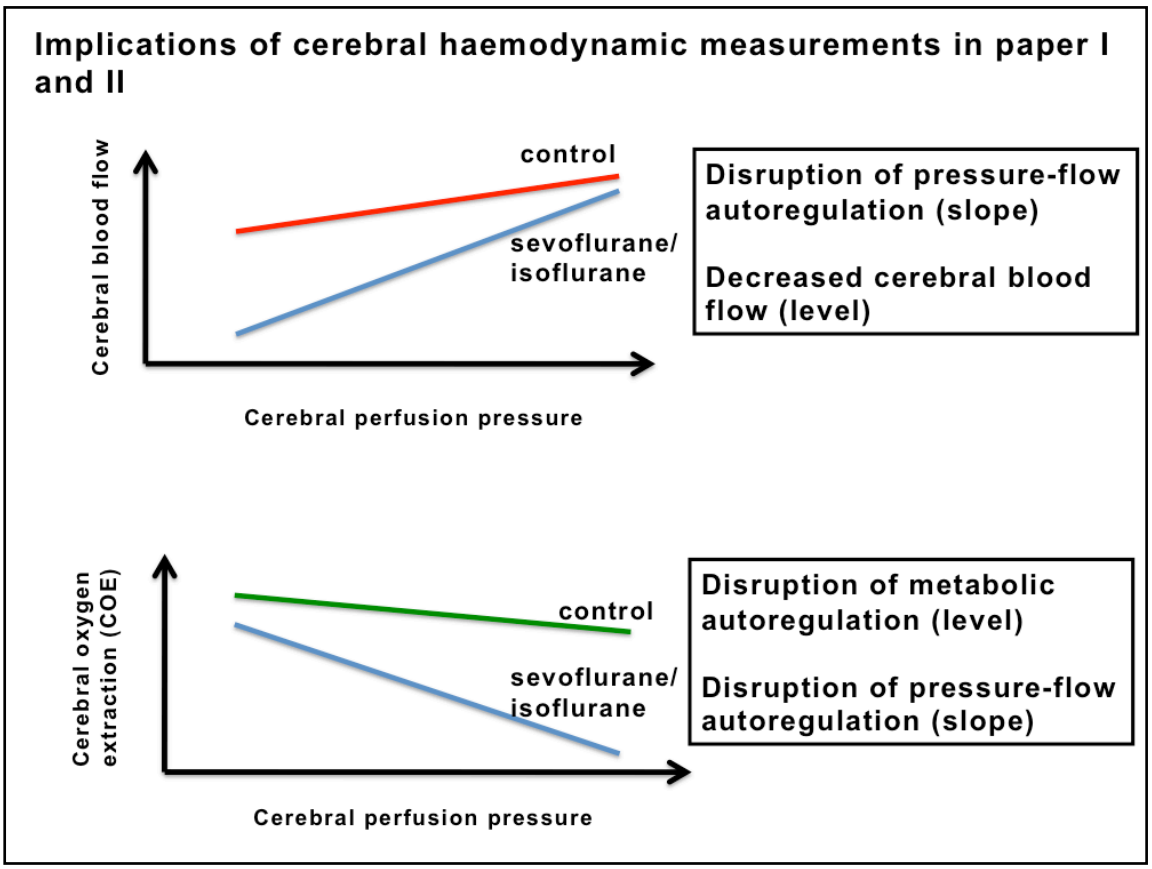

Figure 25: Illustration of the implications of heamodynamic measurements in paper I and II on the relationship between CPP-CBFV (above) And CPP-COE (below).

isoflurane-induced impairment of metabolic autoregulation of CBF, as indicated by unchanged levels of COE when compared to fentanyl/midazolam (28). In our investigation, we found that isoflurane induced a significant decrease in COE, indicating an impairment of metabolic autoregulation of CBF during moderately hypothermic (32°C) CPB. Thus, it seems that isoflurane has a potent direct cerebral vasodilatory effect, which impairs cerebral pressure flow-autoregulation and causes a partial loss of flow-metabolism coupling. These results are in line with previous studies on the effects of isoflurane on CBF and $CMRO_2$ in patients undergoing neurosurgery (94,95). In those studies it was shown that isoflurane decased $CMRO_2$ with no changes in CBF.

The effects of sevoflurane on CBF and metabolism, and on pressure-flow autoregulation have been investigated in non-cardiac surgical patients. Static cerebral pressure-flow autoregulation has been shown to be intact during sevoflurane anaesthesia (96-98). Furthermore, Summors et al demonstrated that the dynamic cerebral pressure-flow autoregulation was better preserved during sevoflurane than isoflurane anaesthesia (99). The results of studies on the effect of sevoflurane on the coupling between cerebral metabolism and CBF are less consistent. One study showed that the addition of 1.5 but not 0.5MAC sevoflurane to propofol anaesthesia decreased COE (100). In contrast, Mielck et al found that cerebral oxygen consumption and CBF remained coupled with 1 MAC sevoflurane when

compared with the awake situation (101). Thus, in non-cardiac surgery patients, the cerebral intrinsic vasodilatory effect of sevoflurane does not seem to be profound, particularly when compared with isoflurane. In contrast, burst-suppression doses of sevoflurane during CPB (paper II) induced a potent direct cerebral vasodilatory effect with a fall in COE and impaired pressure-flow autoregulation. If anything, the effects of sevoflurane on pressure-flow autoregulation and flow-metabolism coupling were more pronounced when compared to burst–suppression doses of isoflurane. This discrepancy could be caused by the fact that the anaesthetic dept was somewhat more profound with sevoflurane compared to isoflurane.

What are the clinical implications of our findings regarding the use of isoflurane or sevoflurane during mild hypothermic CPB? When isoflurane or sevoflurane are added to fentanyl/droperidol anaesthesia, the decline in COE reflects an improved oxygen demand/supply relationship, and one would expect that these agents would improve the cerebral tolerability to severe hypotension during CPB. Although isoflurane and sevoflurane both impaired the cerebral pressure-flow relationship, cerebral oxygenation is still better maintained when compared with fentanyl/droperidol anaesthesia at all levels of cerebral perfusion pressures studied.

Microembolic signals and serum marker evidence of brain injury during TAVI (Paper III)

The main finding in this paper was that we could quantify the total cerebral embolic load during TAVI with emphasis on the mechanisms of microemboli generation, using the transcranial Doppler technique . We also showed that a positive correlation exists between the total embolic load and the degree of CNS injury, as assessed by a glial cell marker.

