Cerebral perfusion during cardiopulmonary bypass with special reference to blood flow

THOMAS TOVEDAL
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Abstract

Cardiopulmonary bypass (CPB) is an important method that enables open heart surgery. There is a risk of neurological complications, and efforts to minimize those include optimization of the cerebral perfusion during CPB. This thesis focuses on such optimization of flow conditions in case of obstructed venous drainage, carotid stenosis and during selective antegrade cerebral perfusion (SACP).

In a pig model of impaired venous drainage from the superior vena cava (SVC), stepwise obstruction increased the central venous pressure (CVP) and caused impaired oxygenation. Cerebral micro-dialysis revealed ischemic responses in some but not all of the pigs.

Further experiments, using the same model, aimed to restore cerebral perfusion pressure (CPP) reduced by 75% superior venous obstruction. Both vasopressor treatment and increased venous drainage were effective in normalizing the CPP and improving the cerebral oxygenation. The intracranial pressure was elevated in the vasopressor group, but no signs of brain damage were observed.

The arterial flow during CPB can be altered between pulsatile and non-pulsatile profiles. Switching between these modes was performed during CPB in 20 patients with or without carotid stenosis. The effects on cerebral oxygenation and mean arterial pressure (MAP) were examined. The MAP was significantly lowered by pulsatile flow, but the flow profile did not affect the cerebral oxygenation. No differences were seen between patients with or without carotid stenosis.

SACP is used to ensure the cerebral perfusion during deep hypothermic circulatory arrest (HCA). The cerebral blood flow (CBF) was examined using positron-emission tomography (PET) technique in 8 pigs divided into HCA and HCA+SACP groups. The CBF was downregulated by 70% to 0.10 ml/cm³/min by 20°C hypothermia. A pump flow of 6 ml/kg/min preserved the CBF level without signs of cerebral desaturation. The fluorodeoxyglucose (FDG) uptake after re-warming to 37°C was similar after SACP compared with HCA alone.

In conclusion, experimental SVC obstruction may impair the cerebral perfusion. Vasopressors can restore the CPP during SVC obstruction and improve cerebral oxygenation. In patients, pulsatile flow can lower the MAP in absence of effects on the cerebral oxygenation. During experimental HCA, SACP at 6 ml/kg/min can preserve the CBF at 0.10 ml/cm³/min.

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To Maria, Martin and Axel
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


III Tovedal, T., Thelin, S., Lennmyr, F. Cerebral oxygen saturation during pulsatile and non-pulsatile cardiopulmonary bypass in patients with carotid stenosis. Accepted by *Perfusion*.


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<tr>
<td>ACT</td>
<td>activated clotting time</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>Caa3</td>
<td>cytochrome 3a</td>
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<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<td>CPB</td>
<td>cardiopulmonary bypass</td>
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<tr>
<td>CPP</td>
<td>cerebral perfusion pressure</td>
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<td>CS</td>
<td>carotid stenosis</td>
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<tr>
<td>CVP</td>
<td>central venous pressure</td>
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<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immune sorbent assay</td>
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<tr>
<td>FDG</td>
<td>fluorodeoxyglucose</td>
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<tr>
<td>FiO2</td>
<td>fraction of inspired oxygen</td>
</tr>
<tr>
<td>Hb</td>
<td>deoxygenated hemoglobin</td>
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<tr>
<td>HbO2</td>
<td>oxygenated hemoglobin</td>
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<tr>
<td>HCA</td>
<td>hypothermic circulatory arrest</td>
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<td>HQ</td>
<td>high flow group (paper I)</td>
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<tr>
<td>ICP</td>
<td>intracranial pressure</td>
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<tr>
<td>IVC</td>
<td>inferior vena cava</td>
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<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
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<tr>
<td>LED</td>
<td>light emitting diode</td>
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<td>L/P</td>
<td>lactate/pyruvate ratio</td>
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<td>LQ</td>
<td>low flow group (paper I)</td>
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<td>MAP</td>
<td>mean arterial blood pressure</td>
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<tr>
<td>MCA</td>
<td>middle cerebral artery</td>
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<td>MD</td>
<td>micro-dialysis</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>NADH</td>
<td>nicotinamide adenine dinucleotide</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NIRS</td>
<td>near-infrared light spectroscopy</td>
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<tr>
<td>NP</td>
<td>non-pulsatile CPB flow</td>
</tr>
<tr>
<td>P</td>
<td>pulsatile CPB flow</td>
</tr>
<tr>
<td>PA</td>
<td>pulmonary arteries</td>
</tr>
<tr>
<td>PaCO$_2$</td>
<td>arterial carbon dioxide partial pressure</td>
</tr>
<tr>
<td>PaO$_2$</td>
<td>arterial oxygen partial pressure</td>
</tr>
<tr>
<td>PET</td>
<td>positron-emission tomography</td>
</tr>
<tr>
<td>PR</td>
<td>partial relief treated group (paper II)</td>
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<tr>
<td>RCP</td>
<td>retrograde cerebral perfusion</td>
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<tr>
<td>S100$\beta$</td>
<td>glial cell damage marker</td>
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<tr>
<td>rSO$_2$</td>
<td>regional tissue oxygen saturation index</td>
</tr>
<tr>
<td>SACP</td>
<td>selective antegrade cerebral perfusion</td>
</tr>
<tr>
<td>SagP</td>
<td>sagittal sinus pressure</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>standard error of means</td>
</tr>
<tr>
<td>SsagO$_2$</td>
<td>sagittal sinus oxygen saturation</td>
</tr>
<tr>
<td>SsvcO$_2$</td>
<td>superior vena cava oxygen saturation</td>
</tr>
<tr>
<td>StO$_2$</td>
<td>tissue oxygenation index (paper II, IV)</td>
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<tr>
<td>StO$_2$abd</td>
<td>inferior/subcostal tissue oxygenation index (paper II)</td>
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<tr>
<td>StO$_2$cer</td>
<td>cerebral tissue oxygenation index (paper II)</td>
</tr>
<tr>
<td>SVC</td>
<td>superior vena cava</td>
</tr>
<tr>
<td>SvjugO$_2$</td>
<td>jugular vein oxygen saturation</td>
</tr>
<tr>
<td>SvO$_2$</td>
<td>mixed venous oxygen saturation</td>
</tr>
<tr>
<td>TOI</td>
<td>tissue oxygenation index (paper I, III)</td>
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<tr>
<td>VP</td>
<td>vasopressor treated group (paper I)</td>
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Ischemic brain injury is a significant area of concern during cardiopulmonary bypass (CPB). Efforts to reduce the risk of such neurological complications include searching for causal mechanisms, making improvements to the surgery, anesthesia and CPB techniques, and refining the CPB equipment. The complications range from minor cognitive disorders of a temporary nature to irreversible cerebral lesions, and the incidence increases up to 16% as surgery becomes more complex. The presence of proximal atherosclerosis has been shown to five-fold the risk. The incidence is also associated with predisposing factors such as age, vascular diseases, diabetes, and factors such as the performance of CPB and the surgical techniques used.(1-6)

The brain can fulfill, within a relatively wide blood pressure range, its requirements for oxygen and nutrients through autoregulation of blood flow. However, in clinical situations, the brain's inflow or outflow of blood can be hampered or the metabolic demand altered.

This thesis aims to investigate both clinical and experimental aspects of arterial flow to, and venous outflow from the brain during conventional CPB and also the quantitation of cerebral blood flow (CBF) during selective arterial cerebral perfusion (SACP).

Cerebral blood flow, metabolism and ischemia

Cerebral blood flow (CBF) in the resting adult human is on average 45-55 ml/100 g brain tissue/min, corresponding to 12-15% of the total cardiac output flow.(7) The flow is determined by several factors, e.g. the mean arterial blood pressure (MAP), the arterial carbon dioxide partial pressure (PaCO₂), the hematocrit, the blood temperature, and the cerebral perfusion pressure (CPP).(8, 9) A significant difference exists between CBF in grey matter (70 ml/100 g/min) and in white matter (34 ml/100 g/min).(10)

The main arterial blood supply to the brain emanates from the two common carotid arteries, which origin from the aortic arch on the left, and from the brachiocephalic trunk on the right side in humans. The carotid arteries form the anterior cerebral circulation, while the vertebral arteries, originating from the subclavian artery bilaterally form the posterior cerebral circulation. (Figure 1) The carotid arteries divide into an internal and an external carotid
branch, of which the internal supplies the frontal brain regions, and the external supplies the face and neck. Together, the vertebral arteries form the basilar artery that supplies the rear brain regions and the brain stem.