Almost 2/3 of the number of cerebral microemboli appeared during balloon valvuloplasty of the native valve, particularly during balloon deflation (22%), and during frame expansion of the valve prosthesis (41%). This could be explained by a considerable trauma to the native valve by balloon expansion of the sclerotic native valve, as well as crushing of the native valve leaflets by the stent frame. However, a considerable amount of microemboli (37%) was also detected during the manipulation of the aortic arch/root and valve by guide-wires and catheters. Thus, catheter/guide-wire manipulation of the ascending aorta or aortic arch in these elderly patients with a high incidence of aortic atheroma, adds considerably to the cerebral embolic load during TAVI. This finding is in line with that of Omran et al who showed that patients with valvular aortic stenosis exposed to retrograde catheterization had focal diffusion-imaging abnormalities on MRI, suggesting acute cerebral embolic events after the procedure (102). S-100B is a Ca2+-binding protein with a low molecular weight found mainly in the astroglial and Schwann cells (80). The cerebrospinal fluid concentration of S-100B is approximately 20 times higher than in serum (103). S-100B has been used as a biochemical marker of ischemic stroke, which correlates with infarct volume, stroke severity and functional outcome (86,104,105). Peak levels of S-100B are, however, reached days after onset of symptoms in stroke patients. In

the present study, peak levels of S-100B occurred within the first hour after the procedure with a rapid decline within 6 hours. One could speculate that the rapid appearance/disappearance of S-100B in serum after TAVI, was caused mainly by an acute dysfunction of the blood-brain barrier (BBB) in combination with the short half-life for elimination of S-100B from the blood stream (106). It has been shown that S-100B may be elevated in patients with MRI-detected BBB dysfunction without brain damage and thus may be a marker of BBB dysfunction (107). Furthermore, it has been suggested that the interaction between cerebral emboli (both solid and gaseous) and cerebral vascular endothelium may cause endothelial activation and secondary disruption of BBB (37).

Lund et al. described the occurrence of cerebral emboli during left heart catheterization including left ventriculography and found that the majority of MES were classified as gaseous and that there was a significant correlation between the number of microemboli and the volume of contrast used (108). Nonetheless, their study showed that new cerebral lesions detected by MRI were associated with the amount of solid, not gaseous, emboli detected. In our study a guide-wire was passed into the left ventricle, but no ventricular fluid injections were performed. Furthermore, in the present investigation, the amount of injected radio-contrast did not correlate to the increase in S-100B after TAVI, suggesting that "showers" of solid emboli immediately after valvuloplasty (balloon deflation) of the native sclerotic valve and frame expansion of the valve prosthesis were the main determinants of cerebral injury after TAVI in the present study.

In paper III, ventricular pacing during the balloon valvuloplasty of the native aortic valve induced deliberate systemic hypotension. Despite the well maintained capacity of the brain to autoregulate cerebral blood flow during propofol anaesthesia (24), cerebral perfusion decreased by 50-60% during this procedure. One could argue that the release of S-100B in the present study after TAVI could to some extent be explained by cerebral hypoperfusion during balloon valvuloplasty of the native aortic valve. However, we could not demonstrate a relationship between the duration of pacing-induced hypotension and post-procedural release of S-100B. The lack of association between the duration of pacing-induced hypotension and release of S-100B, could be explained by the short duration of cerebral hypoperfusion, the lack of total circulatory arrest during pacing and balloon dilation and that pacing-induced hypotension was performed only once.

None of the patients in the present study developed neurological impairment during the first post-procedural 24 hours. This finding is in line with the results from recent studies. Kahlert et al (109) showed a lack of apparent neurological events and measurable impairments of neurocognitive function in 32 patients during the in-hospital period after TAVI. Rodés-Cabau (110) et al evaluated transcatheter aortic valve implantation using the transapical (n=31) and transfemoral (n=29) approach and found that one patient in each group developed a stroke with no detectable decline in cognitive function. Ghanem et al (51) described 30 patients undergoing TAVI and found that one patient developed a permanent neurological impairment. The

latter authors also assessed serum levels of neuron-specific enolase (NSE), as a marker of brain damage, before, within 3 days and 3 months after TAVI. NSE levels did not increase significantly after TAVI in their study. This could be explained by the few samples taken with too long time intervals, in their study, with a high likelihood that peak increases of the biomarker were missed.

There are no direct clinical implications related to the findings in this descriptive study. Nonetheless, it serves as proof of concept of a substantial cerebral microembolic load, which, correlated to serum markers of CNS damage, emerging during the TAVI procedure. The baseline levels of microembolic signals and S-100B release pattern can be used in designing future studies. It must be considered mandatory to include TCD microembolc measurements with a TCD device that is able to differentiate between gas and solid particles, and to perform neurocognitive tests in similar future investigations on TAVI patients.

Cerebral microembolism, blood-brain barrier (BBB) function and cerebrospinal fluid markers of neuronal and glial cell injuries in cardiac surgery (Paper IV)

The main findings were that cardiac surgery induced a pronounced cerebral inflammatory response. Furthermore, markers of glial-cell injury, S-100B and GFAP, increased, in contrast to the markers of neuronal injury, NSE, T-tau and NF-L, which were not affected by cardiac surgery. Furthermore, the structural integrity of the BBB was disrupted and finally, no correlations between the total count of MES recorded during the surgical procedure and the changes in CSF markers of inflammation, glial cell or neuronal cell damage and/or BBB dysfunction were found.

The BBB, established by the tight junctions of the endothelial cells in interaction with astrocytic foot processes, microglial cells and pericytes, is responsible for a tightly regulated microenvironment in the brain (111). This study showed that SAVR with CPB causes a disruption of BBB integrity as measured by increased CSF albumin and an increase in the CSF/serum albumin ratio. One possible explanation to this finding could be that BBB disruption was caused by an unspecific response to surgical stress. However, Anckarsäter et al have shown that, in contrast to the present study, the CSF/serum ratio decreases during e.g. orthopaedic surgery, suggesting that surgical stress, per se, decreases the permeability of macromolecules into the CSF (112). In cardiac surgery with CPB, the combination of impaired integrity of the BBB, with leakage of macromolecules into CSF, and perioperative haemodilution, as demonstrated by a fall in haematocrit and serum albumin, might well explain the previously described observation of cerebral oedema early after on-pump cardiac surgery (41,113).