Figure 1. Schematic overview of the brain’s arterial blood supply routes. The main vessels for cerebral blood supply are the left and right internal carotid arteries and the left and right vertebral arteries.

The internal carotid arteries and the basilar artery connect in the Circle of Willis’, an anastomosis that allows flow distribution to both hemispheres of the brain in the event of unilateral proximal disturbances. (Figure 2) Although this vascular ring structure may be critically important in some cases, 54% of all individuals and 79% of patients presenting with clinical signs of neural dysfunctions do not have a fully developed Circle of Willis’.(11, 12)
Figure 2. Schematic overview of the ‘Circle of Willis’, as seen from below. The basilar artery, which is an extension of the two conjoined vertebral arteries, connects to the two internal carotid arteries via the posterior communicating arteries. A functional blood vessel circle is completed with the connection of the anterior cerebral arteries to the anterior communicating artery, thus ensuring blood supply to both brain hemispheres in the event of a unilateral blood flow obstruction.

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The brain's venous vascular system consists of two main routes. One is the superior sagittal sinus, a superficial longitudinal folding of the dura mater that extends from the frontal to the occipital skull. The other includes the inferior sagittal sinus, which together with the superior sagittal sinus form the transverse sinuses and subsequently the jugular veins which in turn form the brachiocephalic veins that eventually drains into the superior vena cava (SVC) and the right atrium. (Figure 3)
Figure 3. Principal overview of the cerebral venous blood system. The two main routes for the intracranial venous blood flow are the superior and the inferior sagittal sinuses, which are conjoined in the occipital region. From there, the venous blood passes through the two transverse sinuses which will eventually form the internal jugular veins that leads the blood to the superior vena cava.

The brain metabolism depends largely on an uninterrupted supply of oxygen and glucose, and the capacity for anaerobic metabolism is low. A reduction of the CBF below approximately 0.10-0.15 ml/g/min leads to loss of the transmembrane ion balance.(13) The energy reserves are limited to small amounts of glycogen in the astrocytes. During aerobic metabolism in neurons and the astrocytes, glucose-derived pyruvate enters the citric acid cycle, where it is transformed into energy in form of adenosine triphosphate (ATP). The pyruvate metabolism also creates nicotinamide adenine dinucleotide (NADH) which enters the mitochondrial respiratory chain to supply additional ATP. During anaerobic conditions, the respiratory chain is blocked, and pyruvate and NADH are accumulated. Pyruvate then interacts with NADH and lactate dehydrogenase (LDH), forming lactate. Thus, oxygen shortage will increase lactate and decrease pyruvate concentrations. The relationship between the lactate and pyruvate concentration levels, the L/P ratio, is considered to indicate ischemia when >25-30.(14, 15)
The pathogenesis of ischemic brain injuries includes three elements; a depolarization, a biochemical cascade, and a reperfusion injury. Lactic acidosis disturbs the transmembrane ion gradients, allowing an excessive inflow of calcium ions (Ca\(^{2+}\)) into the cytosol. The altered Ca\(^{2+}\) balance triggers a release of neurotoxic glutamate, the neuronal recycling of which is blocked by ischemia. The accumulation of glutamate disables glutamate-operated membrane ion channels, which further enhances the Ca\(^{2+}\) inflow. The increased Ca\(^{2+}\) concentrations and the acidosis trigger the release of oxygen radicals, thereby inducing neuron damage and cell death by proteolysis and lipolysis. (16, 17) The cascades also result in a reperfusion injury involving intravascular accumulation of leukocytes that impairs the micro-circulation and leads to further release of oxygen radicals.

**Autoregulation**

The CBF is driven by the cerebral perfusion pressure (CPP), and as a result of the restrictive nature of the skull, elevations in intracranial pressure (ICP) may affect the CBF. Limited cerebral drainage can produce increases in ICP. (18, 19) The CPP is commonly defined as MAP - ICP, but in case the ICP is not available, other definitions can be used. During CPB, the CPP can be estimated as the MAP - CVP, under the assumption that there is no focal intracranial problem. A CPP of <30 mm Hg has been shown to result in ischemic metabolism in normothermic pigs. (20)

The brain is able to autoregulate its blood flow in order to enable physiological metabolism within certain limits. This autoregulation is believed to be governed by metabolic, neurogenic, and myogenic components. (7, 21-26) A change in the PaCO\(_2\) leads to extracellular pH alterations, which affects the pre-capillary sphincter tonus via a mediator system. Increased PaCO\(_2\) results in dilation, and decreased PaCO\(_2\) constrict the sphincters, (7, 21, 22, 27) while decreased arterial oxygen partial pressure (PaO\(_2\)) <6.7 kPa causes vasodilation. (7, 22) The neurogenic control responds to changes in the balance between the sympathetic and the parasympathetic nerve systems. These changes have an instantaneous effect on the CBF until other regulators are activated. (7) The myogenic response system is affected by variations in the CPP and possibly also by local nitric oxide release, and is functional within a MAP range of 50-150 mm Hg, although the actual width of the range is debated. (28-32) Ranges vary between individuals. (28) and functional autoregulation has even been shown during hypothermia at a MAP level as low as 20-30 mm Hg. (31, 33, 34) The relationship between MAP and the CBF is described in Figure 4. Chronic hypertension shifts the curve to the right.
Figure 4. Relationship between mean arterial pressure (MAP) and mean cerebral blood flow (CBF). The dotted lines represent the upper and lower pressure limits for functional cerebral blood flow autoregulation.

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Comparative anatomy

The central blood vessels of the pig are partially similar to human vessels, especially regarding the coronary arteries and the relative heart size. On the other hand, other aspects differ, such as the venous vessels.(35, 36) The inferior vena cava (IVC) in humans is the main route for the return of venous blood from the lower body regions to the heart, and a right-sided azygos vein drains venous blood from the chest and the abdomen into the superior vena cava (SVC). The hemi-azygos vein is located on the left side of the vertebral column and drains venous blood from the left side of the chest into the SVC.(37)

In pigs, there is a common arterial brachiocephalic trunk from which both carotid and subclavian arteries originate. The pig also has an arterial rete mirabile, which runs through the skull base as an extension of the pharyngeal artery.(35, 38) The circulatory role of this rete is not entirely clear.(39) On the venous side, the azygos vein drains into the SVC, while the hemi-azygos vein is comparably larger than in humans and drains into the coronary sinus.(35)
Both the azygos and the hemi-azygos veins have vascular communication both cranially and caudally.

The cerebral venous blood drainage in pigs differs from humans since the majority of the blood drains into paraspinal veins rather than the jugular veins. However, the cavernous and petrosal sinuses drain into the jugular veins, a circumstance probably related to the prone constitution of the pig. (36)

Cardiopulmonary bypass (CPB)

Cardiac surgery usually relies on a CPB system where the IVC and SVC blood is diverted from the body through plastic cannulas inserted proximal to the right atrium. Thereby, the diverted blood escapes the pulmonary circulation and is pumped from the venous reservoir through an oxygenator where gaseous exchange takes place across a semi-permeable membrane for gas diffusion.

There are two main types of CPB pump; the centrifugal pump and the roller pump, the latter of which was used in all studies in this thesis. In a centrifugal pump the blood is directed into the center of a pump chamber where a rapidly rotating impeller or a set of stacked plastic cones transfers its kinetic energy to the blood, creating a vortex. The blood is then transferred out to the CPB tubing system via a pump chamber periphery outlet. The roller pump is a positive displacement pump constituted of an outer housing, which contains a runway for the CPB tubing. The tubing enters and exits the housing on the same side, where the pump tubing segment is connected to the rest of the CPB tubing system. In the center of the housing is a rotor with peripherally placed rollers, which press the tubing against the housing inner wall. A finite amount of blood is thus enclosed between the rollers, and the rotor movement transports the blood forward.

In the oxygenator, gases such as oxygen and anesthetics enters the blood, and carbon dioxide is removed. Venous drainage through the CPB tubing is usually achieved by the gravity siphonage generated by the level difference between the patient and the venous reservoir. The oxygenated blood is retransfused to the patient’s blood circulation through the CPB tubing and via a cannula, commonly inserted into the aortic arch or a femoral artery. (Figure 5)

When stable hemodynamics are obtained, the aortic arch can be cross-clamped and protection during cardiac arrest can be provided through intracoronary infusion of a cardioplegic solution, typically containing potassium.

The CPB system is usually equipped with a heat exchanger to regulate the patient’s body temperature, suction to retrieve heparinized blood from the surgical wound and pumps to deliver cardioplegic solution.
Figure 5. Schematic presentation of the principle for cardiopulmonary bypass. Venous blood flow is deviated before it enters the heart, and is led to a venous reservoir, from which it is transported by means of a pump to the oxygenator and then onward to the aorta. In the oxygenator, oxygen is added to the blood and excess carbon dioxide is removed.

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Venous drainage

Venous drainage is typically maintained using a “dual stage” venous cannula that is inserted into the IVC through the right atrial auricle. The cannula has distal end openings for IVC drainage, and lateral for the SVC. Alternatively, the SVC and the IVC can be separately cannulated (“bi-caval”). (Figure 6) The SVC and IVC cannulas are connected to a Y-piece outside the patient and then connected to the CPB tubing. The positions of the cannulas can be examined by trans-esophageal ultrasound to confirm that the IVC cannula has not unintentionally entered the hepatic vein instead of the IVC, a position associated with inadequate drainage.

The venous CPB drainage is based on gravity and the siphon effect, and is therefore basically passive. Drainage may be improved by applying a negative pressure to the venous blood reservoir, adding a vacuum effect to the venous tubing.

Obstruction of the blood flow in a dual stage or SVC cannula may lead to congestion in the superior territory, and to elevated CVP that is propagated
into the cerebral vasculature. Consequently, increased ICP can occur and reduce the CPP with impaired cerebral perfusion as a result.

**Figure 6.** Schematic presentation of common venous cannulation alternatives for cardiopulmonary bypass. A: bi-caval cannulation. Cannulas are separately inserted into the superior vena cava (SVC) and the inferior vena cava (IVC), and then interconnected to lead the venous blood to the heart-lung machine reservoir. The respective cannulas are snared to avoid redundant blood flow to the heart. B: a dual stage venous cannula is inserted into the IVC, and positioned so that the SVC is drained via side wall openings in the cannula. IVC = inferior vena cava, SVC = superior vena cava.

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**Arterial blood flow and pressure**

In contemporary practice, the arterial CPB blood flow is commonly 2.2-2.5 l/min/m² body surface area. Commercially available oxygenators are typically designed for blood flows up to about 7 l/min, which covers the requirements for adult CPB in most cases. It is common that heart-lung machines offer the user a choice between pulsatile and non-pulsatile blood flows, and switching between them to achieve optimal organ perfusion is uncontroversial.

Arterial blood pressure during CPB is usually lower than normal blood pressure at equal blood flow, which to some extent can be explained by decreased vascular resistance caused by hematocrit reduction, reduced catecholamine levels, the initial transient low oxygen tension and low pH of the CPB crystalloid priming fluid. The levels of empirically accepted MAP may range from 50 to 95 mm Hg, and while hypotension may be desirable in some situations in order to reduce surgical blood loss, it may also lead to cerebral hypoperfusion, which forms a practical dilemma.
Clinical problems
There are a number of potential risk factors associated with CPB that have significance for the development of cerebral injury, and understanding such risk factors is essential for ensuring safe perfusion during cardiac surgery.

Venous drainage issues
Unsatisfactory positioning of cannulas, inadvertent kinking or dislocation of venous cannulas and CPB tubing, imprecision or malfunction of monitoring or CPB equipment, as well as human errors, are all examples of factors that may contribute to significant hypoperfusion. This was illustrated by one of our animal experiments, in which accidental superior vena cava congestion lead to a fatal outcome, despite the fact that conventional monitoring did not reveal any apparent abnormalities. In that case, the CVP, the mixed venous oxygen saturation (SvO₂), and MAP were all within normal ranges, but simultaneous magnetic resonance imaging (MRI) scanning revealed the absence of cerebral circulation.

To explore the properties of cerebral venous congestion due to SVC obstruction, paper I focused on cerebral oxygen saturation and metabolism during controlled stepwise occlusion of the SVC cannula in increments of 25% until total occlusion. Based on the aforementioned interaction between the CVP, ICP and CPP, the situation allowed us to apply different strategies to preserve the CPP after SVC obstruction. These trials led to the randomization of two treatments in paper II.

Ensuring regional perfusion
A substantial proportion of patients undergoing cardiac surgery also suffer from vascular disease, which may have implications for the arterial supply for the brain in case the cerebral vessels are affected. The CPB flow mode profiles can be adjusted, and such optimization of the CPB can readily be performed by the perfusionist. Hypothetically, post-stenotic perfusion might benefit from the pressure peaks generated by pulsatile blood flow, and paper III addresses the possible advantages of pulsatile CPB blood flow compared to non-pulsatile flow in patients with or without carotid stenosis.

Organ protection during circulatory arrest
When the CPB needs to be interrupted for surgical reasons, mainly during aortic surgery, patient safety relies on rapid surgical management and certain protective strategies. The principal strategy is circulatory arrest in deep hypothermia (HCA), which can be accompanied by selective cerebral perfusion
using the CPB system. Both alternatives offer exsanguinated surgical fields in order to facilitate the rapidness and effectiveness of the surgery.

Selective cerebral perfusion can be performed either with antegrade technique (selective antegrade cerebral perfusion, SACP) via the carotid arteries, or retrograde technique (retrograde cerebral perfusion, RCP) via the venous SVC cannula. Previous studies at our institution were able to define a minimum safe level of arterial blood flow during SACP in pigs.(50) Signs of ischemia could be seen below 6 ml/kg/min in terms of regional increases in lactate concentrations. Furthermore, we observed regional variations in perfusion during SACP. These findings raised additional questions, mainly regarding the translation of this experimental flow level in pigs into humans. This led to paper IV, where the subject was further elaborated using positron-emission tomography (PET) technique to quantify the cerebral blood flow at the 6 ml/kg/min SACP flow level and to determine the glucose metabolism after rewarming from deep HCA with or without SACP.
Aims

Paper I
To investigate the effects on the cerebral perfusion of gradually obstructing the SVC cannula during mild hypothermic (34⁰C) bi-caval CPB in pigs.

Paper II
To investigate the possibility of restoring a reduced cerebral perfusion pressure either by vasopressor or partial relief of supra-caval congestion, in the event of SVC cannula obstruction, during mild hypothermic (34⁰C) bi-caval CPB in pigs.

Paper III
To investigate the effects of changing between pulsatile and non-pulsatile CPB flow on cerebral oxygen saturation and hemodynamics in patients with or without carotid stenosis.

Paper IV
To quantify the cerebral blood flow in pigs during 20°C CPB, and during SACP at the previously defined lowest safe pump flow level, and to examine possible cerebral metabolic differences after re-warming from 20°C HCA and HCA + SACP respectively, using PET technology.
Material and methods

Study designs

Studies I, II and IV were experimental studies on pigs. Study III was a clinical study conducted within the Department of Surgical Sciences, Section of Cardiothoracic Surgery and Anesthesiology, Uppsala University Hospital, Uppsala, Sweden. The animal studies were done in specifically designed animal laboratory environments at the Hedenstierna Laboratory and at the Pre-clinical PET Platform, Uppsala University, Uppsala, Sweden.

Papers I, II, and IV

Norwegian Landrace pigs were used. At the end of each experiment the animals were euthanized by intravenous injection of potassium while in deep anesthesia. All animals received humane care in compliance with the European Convention on Animal Care.

The heart and central blood vessels were accessed through a median sternotomy in all studies. In studies I and II craniotomies were performed. An overview of the technical modalities used is presented in Table 1.

The right external jugular vein and a femoral artery branch were used for pressure monitoring and blood sampling. Sensors for bi-parietal (studies I and IV) and for right-sided (study II) cerebral NIRS were applied and shielded from ambient light. In study I the NIRO-200® was used (Hamamatsu Photonics Deutschland GmbH, Herrsching, Germany), and in studies II and IV the ForeSight® Cerebral Oximeter (Casmed, Branford, CT) was used.

After tracheal intubation the ventilation settings were adjusted to obtain adequate mixed venous saturation (SvO₂; study I: 51.5 ± 9.9, study II: 57.1 ± 11.1, study IV: 57.8 ± 13.8%, means ± SD) and normocapnia (PaCO₂; study I: 5.0 ± 0.3, study II: 4.5 ± 0.5, study IV: 5.1 ± 1.4 kPa, means ± SD).

When the CPB was stable, the vena azygos was ligated (papers I and II). In paper I, the hemi-azygos was left open, while in paper II, the hemi-azygos was ligated. CPB cannula blood flow was measured with ultrasound technique. The urine was deviated through a suprapubic urostomy.