The present study does not provide direct information on the mechanism(s) behind the BBB dysfunction after cardiac surgery. Astrocyte end-feet are a vital structural part of the BBB (111). In the present study, S-100B and GFAP, two biomarkers of astrocyte damage, increased significantly in CSF, which could suggest that astrocyte injury may be involved in the cardiac surgery-induced impaired integrity of the BBB. This was further supported by the positive correlation between postoperative

increases in CSF levels of S- 100B and GFAP. It has been shown that S-100B may be elevated in patients with MRI - detected BBB dysfunction without brain damage and thus may be a marker of BBB dysfunction (107). It has been speculated that the interaction between emboli (both solid and gaseous) and cerebral vascular endothelium, in cardiac surgery, may cause endothelial activation and secondary disruption of BBB (37,114). However, there was no correlation between total embolic load and the increase in CSF/serum albumin ratio or CSF levels of S-100B or GFAP in the present study, indicating that it is less likely that the intra-operative embolic load is responsible for glial cell injury and BBB disruption after cardiac surgery.

Another plausible explanation to the BBB disruption is the effect of diffuse cerebral inflammation, supported by the findings of a several fold increase in CSF levels of IL-6 and IL-8, in the present study, and the positive correlation between increases in CSF levels of IL-6 and CSF to serum albumin ratios. In patients with sepsis or burn injury, the inflammatory response observed, triggers alterations in the cerebral homeostasis with a distinctive feature of BBB breakdown leading to perivascular oedema (115-117). It is well established that CPB activates a systemic inflammatory response (118). The mechanisms are a direct contact activation of the immune system after interaction between circulating blood and artificial material of the CPB circuit, ischemic reperfusion injury to the heart and lungs, as well as surgical trauma, transfusion and hypothermia. The circumventricular organs located in the midline ventricular system can detect this systemic inflammation as they lack a blood-brain barrier and express immune system components such as Toll-like- and cytokine receptors. Blood borne cytokines may enter the brain through these specific regions and induce a cerebral inflammatory response (115,116). Furthermore, cerebral endothelial cells may be activated by pro-inflammatory cytokines with up-regulation of mRNA for local production of cytokines and adhesion molecules with leucocytes sticking to the wall, eventually entering the brain (116). These local changes can induce endothelial dysfunction resulting in blood-brain barrier breakdown.

The best way to assess neuronal or glial cell injury is to analyse established biomarkers in the CSF, which is in direct contact with the cerebral interstitial fluid devoid of any barrier. Data on the effects of cardiac surgery and CSF biomarkers of brain injury are, however, scarce. Åberg et al found increased levels of adenylate kinase in CSF after open-heart surgery which was correlated to changes in postoperative intellectual function (119). Vaagenes et al studied the temporal pattern of the enzymes creatine kinase, lactate dehydrogenase and aspartate aminotransferase as well as lactate in CSF in patients with neurological damage after open-heart surgery, and found a correlation between worsening neurologic impairment and peak CK and lactate (120). Our data are in line with those of Kaukinen et al who showed that postoperative levels of the neuronal marker NSE in CSF after coronary artery bypass surgery were not significantly higher than those from orthopaedic reference patients (121). To our knowledge there are no previous data on the effects of cardiac surgery and CPB on CSF specific biomarkers of glial cell injury,

S-100B and GFAP, or the neuron specific injury markers, NSE, T-tau and NF-L. The latter three markers are released from neurons (NSE), thin unmyelinated cortical (T-tau) and subcortical myelinated axons (NF-L), (122-124). Our data indicate that cardiac surgery with CPB may cause a selective glial cell injury, and the mechanism behind this selectivity is less likely to be caused by cerebral ischemia, in turn caused by e.g. cerebral microembolism, as we found no evidence of neuronal injury. In addition, there was no correlation between embolic load and the CSF release of glial cell markers of injury. It should be noted, however, that we cannot exclude later biochemical signs of neuronal injury, as earlier studies point to peaks in CSF neuronal marker concentrations as long as 7-10 days after cerebral injury (88,89). On the other hand, significant elevations of CSF markers of neuronal injury have been detected within 24 hours after stroke (125), and also in patients with neurologic injury after aortic and thoracoabdominal aortic surgery. (126,127).

The lack of association between the cerebral embolic load and brain injury markers, as shown in the present study, could be explained by the fact that the majority of emboli appeared during weaning from CPB with a high likelihood of introduction of air bubbles to the circulatory system causing less cerebral flow disturbances than solid emboli (50). These findings are in contrast to the study on patients undergoing transcatheter aortic valve implantation (paper III), demonstrating that the TAVI procedure was associated with a substantial amount of cerebral microemboli that correlated closely to the degree of post-procedural serum release of S-100B. The majority of the emboli appeared at events with a high probability of producing solid emboli in that study (balloon expansion, valve frame expansion), which suggest that the majority of emboli diagnosed were solid.

The increase in CSF S-100B could originate from the increased levels of serum S-100B due to "contamination" from extracerebral sources. A strong argument against this theory is the large concentration gradient of S-100B that normally exists between CSF S-100B and serum S-100B. In a normal population this ratio is 18/1 in favour of CSF (103). In our material, the S-100B ratio for CSF/Serum was 10/1 preoperatively. The two-fold increase in serum levels of S-100B after surgery could be explained by the increase in CSF S-100B in combination with a “leaky” BBB and/or the generation of S-100B from extracerebral sources (11,41,113). The fact that we found no correlation between increases in serum and CSF levels of S-100B, suggests that increased levels of S-100B originates from extracerebral sources.

As expected, the microembolic load detected by TCD during the procedure was extensive, but its magnitude correlated neither to the changes in CSF levels of markers of brain damage, nor to the degree of BBB disruption expressed by the CSF/serum albumin ratio. Thus, our data do not support the hypothesis that cerebral (gas)microembolisation is involved in the pathogenesis of brain injury after cardiac surgery with CPB. Instead we would put forward the hypothesis that cardiac surgery with CPB induces a cerebral inflammation, triggered by the systemic inflammation, causing BBB dysfunction, associated to the injury on one of its main cellular constituents, the astroglial cells.

Conclusions

- During mild hypothermic (32-34^{o}C) cardiopulmonary bypass (CPB), cerebral blood flow (CBF) closely follows cerebral perfusion pressure, indicating that pressure-flow autoregulation of cerebral blood flow is impaired, in fentanyl-droperidol anaesthetised patients

- Electroencephalographic burst-suppression doses of isoflurane or sevoflurane further impair the cerebral pressure-flow autoregulation during mild CPB due to their intrinsic cerebral vasodilatory effects.