The monitoring also included a cerebral micro-dialysis catheter inserted into the right hemisphere parenchyma (study I), a laser-Doppler probe inserted through a dural incision for relative CBF measuring (study II) and an 18G epidural catheter resting in a parietal sulcus for ICP registration (study II).
Retrospective data were collected from the medical records of 20 adult cardiac surgery patients included in an earlier quality assurance project within the department. That project comprised a series of patients where the response to pulsatile and non-pulsatile flow during standard CPB was evaluated. Patients with and without carotid stenosis were included. The flow profile was switched once per patient during aortic cross-clamping, and the order of pulsatile/non-pulsatile was random. The endpoints were regional cerebral oxygenation registered by NIRS (NIRO-200®, Hamamatsu Photonics Deutschland GmbH) and the mean arterial pressure (MAP).

Experimental investigation modalities

Near-infrared light spectroscopy (NIRS)

Near-infrared light spectroscopy (NIRS) enables non-invasive measurement of tissue oxygen saturation. The technology is based on the transmission of near-infrared light that is scattered, reflected and partially absorbed by the tissue and then registered by a light receiver. Tissue chromophores include hemoglobin, bilirubin, and melanin and the measurement of tissue oxygenation is based on oxygenated (HbO₂) and deoxygenated hemoglobin (Hb). The NIRS wavelength range used is commonly within 700-900 nm, which is below the absorption peak of tissue water. (Figure 7) At 810 nm, the Hb and HbO₂ curves cross at the so called ‘isobestic point’, where HbO₂ and Hb exhibit the same molar absorptivity, making it possible to calculate total tissue hemoglobin content. (51)
Figure 7. Relative differences in near-infrared light absorbance at various wavelengths for water, melanin, cytochrome 3a, oxygenated hemoglobin and deoxygenated hemoglobin. The most important absorbers of near-infrared light are oxygenated hemoglobin, deoxygenated hemoglobin and water. The lowest absorption wavelength range for water is between 700 and 900 nm, thus suitable for tissue oxygenation readings by near-infrared light spectroscopy. Caa3 = cytochrome 3a, H2O = water, Hb = deoxygenated hemoglobin, HbO2 = oxygenated hemoglobin.

From Murkin et al.(51)

The oxygen saturation is calculated using algorithms that differ between instruments, and the result is presented as an oxygen saturation index, such as rSO2 (INVOS™, Covidien), StO2 (Fore-Sight®, CASMED) and TOI (NIRO®, Hamamatsu). The index calculation is based on proportions of, and concentration changes in oxygenated and deoxygenated hemoglobin, and is based on the Beer-Lambert law, stipulating that there is a proportional relationship between the amount of absorbed light, the pathway length, and the light absorption properties and concentration of a substrate.(51) NIRS measures the oxygen saturation of the total cortical cerebral blood, of which over 70% is considered to be venous, and the remaining part mainly arterial.(51-54)

In papers I and III, TOI (NIRO-200®, Hamamatsu) was used and in papers II and IV, StO2 (Fore-Sight®, CASMED) was used.

Venous blood flow measurements during CPB

The blood flow in the venous CPB cannulas was registered by ultrasound technique. In paper I, the Centrimag Blood Pumping System (Levitronix GmbH, Zürich, Switzerland) was used and in papers II and IV, the M3 system (Spectrum Medical Ltd, Gloucester, England) was used. Both systems have clip-on flow detectors for non-invasive external tubing application.
**S100β**

S100β proteins are Ca$^{2+}$-binding mediators of intracellular response to external stimuli, which interact with several effector proteins and contribute to qualities such as contractility, motility, and protection from oxidative cell damage. The proteins are divided into two isomeric subgroups; S100α and S100β, the latter of which is predominantly found in the astrocytes. Elevated S100β serum concentration has been associated with blood-brain barrier disruption,(55) size of brain infarction,(56-58) and with neuropsychological outcome after cardiac surgery.(59, 60)

The appropriate time window for sampling and the S100β release pattern is debated, and the biological half-life of S100β is only about 30 minutes.(61-64) Serum levels of S100β can be analyzed with enzyme-linked immunosorbent assay (ELISA) technique.(64) For quantification of S100β, a commercially available human ELISA kit with documented porcine cross-reactivity was used.

The S100β concentrations may be confounded by contribution of S100β from bone marrow and fatty tissue, although the importance of the latter is uncertain.(65) To minimize the admixture of non-cerebral venous blood, serum was derived from samples retrieved directly from the sagittal sinus.

**Micro-dialysis**

Micro-dialysis is performed by insertion of a thin double-lumen catheter with a semi-permeable membrane at the tip, into the cerebral parenchyma. The catheter is perfused to its tip with a fluid of known composition (perfusate), isotonic to the membrane’s surrounding environment. After reaching the membrane at the catheter tip, the returning fluid (dialysate) is continuously pumped back through the exterior catheter lumen to collecting vials, harvested one-by-one at predetermined intervals. Exchange of substrates between the perfusate and the surrounding extra-cellular fluid takes place by diffusion via the membrane. (Figure 8) As the dialysate is in constant movement, an accurate estimation of extra-cellular substrate concentration requires a correction factor (“recovery”) to compensate for the somewhat lower concentrations in the dialysate. The recovery is mainly determined by factors such as the perfusate composition, flow velocity, the membrane area, temperature and the substrate concentrations.(66)

The ischemic cell exhibits anaerobic glycolysis, resulting in decreased glucose levels and increased lactate levels.(67-69) This process is commonly monitored in studies on cerebral ischemia and includes measurement of lactate, pyruvate, and glucose.(67) Cerebral ischemia results in increased lactate levels, lactate/pyruvate ratio and lactate/glucose ratio, and falling levels of glucose and pyruvate.(67) The lactate/pyruvate ratio and the lactate/glucose
ratio have the advantage of being relatively independent of recovery. Disrupted cellular membrane integrity is commonly detected by analysis of glutamate and glycerol.

The introduction of the micro-dialysis catheter creates local cell membrane damages, and a stabilization period of 30 minutes is required before measuring may begin.

Figure 8. The principle for micro-dialysis substrate exchange. A perfusate of known composition, isotonic to the surroundings at the investigation site, is slowly pumped through a thin double-lumen catheter inserted into the tissue. The catheter end is equipped with a membrane, permeable for the substances of interest. At the catheter tip, the dialysate flow continues into the exterior catheter channel and is led to a collecting vial. Exchange of substrates between the perfusate and the surrounding extracellular fluid takes place by diffusion via the membrane.

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Intracranial monitoring

The intracranial space was accessed through a burr craniotomy in order to draw blood from the sagittal sinus (papers I and II), and to measure sagittal venous pressure (SagP, paper II), ICP (paper II) and CBF (paper II). For the ICP measurements, an 18G epidural catheter was inserted into a parietal sulcus. The SagP showed a good correlation with the ICP, but was less susceptible to disturbances such as ICP catheter tip occlusion caused by tissue swell-
ing. Therefore, the SagP was used to calculate the CPP. For the CBF measurements, a laser-Doppler probe was applied onto the parietal brain surface. The measuring device presents unitless values, thus indicating relative CBF changes.

**Positron-emission tomography (PET)**

Positron-emission tomography (PET) enables quantification of processes such as regional blood flow or metabolic activity. The method depends on radioactive compounds that are injected into the bloodstream. Via $\beta^+$-decay, positrons are emitted and merge with electrons in the immediate vicinity. This process is called annihilation and results in two gamma-photons of opposite directions. A multitude of such annihilations occur in close temporal proximity and based on the registration of coincidence in a PET scanner, measurements of the radioactivity can be mapped and images constructed.\(^{(71)}\) (Figure 9)

Properties such as extremely short compound half-life enable blood flow measurements to be calculated in conjunction with arterial input functions, and metabolic trapping enables measurement of tracer uptake, thus allowing estimations of the metabolism.

In paper IV, $^{15}$O-labeled water was used to determine the CBF, and the glucose metabolism was estimated by quantifying the uptake of $^{18}$F-labeled glucose (fluorodeoxyglucose, FDG) in the brain parenchyma.

*Figure 9.* Principle illustration of the annihilation reaction, which is a prerequisite for positron-emission tomography (PET). Intravascularly administered isotope-labeled substances (tracers) pass or accumulate in the target organ, where they emit positrons by $\beta^+$-decay. The positrons annihilate with negatively charged electrons in the vicinity, and their contained energy is converted into two gamma-photons. The photons are detected as time coincidences by an encircling PET scanner, enabling determination of tracer position and concentration.

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An outline of technical modalities and samplings used in the experimental studies is presented in Table 1.

Table 1. Technical specification survey of papers I, II, and IV. CBF = cerebral blood flow, FDG = fluorodeoxyglucose, HQ = high flow group in paper I, IC cath = intracranial pressure monitoring catheter, ICP = intracranial pressure, L/P ratio = lactate/pyruvate ratio, NIRS = near-infrared light spectroscopy, Ox. Sat = oxygen saturation, PET = positron-emission tomography, S100β = neuroglial marker, S Sag = superior sagittal sinus, StO2 = tissue oxygenation index (ForeSight ®), TOI = tissue oxygenation index (NIRO-200 ®).

<table>
<thead>
<tr>
<th>Paper</th>
<th>Arterial cannula</th>
<th>Venous cannulas</th>
<th>Azygos/ hemi-az.</th>
<th>NIRS monitor</th>
<th>Specific sampling /monit.</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>90 ° angled 28 + 28Fr lig/open</td>
<td>NIRS S Sag (HQ) MD</td>
<td>Ox. sat Lactate Pyruvate L/P ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>FemFlex 18Fr 24 + 28Fr lig/lig</td>
<td>ForeSight</td>
<td>NIRS S Sag Ox. Sat Pressure Doppler IC cath</td>
<td>CBF ICP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>FemFlex 20Fr 28 + 28Fr Open/open</td>
<td>ForeSight</td>
<td>NIRS [15O]water PET [18F]FDG PET</td>
<td>CBF Glucose metab.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Experimental protocols

Paper I

Twelve pigs (29-39, mean 33 kg) were subjected to mild hypothermic (34°C) normocapnic non-pulsatile CPB with bi-caval cannulation. The animals were divided into two observation groups; one low flow group (LQ) where the arterial CPB flow was 50 ml/kg/min, and one high flow group (HQ) with CPB flow 100 ml/kg/min. The LQ group mimicked the situation of low arterial flow due to inadequate venous drainage, while the HQ group represented congestion with preserved arterial flow. Two animals in the LQ were excluded due to inadequate baseline perfusion, leaving 10 pigs included (LQ n = 4, HQ n = 6).
After establishing stable baseline perfusion, SVC flows were reduced by clamping to 75, 50, 25 and 0% of baseline, before finally being restored to 100%. The observation periods were 30 minutes per level. (Figure 10) Arterial blood gases, mixed venous hematocrit and oxygen saturation (SvO₂) were continuously monitored. Sagittal sinus (HQ) and SVC blood gases were analyzed every 10 minutes, and every 15 minutes at each congestion level from the arterial and the common venous CPB tubing. Regional cerebral oxygen saturation was measured using NIRS (NIRO-200®). A kaolin-activated clotting time (ACT) >450 sec was maintained.

Figure 10. Design and timeline for sampling of paper I. SVC blood flow was reduced stepwise in increments of 25%, and finally the SVC obstruction was released, enabling full restoration of the flow. Each observation period was 30 minutes, during which repeated blood gases and one cerebral micro-dialysis sampling was performed.

MD = micro-dialysis, SVC = superior vena cava.

Paper II
Fourteen pigs (30-39, mean 36 kg) received non-pulsatile CPB with bi-caval venous drainage, normocapnic ventilation and mild hypothermia (34°C). After obtaining stable baseline CPB conditions, a 75% SVC flow reduction was achieved by clamping the SVC cannula. Thereafter, the pigs were randomized to either vasopressor treatment by the use of a norepinephrine infusion (Noradrenalin, Abcur AB, Helsingborg, Sweden) (VP, n=7),(72) or partial relief of the congestion by releasing the clamp (PR, n=7). Both methods were adjusted to restore the CPP.
To investigate the effects on cerebral perfusion, cerebral oxygen saturation by NIRS, CBF by laser-Doppler technique, ICP and SagP were continuously measured, and registered at predefined time points together with perfusion parameters, blood gas analyses and sampling for analysis of the glial cell damage marker S100β in sagittal sinus blood.

Time points for registration and sampling were; BL1 (baseline 1 after anesthesia induction), BL2 (on stable CPB), T1 (10 minutes after application of SVC congestion), T2 (30 minutes after intervention), and T3 (60 minutes after intervention). (Figure 11)

The CPB flow was adjusted to 84-104 ml/kg/min to obtain an adequate SvO₂ at a PaCO₂ of 4.7 (4.3-5.0) kPa at time point BL2. Once on CPB, the left-sided hemi-azygos vein was ligated to avoid non-physiological shunting of blood from superior to inferior venous territories.

![Figure 11. Design and timeline for sampling of paper II. After establishing stable CPB, the SVC cannula flow was reduced by 75%, and the animals were randomized to receiving either vasopressor treatment or relief of SVC occlusion in order to re-establish baseline cerebral perfusion pressure. Blood gases, perfusion parameters and sagittal sinus blood samples for S100β analysis were acquired at time points BL1 (baseline 1, after anesthesia induction), BL2 (on stable CPB), T1 (10 minutes after application of SVC congestion), T2 (30 minutes after intervention) and T3 (60 minutes after intervention). CPB = cardiopulmonary bypass, SVC = superior vena cava.](image-url)
Paper III
Twenty adult patients underwent standard cardiac surgery with CPB and cross-clamping of the aorta. Both pulsatile and non-pulsatile flow modes were applied for each patient, and the order of flow mode was random.

The patient selection was made openly, based on the known presence (CS, n = 10) or clinical absence of carotid stenosis (Controls, n = 10). None of the CS patients were stated to have symptoms from their carotid stenosis.

The hemodynamics, regional NIRS, and the CPB flow and pressure parameters were observed during the entire operation and registrations were made with 1 min intervals during observation periods of 6-8 min per flow mode at 32°C during the aortic cross-clamping. Hemodynamic stabilization after administration of cardioplegia was awaited.

The data were collected prospectively and the study was performed retrospectively based on the patient’s medical records.

Paper IV
Eight pigs (33-39, mean 35.5 kg), were openly assigned to two experimental groups, SACP (n = 4) and HCA (n=4).

Both groups were subjected to deep hypothermic (20°C naso-pharyngeal temperature) non-pulsatile CPB. The SACP group obtained total body circulatory arrest with selective antegrade cerebral perfusion with a CPB flow of 6 ml/kg/min (kg body weight) for 45 minutes. The HCA group underwent 45 minutes of total circulatory arrest. Thereafter, both groups were re-warmed to 37°C.

Cerebral blood flows in the SACP group were quantified before and during SACP, and after re-warming, and in the HCA group before circulatory arrest and after re-warming, by [15O]water PET scans. In both groups, cerebral metabolism was evaluated after re-warming by a fluorodeoxyglucose [18F]FDG PET scan. Repeated arterial and venous blood gases, along with cerebral NIRS and routine CPB monitoring was performed. (Figure 12)

An outline of all experimental protocols is presented in Table 2.
Figure 12. Design and timeline of paper IV. After establishment of stable CPB, both study groups were cooled down to a naso-pharyngeal temperature of 20°C. The SACP group then received selective antegrade cerebral perfusion (SACP) with a pump flow speed of 6 ml/kg/min (kg body weight) for 45 minutes, while group HCA received a total circulation arrest for 45 minutes. Thereafter, all the animals were re-warmed to 37°C. [15O]water PET scans were performed repeatedly for cerebral blood flow quantifications (red arrows). An [18F]FDG PET scan for analysis of cerebral metabolic status was conducted after re-warming (blue dotted arrow). CPB = cardiopulmonary bypass, FDG = fluorodeoxyglucose, HCA = hypothermic circulatory arrest, PET = positron-emission tomography, SACP = selective antegrade cerebral perfusion.
Table 2. Overview of the protocols of the studies included in the thesis. CBF = cerebral blood flow, CS = carotid stenosis, HCA = hypothermic circulatory arrest (paper IV, HQ = high flow (paper I), ICP = intracranial pressure, LQ = low flow (paper I), PR = partial relief (paper II), SACP = selective antegrade cerebral perfusion (paper IV), StO2 = tissue oxygenation index (ForeSight ®), TOI = tissue oxygenation index (NIRO-200 ®), VP = vasopressor (paper II).