- Isoflurane and sevoflurane, decrease both CBF and cerebral oxygen extraction (COE) during mild hypothermic CPB. The decrease in COE indicates that CBF is in excess relative to cerebral oxygen demand. Thus, these anaesthetics, in addition to their effects on cerebral metabolism, have direct cerebral vasodilatory effects, which partly uncouples CBF from metabolism. .

- In spite of the impaired pressure-flow autoregulation, cerebral oxygenation is better maintained with isoflurane or sevoflurane compared to fentanyl-droperidol anaesthesia at all levels of cerebral perfusion pressures studied.

- Transcatheter valve implantation is associated with a substantial microembolic load. The majority of these emboli appears during dilatation of the native aortic valve and during expansion of the valve prosthesis. A positive correlation exists between the total embolic load and the degree of CNS injury, as assessed by a glial cell marker in serum.

- After surgical aortic valve replacement, markers of cerebral inflammation, glial-cell injury, but not neuronal injury, increase in the cerebrospinal fluid. Furthermore, the structural integrity of the blood-brain barrier is disrupted. These cerebral effects of cardiac surgery with CPB are not associated with cerebral microembolism but could be explained by an inflammatory brain response.

Acknowledgements

Sven-Erik Ricksten, supervisor in the true sense of the word.

Anne Westerlind, co-supervisor and the source of energy in this field of science at our department.
Henrik Zetterberg, co-author and an explosive inspirational force.
Johan Fedén-Lindqvist, co-author and generous educator in the field of transcranial Doppler.
Marita Ahlqvist, brilliant organiser of practical issues surrounding attempts to perform science.
Klaus Kirnö, clinical wizard, and true organising force making it possible for me and so many other clinicians to perform science .
Per Nellgård, former head of department, then and now always generously supportive
Monica Hyllner, present head of department, making things happen, right now.
Sonny Ederberg, Erik Houltz, Mikael Elam, Dan Ioanes and Kaj Blennow; clever co-authors.
Anaesthesiologists, assistant nurses, nurses, perfusionists and cardiac surgeons; colleagues always offering supportive help and patience.

A warm gratitude and appreciation to all of You.

References

1. Anyanwu AC, Filsoufi F, Salzberg SP, Bronster DJ, Adams DH. Epidemiology of stroke after cardiac surgery in the current era. *J Thorac Cardiovasc Surg* 2007;134:1121-7.
2. Newman MF, Mathew JP, Grocott HP, Mackensen GB, Monk T, Welsh-Bohmer KA, Blumenthal JA, Laskowitz DT, Mark DB. Central nervous system injury associated with cardiac surgery. *Lancet* 2006;368:694-703.
3. Selim M. Perioperative Stroke. *N Engl J Med* 2007;356:706-13.
4. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, Metz S, Falk V, Mohr FW. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. *Ann Thorac Surg* 2003;75:472-8.
5. McKhann GM, Grega MA, Borowicz Jr LM, Baumgartner WA, Selnes OA. Stroke and Encephalopathy After Cardiac Surgery.An Update. *Stroke* 2006;37:562-71.
6. Roach G, Kanchuger M, Mangano C, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K. Adverse Cerebral Outcomes after Coronary Bypass Surgery. *N Engl J Med* 1996;335:1857-63.
7. Koster S, Hensens AG, van der Palen J. The Long-Term Cognitive and Functional Outcomes of Postoperative Delirium After Cardiac Surgery. *Ann Thorac Surg* 2009;87:1469-74.
8. Brodal P. The Central Nervous System. 2010:104-6.
9. Cardoso FL, Brites D, Brito MA. Looking at the blood-brain barrier: Molecular anatomy and possible investigation approaches. *Brain Research Reviews* 2010;64:328-63.
10. Neuwelt EA, Greig NH, Raffel C, Amar AP, Apuzzo MLJ, Antel JP, Rosenberg GA. Mechanisms of Disease: The Blood-Brain Barrier. *Neurosurgery* 2004;54:131-42.
11. Moody DM. The blood-brain barrier and blood-cerebral spinal fluid barrier. *Semin Cardiothorac Vasc Anesth* 2006;10:128-31.
12. Paulson OB, Hasselbalch SG, Rostrup E, Knudsen GM, Pelligrino D. Cerebral blood flow response to functional activation. J Cereb Blood Flow Metab 2009;30:2-14.
13. Roy CS, Sherrington CS. On the Regulation of the Blood-supply of the Brain. *The Journal of Physiology* 1890;11:85-158.
14. Leithner C, Royl G, Offenhauser N, Fuchtemeier M, Kohl-Bareis M, Villringer A, Dirnagl U, Lindauer U. Pharmacological uncoupling of activation induced increases in CBF and CMRO2. *J Cereb Blood Flow Metab* 2009;30:311-22.
15. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 1959;39:183-238.
16. Lucas SJE, Tzeng YC, Galvin SD, Thomas KN, Ogoh S, Ainslie PN. Influence of Changes in Blood Pressure on Cerebral Perfusion and Oxygenation. *Hypertension* 2010;55:698-705.

17. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. *The Journal of Physiology* 2011;589:3039-48.
18. Powers WJ, Videen TO, Markham J, Walter V, Perlmutter JS. Metabolic control of resting hemispheric cerebral blood flow is oxidative, not glycolytic. *J Cereb Blood Flow Metab* 2011;31:1223-8.
19. Nemoto EM, Yao L, Yonas H, Darby JM. Compartmentation of whole brain blood flow and oxygen and glucose metabolism in monkeys. *J Neurosurg Anesthesiol* 1994;6:170-4.
20. Grocott HP, Homi HM, Puskas F. Cognitive Dysfunction After Cardiac Surgery: Revisiting Etiology. *Seminars in Cardiothoracic and Vascular Anesthesia* 2005;9:123-9.
21. Govier AV, Reves JG, McKay RD, Karp RB, Zorn GL, Morawetz RB, Smith LR, Adams M, Freeman AM. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg* 1984;38:592-600.
22. Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G. Cerebral Autoregulation and Flow/Metabolism Coupling during Cardiopulmonary Bypass: The Influence of Paco2. *Anesth Analg* 1987;66:825-32.
23. Newman MF, Croughwell ND, White WD, Lowry E, Baldwin BI, Clements FM, Davis RD, Jr., Jones RH, Amory DW, Reves JG. Effect of perfusion pressure on cerebral blood flow during normothermic cardiopulmonary bypass. *Circulation* 1996;94:II353-7.
24. Ederberg S, Westerlind A, Houltz E, Svensson S-E, Elam MM, Ricksten S-E. The Effects of Propofol on Cerebral Blood Flow Velocity and Cerebal Oxygen Extraction During Cardiopulmonary Bypass. *Anesth Analg* 1998;86:1201-6.
25. Schell RM, Kern FH, Greeley WJ, Schulman SR, Frasco PE, Croughwell ND, Newman M, Reves JG. Cerebral blood flow and metabolism during cardiopulmonary bypass. *Anesth Analg* 1993;76:849-65.
26. Garner A, Hirsch N. Pharmacological and pathological modulation of cerebral physiology. *Anaesthesia & Intensive Care Medicine* 2007;8:413-7.
27. Aladj LJ, Croughwell N, Smith LR, Reves JG. Cerebral Blood Flow Autoregulation Is Preserved During Cardiopulmonary Bypass in Isoflurane-Anesthetized Patiens. *Anesth Analg* 1991;72:48-52.
28. Newman MF, Croughwell ND, White WD, Sanderson I, Spillane W, Reves JG. Pharmacologic electroencephalographic suppression during cardiopulmonary bypass: a comparison of thiopental and isoflurane. *Anesth Analg* 1998;86:246-51.
29. Woodcock TE, Murkin JM, Farrar JK, Tweed WA, Guiraudon GM, McKenzie FN. Pharmacologic EEG Suppression during Cardiopulmonary Bypass: Cerebral Hemodynamic and Metabolic Effects of Thiopental or Isoflurane during Hypothermia and Normothermia. *Anesthesiology* 1987;67:218-24.
30. Nussmeier NA. Management of temperature during and after cardiac surgery. *Tex Heart Inst J* 2005;32:472-6.
31. Grigore AM, Murray CF, Ramakrishna H, Djaiani G. A Core Review of Temperature Regimens and Neuroprotection During Cardiopulmonary Bypass: Does Rewarming Rate Matter? *Anesthesia & Analgesia* 2009;109:1741-51.

32. Shann KG, Likosky DS, Murkin JM, Baker RA, Baribeau YR, DeFoe GR, Dickinson TA, Gardner TJ, Grocott HP, O'Connor GT, Rosinski DJ, Sellke FW, Willcox TW. An evidence-based review of the practice of cardiopulmonary bypass in adults: a focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. *J Thorac Cardiovasc Surg* 2006;132:283-90.
33. Martin KK, Wigginton JB, Babikian VL, Pochay VE, Crittenden MD, Rudolph JL. Intraoperative cerebral high-intensity transient signals and postoperative cognitive function: a systematic review. *Am J Surg* 2009;197:55-63.
34. Moody DM, Brown WR, Challa VR, Stump DA, Reboussin DM, Legault C. Brain microemboli associated with cardiopulmonary bypass: a histologic and magnetic resonance imaging study. *Ann Thorac Surg* 1995;59:1304-7.
35. Braekken SK, Russell D, Brucher R, Abdelnoor M, Svennevig JL. Cerebral Microembolic Signals During Cardiopulmonary Bypass Surgery: Frequency, Time of Occurrence, and Association With Patient and Surgical Characteristics. *Stroke* 1997;28:1988-92.
36. Ringelstein EB, Droste DW, Babikian VL, Evans DH, Grosset DG, Kaps M, Markus HS, Russell D, Siebler M. Consensus on Microembolus Detection by TCD. *Stroke* 1998;29:725-9.
37. Muth CM, Shank ES. Gas Embolism. *The New England Journal of Medicine* 2000;342:476-82.
38. Prasongsukarn K, Borger MA. Reducing Cerebral Emboli During Cardiopulmonary Bypass. *Seminars in Cardiothoracic and Vascular Anesthesia* 2005;9:153-8.
39. van der Linden J, Casimir-Ahn H. When do cerebral emboli appear during open heart operations? A transcranial Doppler study. *Ann Thorac Surg* 1991;51:237-41.
40. Moody DM. The blood-brain barrier and blood-cerebral spinal fluid barrier. *Seminars in Cardiothoracic and Vascular Anesthesia* 2006;10:128-31.
41. Harris DNF, Bailey SM. Brain swelling in first hour after coronary artery bypass surgery. *Lancet* 1993;342:586.
42. Hall RI, Smith MS, Rocker G. The systemic inflammatory response to cardiopulmonary bypass: pathophysiological, therapeutic, and pharmacological considerations. *Anesth Analg* 1997;85:766-82.
43. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest* 1997;112:676-92.
44. Mielck F, Ziarkowski A, Hanekop G, Armstrong VW, Hilgers R, Weyland A, Quintel M, Sonntag H. Cerebral inflammatory response during and after cardiac surgery. *European Journal of Anaesthesiology* 2005;22:347-52.
45. Kalman J, Juhasz A, Bogats G, Babik B, Rimanoczy A, Janka Z, Penke B, Palotas A. Elevated levels of inflammatory biomarkers in the cerebrospinal fluid after coronary artery bypass surgery are predictors of cognitive decline. *Neurochem Int* 2006;48:177-80.
46. Kadoi Y, Goto F. Factors Associated with Postoperative Cognitive Dysfunction in Patients Undergoing Cardiac Surgery. *Surgery Today* 2006;36:1053-7.
47. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* 2001;344:395-402.