<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Groups</th>
<th>Endpoints</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Open, non-randomized</td>
<td>HQ/LQ</td>
<td>TOI, micro-dialysis, superior oxygen saturation, blood gases</td>
</tr>
<tr>
<td>II</td>
<td>Open, randomized</td>
<td>VP/PR</td>
<td>StO2, superior oxygen saturation, neuron damage marker S100β, CBF, ICP</td>
</tr>
<tr>
<td>III</td>
<td>Open, observational</td>
<td>CS/Controls</td>
<td>TOI, arterial blood pressure, oxygenator pressure</td>
</tr>
<tr>
<td>IV</td>
<td>Open, non-randomized</td>
<td>SACP/HCA</td>
<td>StO2, superior oxygen saturation, CBF, cerebral glucose metabolism</td>
</tr>
</tbody>
</table>
Ethical approvals

The animal studies were approved by the Uppsala Ethical Committee on Laboratory Animal Research, and study III was approved by the Uppsala Regional Ethical Review Board. Consent was collected from all patients.
Statistics

Data are reported as means with standard deviations or standard error of means, except where otherwise stated.

Within-group comparisons were made with paired t-tests, Wilcoxon's matched pairs test and one-way ANOVA with post-hoc analysis of linear trend. Between-group comparisons were performed with un-paired t-tests, the Mann-Whitney test, the Kruskal-Wallis test and Dunn's multiple comparisons test. Correlation analyses were carried out with the Pearson test for parametric data and the Spearman rho test for non-parametric data.

The calculations were conducted with GraphPad Prism v. 5.01 and v. 6.01 (papers I and II) and GraphPad Prism v. 6.02 (papers III and IV) (GraphPad Software Inc., San Diego, CA).
Results and Discussion

Venous blood flow aspects (paper I, II)

Main findings

**Paper I**
SVC obstruction caused increased CVP and signs of reversible regional perfusion disturbances, but no consistent metabolic effects. However, differences were observed between individual responses and ischemic patterns were present in multiple cases. The total venous drainage was unchanged despite the SVC obstruction, due to an increase in IVC drainage.

**Paper II**
SVC obstruction caused superior venous congestion with a reciprocal decrease in CPP and signs of impaired cerebral perfusion. Both vasopressor and partial relief of the obstruction improved short-term cerebral perfusion.

Variations in response to venous congestion (paper I, II)
In paper I, the SvO$_2$ decreased significantly in the LQ group upon SVC obstruction. The HQ group showed a similar tendency, although non-significant. The NIRS oxygen saturation (TOI) and the venous saturations tended to decline with increased SVC obstruction and to increase when the drainage was restored.

Cerebral parenchymal micro-dialysis was used in paper I only, and the group analyses of lactate, pyruvate, glucose and glycerol showed no significant trends with increasing SVC obstruction. However, individual analysis of ischemic patterns defined as decreasing TOI and superior vena cava oxygen saturation (SsvcO$_2$) together with increased L/P revealed possible ischemic responders that were not distinguished at the group level. The number of such responders was 4 of 10 pigs. Interestingly, the increase in L/P ratio was seen at total occlusion in two animals, and after the release of occlusion in two other animals.

In paper II, the effects were similar to paper I with decreased venous saturations and NIRS oxygen saturation (StO$_2$cere) upon SVC congestion. The VP intervention resulted in a significant increase in the SsvcO$_2$ and the sagittal
sinus oxygen saturation (SsagO2), and a similar tendency was observed for the StO2cer.

In a population of CPB cases, subgroups of increased neurological risk can be identified. These include patients undergoing valve surgery, especially mitral valve surgery and combined mitral and aortic valve surgery. Furthermore, stroke predictors have been identified by multivariable analysis and include e.g. diabetes, hypertension, and vascular diseases.(1-6)

The brain is sensitive to disturbed nutritive blood supply,(73, 74) and meticulous care must be taken to meet the metabolic demands. The first signs of hypoxic metabolism are seen at PaO2 levels between 3.29 and 5.33 kPa.(74)

Continuous jugular oxygen saturation monitoring (SvjugO2) gives a crude estimate of the cerebral oxygen saturation, but is relatively invasive compared with NIRS. Venous admixture limits the measurement accuracy and the method has been shown to reflect cerebral desaturation poorly.(75) Single SvjugO2 and NIRS readings exhibit some variance,(76-78) but the consistency regarding trend development is better.(78) NIRS is a non-invasive monitoring method that is easily applicable but insensitive to differences in the mixture of venous, capillary and arterial cortical blood.(51-54)

In contrast to the ubiquitous clinical problem, the literature on SVC obstruction is relatively sparse with a very limited number of controlled trials,(40) and case reports.(79-82) Sakamoto et al studied small piglets at 25°C and with 50% and 100% abrupt obstructions of the SVC cannula.(40) Their findings show regional blood flow disturbances and ischemic changes in terms of decreased NIRS readings at 100% but not at 50% of SVC obstruction. No other significant signs of anaerobic metabolism or insufficient oxygen supply were seen.

In paper I, two groups were formed to compare impaired (LQ) and normal (HQ) arterial flow. The groups differed as expected in terms of general perfusion, but interestingly, there were ischemic responders in both groups (two in LQ and two in HQ). This suggests that the susceptibility to SVC congestion might not primarily be an effect of the arterial flow level.

Blood flow conditions and undetected alterations in drainage (paper I)

The perfusionist role during CPB includes monitoring of multiple parameters, such as blood flow, tubing and oxygenator pressures, temperature, and blood gas analysis. The measurement of the arterial roller pump flow is based on the pump head rotation speed and the tubing diameter and displayed on the heart-lung machine. There may be errors with this method, for instance if the degree of tubing occlusion in the pump head is not taken into account. More accurate
readings can be obtained if the flow is measured directly in the tubing, however this method is more expensive and not consistently applied during standard CPB.

On the venous side, a relationship of 1:2 between the SVC and the IVC cannula can be expected with a bi-caval setup. Paper I showed that decreases in SVC drainage can be compensated by an increase from the IVC. It is possible that the porcine anatomy is more predisposed to this phenomenon than the human, and notably, the azygos/hemi-azygos was not completely ligated in paper I. Nonetheless, it is noteworthy that the loss of SVC drainage passed without immediate warning signs, and it underscores the importance of multiple monitoring during CPB. In practice, there is a risk that the CVP monitoring is misinterpreted as noise since technical artefacts due to for instance manipulations at the surgical site are common. When diagnosed, impaired SVC flow requires corrective actions such as repositioning of the venous cannulas, raising the operating table level and applying vacuum assisted drainage. If unsuccessful, arterial flow may be impaired and protective actions such as hypothermia may be required to avoid ischemia.

Partial SVC obstruction affects the CPP (paper I, II)

In paper I, the CVP increased significantly in response to the SVC obstruction and returned to baseline upon release. In paper II, 75% obstruction of the SVC caused an almost 20-fold increase in CVP which caused a significant reduction of the CPP. Both interventions restored the CPP to baseline levels, but in the VP group the ICP and the SagP remained elevated during the intervention, while in the PR group these pressures returned to baseline.

While paper I demonstrated the effects on cerebral perfusion by progressive congestion, paper II suggests that maintaining appropriate CPP is important to preserve cerebral perfusion at least in the initial stage of SVC congestion. The congestion and the responses to the interventions were rapidly reflected in the NIRS monitoring, and the congruence with the induced changes supports the use of this cerebral monitoring during suspected SVC congestion.

Whereas superior venous congestion may negatively affect cerebral perfusion, evidence also suggests that moderate SVC obstruction can sometimes be well tolerated. In Sakamoto’s study, a 50% SVC flow reduction and a CVP level of 20 mm Hg did not adversely affect cerebral saturation. Maekawa et al reported preserved cerebral oxygenation at a CVP of 20 mm Hg when clamping the left SVC in patients with congenital heart disease. Their study proposed a CVP <30 mm Hg as safe in this respect. It seems possible that a CVP of 20-30 mm Hg represents a dangerous level, although the impact on CBF may not be entirely consistent.

Haugen et al described in 2006 that a CPP level of 50 mm Hg preserved the cerebral metabolism in pigs, while manifest ischemia occurred at a CPP of
20-25 mm Hg.(86) In an experimental study by Tanaka et al, cerebral auto-regulation remained intact in dogs even at a CPP of 30-40 mm Hg at a core body temperature of 20°C.(34) Also, the cerebral metabolic rate of oxygen was maintained down to a CPP of 30 mm Hg, before falling steeply. Tanaka’s findings were recently corroborated by Purins et al, who describe increased L/P ratios indicating ischemic metabolism below a CPP of 30 mm Hg in pigs.(20) In paper II, the results would be consistent with a threshold near a CPP of 33 mm Hg, which would be in line with previous findings, although autoregulation was not specifically examined.

Vasopressor treatment can temporarily improve cerebral perfusion (paper II)

Both the intracranial and the sagittal sinus pressures were increased by obstruction. In the VP group, these pressures remained elevated throughout the experiment, while in the PR group, where they returned almost to baseline. However, both strategies improved regional oxygenation, suggesting that both methods may be useful. The VP treatment aimed to raise the MAP within the autoregulatory range in order to increase the CPP and to thereby supersede the outflow resistance. This may lead to extravasation of fluid and a risk of edema, but whether this would be of relevance in the short term is unclear compared with the possible advantages associated with increased time margins to finish surgery. Long-term effects of vasopressor treatment are beyond the scope of the present study.

A confounding factor is that vasopressors have been reported to reduce cerebral oxygenation and CBF dose-dependently in volunteers.(87-89) However, in paper II, the effects of the two treatments appeared largely comparable regarding the CPP and cerebral oxygenation.

The S100β analysis showed no significant difference between the groups. This glial marker is a common tool to identify cerebral ischemic injury.(57) Increased release of S100β has been associated with cognitive dysfunction after CPB,(90, 91) but for prognostic purposes the evaluation of S100β is complicated by additional contribution from extra-cerebral sources, and by the so far non-clarified issue of an appropriate time window for sampling.(61-64) Even though the present data did not reveal any changes in S100β injurious effects of the SVC obstruction and/or interventions cannot be entirely excluded by the present study.
Arterial blood flow aspects (paper III, IV)

Main findings

Paper III
Pulsatile flow (P) during aortic cross-clamp did not enhance cerebral oxygenation compared with non-pulsatile flow (NP). The responses were subtle and varied between flow modes. MAP was significantly lowered by pulsatile CPB flow in all patients.

Paper IV
Hypothermia 20°C during CPB decreased the cortical CBF by 68%, from 0.31 ± 0.06 to 0.10 ± 0.02 ml/cm³/min (all animals). A SACP level of 6 ml/kg/min preserved that level of CBF. The cerebral glucose metabolism, measured by FDG uptake, did not differ between the two groups after re-warming the animals to 37°C.

The arterial flow profile did not affect the cerebral oxygenation (paper III)
We were not able to demonstrate any enhancement of cerebral oxygenation by applying pulsatile flow compared with non-pulsatile during aortic arch cross-clamping. The responses in cerebral oxygenation showed some variations, but the differences were subtle and the clinical significance uncertain.

The literature on possible benefits of changing flow profiles is not unanimous. In a study similar to ours, Grubhofer et al also examined pulsatile and non-pulsatile CPB flow impact with cerebral NIRS, but could not conclude that one mode was superior to the other.(92) Notably, patients with CS were not included in their study.

Pulsatile CPB has been advocated by some investigators, claiming advantages compared with non-pulsatile flow. Murkin et al have suggested that pulsatile CPB flow may decrease the incidence of myocardial infarction, major complications and death.(93, 94) Others demonstrate beneficial effects such as increased overall cerebral blood flow and cerebral oxygen saturation levels, reduced vascular resistance, and lower plasma free hemoglobin levels.(95, 96) In a review of 159 papers, Ji et al reports no evidence of adverse effects of pulsatile flow.(97) Instead, several papers described positive effects on hormone release, lung function, inflammatory response, and perfusion of vital organs.(97) However, other authors have remained skeptical and negative effects or conflicting findings have been described as well.(92, 98, 99)
Pulsatile flow decreased the arterial blood pressure (paper III)

MAP decreased during pulsatile flow compared with non-pulsatile, a phenomenon also described by Nakamura et al at clinically relevant CPB flow levels.(100) In line with this, increased MAP by non-pulsatile CPB flow has been reported by Mandelbaum et al and Giron et al.(101, 102)

MAP was significantly lower during pulsatile flow (P) than during non-pulsatile flow (NP) (P: 71.1 ± 5.5, NP: 75.5 ± 7.7 mm Hg, p = 0.025, all patients), but at the subgroup level, the reduction was significant only in the Controls (Controls; P: 70.1 ± 6.2, NP: 74.5 ± 5.3 mm Hg, p = 0.038 and CS; P: 72.2 ± 4.8, NP: 76.5 ± 9.8 mm Hg, p = NS).

The changes in MAP and the TOI across each observation period were calculated and tested for correlation, which was statistically significant when testing the entire material (r = 0.533, p = 0.015), but not at the sub-group level.

Studies of cerebral blood flow autoregulation in patients with carotid stenosis are sparse, but describes increased risk for cerebral damages in patients with impaired post-stenotic cerebral blood flow autoregulation due to exhausted vaso-reactivity, especially in association with high grade stenosis.(103, 104)

Modern CPB equipment offers the user a possibility to choose between pulsatile and non-pulsatile blood flow. Different practices exist, and it is not considered controversial to switch between the flow types in order to optimize organ perfusion. In case of arterial stenosis, induced hypertension can contribute to maintained post-stenotic flow by compensating for the pressure drop across the stenosis. From this perspective, the pressure peaks of the pulsatile flow may be of interest to ensure post-stenotic perfusion pressure.

However, the pulsatile technology is associated with some negative side effects. The properties of blood flow dynamics in constricted blood vessels, and technical limitations of the CPB system must be taken into account. Piskin et al describes that increased flow velocity generates post-stenotic turbulence with vortex formations, and non-linear relationships between post-stenotic pressure, flow velocity, wall shear stress and flow distribution.(105)

Moreover, when pressure peaks are generated by variations in the roller pump speed, the pump cycle contains an element of an instant pump speed reduction. This causes a transient phase of negative pressure in the oxygenator, which hypothetically could lead to the formation of gaseous CPB tubing emboli due to cavitation and possibly to excessive gas transfer across the porous oxygenator membrane.(106) Moreover, cavitation causes hemolysis and increased release of oxygen radicals.(107-109) Mulholland et al have demonstrated a linearly increasing rate of change in plasma free hemoglobin beyond a negative blood pressure threshold of approximately - 120 mm Hg, with exposure of the patient’s blood to the venous reservoir air interface as a superimposing factor.(110) Others regard negative blood pressures to be of minor
importance to hemolysis compared with other factors during CPB, such as blood contact with the pericardial cavity.(111)

The lower MAP during pulsatile flow is consistent with the findings by Nakamura et al,(100) and indicates that it may be possible to adjust the pulse settings to achieve a favorable MAP, preferably by reducing the pulse-cycle base flow or narrowing the pulse width. However, in our experience such measures appears to have very limited impact on general perfusion parameters. We applied a bench model in vitro to optimize the setting to avoid negative pressure cavitation, which was successful in the sense that the derived pulse wave settings generated peak blood flows that were close to the maximum oxygenator flows recommended by the manufacturers. On the other hand, the margins left to risk hemolysis due to negative pressure were safe.(110) Therefore, the potential of roller pump-induced pulsatility in order to improve post-stenotic flow conditions is likely to be limited.

The CBF at 20°C was downregulated (paper IV)

The CBF was measured using PET technique as described. The baseline level prior to CBP was on average (all animals) 0.29 ± 0.08 ml/cm³/min and on CBP 0.31 ± 0.06 ml/cm³/min. Cooling to 20°C reduced the CBF to 0.10 ± 0.02 ml/cm³/min which corresponds to -68%. The autoregulated flow level at deep hypothermia is of particular interest, since it may serve as a reference level in the search for adequate flow targets during SACP. Interestingly, the autoregulated CBF level of approximately 0.10 ml/cm³/min at 20°C coincided with the CBF generated by SACP (6 ml/kg/min), a flow level previously suggested to represent the minimal flow level to avoid ischemia in the present model.(50) (Figure 13) Similar observations have been made in dogs, where CPB at 20°C, resulted in a CBF of 10.0 ± 1.1 ml/100 g/min.(34)

SACP maintained the cerebral perfusion at 20°C (paper IV)

The SACP was maintained at 6 ml/kg/min for 45 minutes without any signs of impaired cerebral oxygenation on the StO₂ monitor. There were no significant differences either within- or between-groups that indicated ineffective cerebral perfusion at any time point.
Figure 13. Cerebral blood flow (CBF) [$^{15}$O]water PET scans in a pig subjected to selective antegrade cerebral perfusion (SACP) during 20°C cardiopulmonary bypass (CPB). The upper row shows a chronological order of sagittal images, and the lower row displays the simultaneously recorded transaxial view. Time points are, in order: at baseline rest, at 37°C CPB, at 20°C CPB, at 20°C SACP, and finally at full flow CPB after re-warming of the animal to 37°C. An autoregulated reduction of the CBF to a 0.10 ml/cm³/min level can be seen upon cooling the animal to 20°C. This flow level is then maintained during SACP with a 6 ml/kg/min (kg body weight) flow. CBF returns almost to baseline level upon re-warming to 37°C.