48. Hogue CW, Jr., Palin CA, Arrowsmith JE. Cardiopulmonary Bypass Management and Neurologic Outcomes: An Evidence-Based Appraisal of Current Practices. *Anesth Analg* 2006;103:21-37.
49. Guarracino F, Dullenkopf A Fau - Baulig W, Baulig W Fau - Weiss M, Weiss M Fau - Schmid ER, Schmid ER, Hoffman GM. Cerebral monitoring during cardiovascular surgery. *Current Opinion in Anaesthesiology* 2008.
50. Abu-Omar Y, Balacumaraswami L, Pigott DW, Matthews PM, Taggart DP. Solid and gaseous cerebral microembolization during off-pump, on-pump, and open cardiac surgery procedures. *The Journal of Thoracic and Cardiovascular Surgery* 2004;127:1759-65.
51. Ghanem A, Muller A, Nähle CP, Kocurek J, Werner N, Hammerstingl C, Schild HH, Schwab JO, Mellert F, Fimmers R, Nickenig G, Thomas D. Risk and Fate of Cerebral Embolism After Transfemoral Aortic Valve Implantation: A Prospective Pilot Study With Diffusion-Weighted Magnetic Resonance Imaging. *J Am Coll Cardiol* 2010;55:1427-32.
52. Shann K, Likosky D, Murkin J, Baker R, Baribeau Y, DeFoe G, Dickinson T, Gardner T, Grocott H, O' Connor G, Rosinski D, Sellke F, Willcox T. An evidence-based review of the practice of cardiopulmonary bypass in adults: A focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. *J Thorac Cardiovasc Surg* 2006;132:283-90
53. Svenarud P, Persson M, van der Linden J. Effect of CO2 Insufflation on the Number and Behavior of Air Microemboli in Open-Heart Surgery: A Randomized Clinical Trial. *Circulation* 2004;109:1127-32.
54. Chaudhuri K, Marasco SF. The Effect of Carbon Dioxide Insufflation on Cognitive Function During Cardiac Surgery. *J Card Surg* 2011;26:189-96.
55. Kawaguchi M, Furuya H, Patel PM. Neuroprotective effects of anesthetic agents. *J Anesth* 2005;19:150-6.
56. Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric Complications after Cardiopulmonary Bypass: Cerebral Protection by a Barbiturate. *Anesthesiology* 1986;64:165-70.
57. Zaidan JR, Klochany A, Martin WM, Ziegler JS, Harless DM, Andrews RB. Effect of Thiopental on Neurologic Outcome Following Coronary Artery Bypass Grafting. *Anesthesiology* 1991;74:406-11.
58. Roach GW, Newman MF, Murkin JM, Martzke J, Ruskin A, Li J, Guo A, Wisniewski A, Mangano DT. Ineffectiveness of burst suppression therapy in mitigating perioperative cerebrovascular dysfunction. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. *Anesthesiology* 1999;90:1255-64.
59. Litvan H, Jensen EW, Revuelta M, Henneberg SW, Paniagua P, Campos JM, MartÌnez P, Caminal P, Landeira JMV. Comparison of auditory evoked potentials and the A-line ARX Index for monitoring the hypnotic level during sevoflurane and propofol induction. *Acta Anaesthesiologica Scandinavica* 2002;46:245-51.
60. Aaslid R, Markwalder T, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg* 1982;57:769-74.
61. Moppett K, Mahajan RP. Transcranial Doppler ultrasonography in anaesthesia and intensive care. *Br J Anaesth* 2004;93:710-24.

62. Fodale V, Schifilliti D, Conti A, Lucanto T, Pino G, Santamaria LB. Transcranial Doppler and anesthetics. *Acta Anaesthesiologica Scandinavica* 2007;51:839-47.
63. Ringelstein EB, Kahlscheuer B, Niggemeyer E, Otis SM. Transcranial doppler sonography: Anatomical landmarks and normal velocity values. *Ultrasound Med Biol* 1990;16:745-61.
64. Nicoletto HA, Burkman MH. Transcranial Doppler Series Part II: Performing a Transcranial Doppler. *American Journal of Electroneurodiagnostic Technology* 2009;49:14-27.
65. Lupetin AR, Davis DA, Beckman I, Dash N. Transcranial Doppler sonography. Part 1. Principles, technique, and normal appearances. *Radiographics* 1995;15:179-91.
66. Giller CAPMD, Hatab MRP, Giller AMRNRVT. Estimation of Vessel Flow and Diameter during Cerebral Vasospasm Using Transcranial Doppler Indices. *Neurosurgery* 1998;42:1076-1081.
67. Moppett IK, Sherman RW, Wild MJ, Latter JA, Mahajan RP. Effects of norepinephrine and glyceryl trinitrate on cerebral haemodynamics: transcranial Doppler study in healthy volunteers. *Br J Anaesth* 2008;100:240-4.
68. Bishop CC, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. *Stroke* 1986;17:913-5.
69. Newell DW, Aaslid R, Lam A, Mayberg TS, Winn HR. Comparison of flow and velocity during dynamic autoregulation testing in humans. *Stroke* 1994;25:793-7.
70. Trivedi FUH, Patel FRL, Turtle PMRJ, Venn FGE, Chambers PDJ. Relative Changes in Cerebral Blood Flow During Cardiac Operations Using Xenon-133 Clearance Versus Transcranial Doppler Sonography. *The Annals of Thoracic Surgery* 1997;63:167-74.
71. van Beek AHEA, Claassen JAHR, Rikkert MGMO, Jansen RWMM. Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. *J Cereb Blood Flow Metab* 2008;28:1071-85.
72. Schell RM, Cole DJ. Cerebral monitoring: jugular venous oximetry. *Anesth Analg* 2000;90:559-66.
73. Nakajima T, Ohsumi H, Kuro M. Accuracy of Continuous Jugular Bulb Venous Oximetry During Cardiopulmonary Bypass. *Anesth Analg* 1993;77:1111-5.
74. Nakajima T, Kuro M, Hayashi Y, Kitaguchi K, Uchida O, Takaki O. Clinical evaluation of cerebral oxygen balance during cardiopulmonary bypass: on-line continuous monitoring of jugular venous oxyhemoglobin saturation. *Anesth Analg* 1992;74:630-5.
75. Freye E, Levy JV. Cerebral monitoring in the operating room and the intensive care unit: an introductory for the clinician and a guide for the novice wanting to open a window to the brain. Part I: The electroencephalogram. *J Clin Monit Comput* 2005;19:1-76.
76. Schaul N. The fundamental neural mechanisms of electroencephalography. *Electroencephalogr Clin Neurophysiol* 1998;106:101-7.
77. Dittrich R, Ritter MA, Droste DW. Microembolus detection by transcranial doppler sonography. *Eur J Ultrasound* 2002;16:21-30.
78. Moehring MA, Spencer MP. Power M-mode Doppler (PMD) for observing cerebral blood flow and tracking emboli. *Ultrasound Med Biol* 2002;28:49-57.

79. Saqqur M, Dean N, Schebel M, Hill MD, Salam A, Shuaib A, Demchuk AM. Improved Detection of Microbubble Signals Using Power M-Mode Doppler. *Stroke* 2004;35:e14-7.
80. Van Eldik LJ, Jensen RA, Ehrenfried BA, Whetsell WO, Jr. Immunohistochemical localization of S100 beta in human nervous system tumors by using monoclonal antibodies with specificity for the S100 beta polypeptide. *J Histochem Cytochem* 1986;34:977-82.
81. Rosengren LE, Wikkelso C, Hagberg L. A sensitive ELISA for glial fibrillary acidic protein: application in CSF of adults. *J Neurosci Methods* 1994;51:197-204.
82. Rogers A, Stump D, Gravlee G. Response of cerebral blood flow to phenylephrine infusion during hypothermic cardiopulmonary bypass: influence of PaCO2 management. *Anesthesiology* 1988;69:547-51.
83. Rogers AT, Prough DS, Stump DA, Gravlee GP, Angert KC, Roy RC, Mills SA, Hinshelwood L. Cerebral blood flow does not change following sodium nitroprusside infusion during hypothermic cardiopulmonary bypass. *Anesth Analg* 1989;68:122-6.
84. Strebel SP, Kindler C, Bissonnette B, Tschaler G, Deanovic D. The impact of systemic vasoconstrictors on the cerebral circulation of anesthetized patients. *Anesthesiology* 1998;89:67-72.
85. Ho KM, Tan JA. Benefits and risks of maintaining normothermia during cardiopulmonary bypass in adult cardiac surgery: A systematic review. *Cardiovascular Therapeutics* 2011;29:260-79.
86. Missler U, Wiesmann M, Friedrich C, Kaps M. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. *Stroke* 1997;28:1956-60.
87. Herrmann M, Ehrenreich H. Brain derived proteins as markers of acute stroke: Their relation to pathophysiology, outcome prediction and neuroprotective drug monitoring. *Restorative Neurology and Neuroscience* 2003;21:177-90.
88. Hesse C, Rosengren L, Andreasen N, Davidsson P, Vanderstichele H, Vanmechelen E, Blennow K. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. *Neurosci Lett* 2001;297:187-90.
89. Zetterberg H, Hietala MA, Jonsson M, Andreasen N, Styrud E, Karlsson I, Edman A, Popa C, Rasulzada A, Wahlund LO, Mehta PD, Rosengren L, Blennow K, Wallin A. Neurochemical aftermath of amateur boxing. *Arch Neurol* 2006;63:1277-80.
90. Grocott HP, Amory DW, Lowry E, Croughwell ND, Newman MF. Transcranial Doppler blood flow velocity versus 133Xe clearance cerebral blood flow during mild hypothermic cardiopulmonary bypass. *J Clin Monit Comput* 1998;14:35-9.
91. Weyland A, Stephan H, Kazmaier S, Weyland W, Schorn B, Grune F, Sonntag H. Flow velocity measurements as an index of cerebral blood flow. Validity of transcranial Doppler sonographic monitoring during cardiac surgery. *Anesthesiology* 1994;81:1401-10.
92. Brucher R, Russell D. Automatic Online Embolus Detection and Artifact Rejection With the First Multifrequency Transcranial Doppler. *Stroke* 2002;33:1969-74.
93. Darbellay GA, Duff R, Vesin JM, Despland PA, Droste DW, Molina C, Serena J, Sztajzel R, Ruchat P, Karapanayiotides T, Kalangos A, Bogousslavsky J, Ringelstein

EB, Devuyst G. Solid or gaseous circulating brain emboli: Are they separable by transcranial ultrasound? *J Cereb Blood Flow Metab* 2004;24:860-8.
94. Algotsson L, Messeter K, Nordstrom C, Ryding E. Cerebral blood flow and oxygen consumption during isoflurane and halothane anesthesia in man. *Acta Anaesthesiologica Scandinavica* 1988;32:15-20.
95. Madsen J, Cold G, Hansen E, Bardrum B. The effect of isoflurane on cerebral blood flow and metabolism in humans during craniotomy for small supratentorial cerebral tumors. *Anesthesiology* 1987;66:332-6.
96. Kitaguchi K, Ohsumi H, Kuro M, Nakajima T, Hayashi Y. Effects of sevoflurane on cerebral circulation and metabolism in patients with ischemic cerebrovascular disease. *Anesthesiology* 1993;79:704-9.
97. Gupta S, Heath K, Matta BF. Effect of incremental of Sevoflurane on cerebral pressure autoregulation in humans. *British Journal of Anaesthesia* 1997;1997:469-72.
98. Cho S, Fujigaki T, Uchiyama Y, Fukusaki M, Shibata O, Sumikawa K. Effects of sevoflurane with and without nitrous oxide on human cerebral circulation. Transcranial Doppler study. *Anesthesiology* 1996;85:755-60.
99. Summors AC, Gupta AK. Dynamic Cerebral Autoregulation During Sevoflurane Anesthesia: A Comparison with Isoflurane. *Anesth Analg* 1999;88:341-5.
100. Heath KJ, Gupta S, Matta BF. The effects of sevoflurane on cerebral hemodynamics during propofol anesthesia. *Anesth Analg* 1997;85:1284-7.
101. Mielck F, Stephan H, Weyland A, Sonntag H. Effects of One Minimum Alveolar Anesthetic Concentration Sevoflurane on Cerebral Metabolism, Blood Flow, and CO2 Reactivity in Cardiac Patients. *Anesth Analg* 1999;89:364-9.
102. Omran H, Schmidt H, Hackenbroch M, Illien S, Bernhardt P, von der Recke G, Fimmers R, Flacke S, Layer G, Pohl C, Luderitz B, Schild H, Sommer T. Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. *Lancet* 2003;361:1241-6.
103. Reiber H. Dynamics of brain-derived proteins in cerebrospinal fluid. *Clin Chim Acta* 2001;310:173-86.
104. Nash DL, Bellolio MF, Stead LG. S100 as a marker of acute brain ischemia: a systematic review. *Neurocrit Care* 2008;8:301-7.
105. Dassan P, Keir G, Brown MM. Criteria for a clinically informative serum biomarker in acute ischaemic stroke: A review of S100B. *Cerebrovasc Dis* 2009;27:295-302.
106. Townend W, Dibble C, Abid K, Vail A, Sherwood R, Lecky F. Rapid elimination of protein S-100B from serum after minor head trauma. *J Neurotrauma* 2006;23:149-55.
107. Kanner AA, Marchi N, Fazio V, Mayberg MR, Koltz MT, Siomin V, Stevens GH, Masaryk T, Aumayr B, Vogelbaum MA, Barnett GH, Janigro D. Serum S100beta: a noninvasive marker of blood-brain barrier function and brain lesions. *Cancer* 2003;97:2806-13.
108. Lund C, Bang Nes R, Pynten Ugelstad T, Due-Tønnessen P, Andersen R, Hol PK, Brucher R, Russell D. Cerebral emboli during left heart catheterization may cause acute brain injury. *European Heart Journal* 2005;26:1269-75.
109. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H. Silent and

apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation* 2010;121:870-8.
110. Rodés-Cabau J, Dumont E, Boone RH, Larose E, Bagur R, Gurvitch R, Bédard F, Doyle D, De Larochellière R, Jayasuria C, Villeneuve J, Marrero A, Coté M, Pibarot P, Webb JG. Cerebral embolism following transcatheter aortic valve implantation: Comparison of transfemoral and transapical approaches. *J Am Coll Cardiol* 2010;57:18-28.
111. Bernacki J, Dobrowolska A, Nerwinska K, Malecki A. Physiology and pharmacological role of the blood-brain barrier. *Pharmacological Reports* 2008;60:600-22.
112. Anckarsäter R, Vasic N, Jidéus L, Kristiansson M, Zetterberg H, Blennow K, Anckarsäter H. Cerebrospinal fluid protein reactions during non-neurological surgery. *Acta Neurol Scand* 2007;115:254-9.
113. Anderson RE, Li TQ, Hindmarsh T, Settergren G, Vaage J. Increased extracellular brain water after coronary artery bypass grafting is avoided by off-pump surgery. *J Cardiothorac Vasc Anesth* 1999;13:698-702.
114. Stump DA. Deformable emboli and inflammation: Temporary or permanent damage? *J Extra Corpor Technol* 2007;39:289-90.
115. Ebersoldt M, Sharshar T, Annane D. Sepsis-associated delirium. *Intensive Care Med* 2007;33:941-50.
116. Burkhart C, Siegemund M, Steiner L. Cerebral perfusion in sepsis. *Critical Care* 2010;14:215.
117. Flierl MA, Stahel PF, Touban BM, Beauchamp KM, Morgan SJ, Smith WR, Ipaktchi KR. Bench-to-bedside review: Burn-induced cerebral inflammation--a neglected entity? *Critical Care* 2009;13:215.
118. Gao L, Taha R, Gauvin D, Othmen LB, Wang Y, Blaise G. Postoperative cognitive dysfunction after cardiac surgery. *Chest* 2005;128:3664-70.
119. Aberg T, Ronquist G. Ischemic brain damage and open heart surgery. *Lancet* 1982;2:822.
120. Vaagenes P, Kjekshus J, Sivertsen E, Semb G. Temporal pattern of enzyme changes in cerebrospinal fluid in patients with neurologic complications after open heart surgery. *Crit Care Med* 1987;15:726-31.
121. Kaukinen L, Porkkala H, Kaukinen S, Pehkonen E, Karkela J, Aaran RK, Tarkka M. Release of brain-specific creatine kinase and neuron-specific enolase into cerebrospinal fluid after hypothermic and normothermic cardiopulmonary bypass in coronary artery surgery. *Acta Anaesthesiologica Scandinavica* 2000;44:361-8.
122. Rosen H, Karlsson JE, Rosengren L. CSF levels of neurofilament is a valuable predictor of long-term outcome after cardiac arrest. J Neurol Sci 2004;221:19-24.
123. Martens P, Raabe A, Johnsson P. Serum S-100 and neuron-specific enolase for prediction of regaining consciousness after global cerebral ischemia. *Stroke* 1998;29:2363-6.
124. Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. *The Lancet Neurology* 2003;2:605-13.

125. Brouns R, DeVil B, Cras P, De Surgeloose D, Marien P, DeDeyn P. Neurobiochemical Markers of Brain Damage in Cerebrospinal Fluid of Acute Ischemic Stroke Patients. *Clinical Chemistry* 2010;56:451-458.
126. Anderson RE, Winnerkvist A, Hansson LO, Rosengren L, Settergren G, Vaage J. Biochemical Markers of Cerebrospinal Ischemia after Repair of Aneurysms of the Descending and Thoracoabdominal Aorta. *J Cardiothorac Vasc Anesth* 2003;17:598-603.
127. Shiiya N, Kunihara T, Miyatake T, Matsuzaki K, Yasuda K. Tau protein in the cerebrospinal fluid is a marker of brain injury after aortic surgery. *Ann Thorac Surg* 2004;77:2034-8.

Populärvetenskaplig sammanfattning

Hjärtkirurgi och dess effekter på hjärnan

-studier kring reglering av hjärnans blodflöde och mekanismer bakom hjärnpåverkan.

I efter-förloppet av hjärtoperationer drabbas 50-70% av hjärnpåverkan, sk. kognitiv dysfunktion. Detta tillstånd kännetecknas bl.a. minnesstörning, personlighets-förändring, koncentrationssvårigheter, psykiskt uttröttbarhet och emotionella störningar. Postoperativ kognititiv dysfunktion anses orsakas av bl.a. störning i balansen mellan hjärnans tillgång och efterfrågan på syrgas, tillförsel av fasta- eller gas partiklar till hjärnan (mikroembolisering) under operationen, dysfunktion av den s.k. blod-hjärnbariären (BBB), effekten av anestesimedel eller olika kombinationer av dessa.

I denna avhandling studerades effekterna av anestesimedlen isoflurane och sevoflurane på hjärnans blodflöde och syresättning vid hjärtkirurgi med hjärt-lungmaskin. Vidare kvantifierades antalet mikroembolier till hjärnan i samband med öppen aortaklaffskirurgi eller vid byte av aortaklaffen via katetrar i ljumsken (TAVI). Utsöndringen av biomarkörer i blodet och ryggmärgsvätskan, signalerande cellskada, inflammation i hjärnan eller störd funktion av BBB, mättes också vid dessa operationer.

Narkosmedlen isoflurane och sevoflurane sänker hjärnans metabolism och därmed syrebehov. Dessutom utöver de en direkt kärlvidgande effekt på hjärnans blodkärl. Detta leder till en förbättrad syresättning av hjärnan. Dessa anestesimedel skyddar därmed hjärnan genom att öka hjärnans tolerans för accidentellt uppkomna blodtrycksfall och kritisk låga blodflöden till hjärnan under operationen.

I samband med TAVI ses en betydande mikroembolisering till hjärnan vid "ballongsprängning" av den gamla och vid insättning av den nya klaffprotesen. Graden av mikroembolier korrelerar till frisättning i serum av hjärnskademarkören S-100B från hjärnans stödjeceller (astrocyter).

Efter aortaklaffkirurgi ses i ryggmärgsvätskan kraftigt förhöjda värden av inflammatoriska mediatorer samt markörer från skadade astrocyter, men inte från skadade nervceller. Denna hjärninflammationen tycks orsaka en störd funktion av BBB. Däremot ses inget samband mellan antalet mikroembolier till hjärnan och graden av hjärninflammation, astrocytskada eller BBB påverkan. Hjärtkirurgi med hjärt-lungmaskin ger således en kraftig hjärninflammation och påverkat BBB, vilket skulle kunna förklara den nedsatta kognitiva förmågan efter hjärtkirurgi med hjärt-lungmaskin.