CBF and FDG uptake after re-warming (paper IV)

The repeated CBF measurements revealed that the CBF after re-warming was similar to baseline in both groups. Likewise, there was no significant difference in CBF between the groups at any time point.

In order to assess the cerebral glucose metabolism after re-warming to 37°C, the cortical net uptake ($K_i$) of FDG was measured after the decay of the last CBF measurement. There were no significant differences between the two groups, although some variability was seen, especially in the HCA group.

The limited number of experiments in paper IV does not allow for firm conclusions regarding post-ischemic metabolism. However, it appears that HCA does not extinguish the glucose metabolism after re-warming, and the same is true for HCA and SACP. This notion may be associated with both viability and ischemic susceptibility depending on clinical and environmental factors, and longer survival will be warranted in future experiments in order to clarify the optimal degree of early metabolic recovery after HCA, with or without SACP.

General aspects of cerebral protection during CPB (IV)

In this thesis, cerebral perfusion is regarded from a perspective of total organ perfusion or regional tissue perfusion. While it may appear uncontroversial to secure the nutritive requirements at a regional level, it is also important to recognize the differences in ischemic susceptibility between individual cells or groups of cells.
In an experimental study by Heiss et al, spontaneous single cell activity and local cerebral blood flow was measured in cats. The spontaneous electrical activity ceased in most cells at a CBF of 0.18 ml/g/min and neurons exposed to a mean blood flow of <0.14 ml/g/min for more than 45 minutes had a poorer prognosis for recovery. (112) Interestingly, there were also cells that tolerated extreme degrees of ischemia (<0.09 ml/g/min for 20 minutes) without losing ability to recover without losing ability to recover after circulation was restored.

Selective vulnerability of particular brain regions following global ischemia is correlated to local hypoperfusion, hyperglycemia and local temperature variations. Moreover, regional heterogeneity of glucose metabolism has been found to be predictive of cerebral tissue injury. (113) The difference in susceptibility between cells may be of relevance to the cell injury in areas of partial ischemia, the penumbra. It also underlines the importance of mechanisms beyond the numerical blood flow levels in the handling of SACP, (114, 115) although blood flow remains a biological fundament that is necessary to provide at a level compatible with survival. To that end, NIRS is a useful and reliable tool that promptly reacts to changes in perfusion, and the role of NIRS in standard monitoring is becoming increasingly established in cardiac surgery. (51)

In consistency with the stable hemodynamics, the SvO₂ and StO₂ levels were generally stable throughout the experiments. The observed decreases in StO₂ were below the threshold of 20-25% from baseline that has been suggested predictive of neurological injury. (116-118) However, there was an increase in systemic lactate, starting at CPB baseline. This indicates, at least partially, that there were other explanatory mechanisms than the HCA or SACP. We were not able to identify such mechanisms, and the stable hemodynamics throughout the experiment did not indicate anaerobic metabolism in any group.

While HCA has a long-standing tradition as a widespread method for ischemic protection, the clinical conduct of SACP has not been strictly defined with respect to flow rate and monitoring. Hopefully, this study and other works on the characteristics of these two protective approaches can contribute to a better understanding of key mechanisms and further refinement of the clinical practice.
Limitations

Paper I
The open and non-randomized protocol combined with the small number of experiments limited the possibility to make direct comparisons between the LQ and HQ groups. The lower MAP in the LQ group is likely to have generated lower CPP, possibly influencing the cerebral perfusion. Nevertheless, individual animals with signs of ischemic patterns appeared in both groups on combined analysis of TOI, SsvcO₂, and L/P ratio.

Paper II
The study lacks reliable predictors of cerebral outcome, although S100β has been associated with cognitive dysfunction after CPB,(91) albeit not undisputed.(90, 91) Sampling of cell damage markers directly from the cerebrospinal fluid might improve the sensitivity,(119, 120) but does not provide a definite surrogate for outcome studies.

Paper III
The study design was retrospective, open and merely observational. The degree of, or localization of stenotic carotid vessels was not taken into account. The observation time was brief and the power of the study did not allow multifactorial analysis.

Paper IV
The relatively low spatial resolution of the PET images in combination with the relatively small pig brain does not allow extensive interpretations of the image material with regards to anatomy. The limited number of animals in each study group does only enable estimates of the cerebral metabolism after SACP and HCA, and the width of the gap to the clinical situation is uncertain.
Summary and future perspectives

This thesis focuses on important aspects of clinical problems during cardio-pulmonary bypass (CPB). The experimental model used in paper I demonstrated ischemic patterns in the brain of animals subjected to superior venous congestion in a common clinical setup. In paper II, the same model was applied in a therapeutic experiment where two interventions to normalize the cerebral perfusion pressure (CPP) during venous congestion were tested. We could demonstrate that both strategies were successful and that the model, to that end, was adequate.

Besides the venous drainage, the other main aspect of CPB is the arterial flow, of which 1) the arterial flow level and 2) the flow profile (pulsatile, non-pulsatile) represent two main clinical parameters. The arterial flow level is commonly derived from a stipulated flow index and an anthropometric estimate of the body surface area. However, both the flow level and profile may need adjustments due to individual circumstances. In paper III, the effects on cerebral oxygenation and hemodynamics by switching between pulsatile and non-pulsatile flow were tested during standard CPB. The effects were subtle both in patients with and without carotid stenosis, and the main observation was that the arterial pressure was lower during pulsatile flow.

In paper IV, we quantified the cerebral blood flow (CBF) during selective antegrade cerebral perfusion (SACP), a common method used to protect the brain from ischemia during aortic surgery in hypothermic circulatory arrest (HCA). The arterial flow level used was derived from a previous study where the minimal safe pump flow level was determined as 6 ml/kg/min in the same model. The CBF was measured with positron-emission tomography (PET) and the level was found to be approximately 0.1 ml/g/min.

The intention with all studies was to improve the understanding of physiology during CPB. For the experimental animal studies, an important purpose was also to contribute to the development of functional models that enable controlled test environments for clinical problems related to CPB. It is my hope that this thesis may convey insights that turn useful in clinical practice and future CPB research.
Conclusions

- Experimental SVC obstruction can impair cerebral perfusion, and the response varies between individuals
- During bi-caval CPB, obstruction of the SVC may be underestimated or pass undetected due to redistribution of venous flow to the IVC
- Both vasopressor and increased venous drainage were effective as strategies to restore the CPP after 75% superior venous congestion
- Pulsatile, compared to non-pulsatile, flow was associated with decreased arterial pressure but not with altered cerebral oxygenation in patients with or without carotid stenosis
- The CBF was autoregulated to approximately 0.10 ml/g/min which corresponds to -68% compared to baseline during deep hypothermia
- A SACP pump flow of 6 ml/kg/min maintained the CBF at approximately 0.10 ml/g/min
- The FDG uptake, reflective of cerebral glucose metabolism, was comparable at normothermia in SACP compared with HCA alone
Optimering av hjärnans blodflöde och metabolism är viktigt för att minska risken för neurologiska skador i samband med hjärtkirurgi där hjärt-lungmaskin (extra-korporeal cirkulation, ECC) används.

Denna avhandling baseras på djurexperimentella och kliniska studier med ECC. I det första arbetet studeras försämrat venöst avflöde från den övre kroppshalvan och dess effekter på hjärnans cirkulation hos gris. Denna situation medför stegrade venösa tryck vilket i sin tur kan påverka hjärnans cirkulation negativt, vilket avspeglades i nedsatt syresättning i hjärnvävnaden. Man kunde även iaktta att negativ balans mellan ämnesomsättning och tillförsel av syre, så kallad ischemi, förekom i vissa djur men inte i alla. En annan effekt av att avflödet från den övre kroppshalvan minskades var att motsvarande flöde från den nedre kroppshalvan ökade. Detta fenomen riskerar att undgå upptäckt om det inte kontrolleras specifikt.

I det andra arbetet användes samma experimentella modell för att testa två metoder att återställa hjärnans blodflöde trots det försämrade venösa avflödet. Efter att avflödet från den övre kroppshalvan minskats med 75% sågs en minskning av det blodtryck som avgör hjärnans cirkulation, det cerebrala perfusionstrycket (CPP), som förväntat. Djuren lottades till behandling med ansting av kärlsammandragande läkemedel eller med förbättrat venöst avflöde. Båda metoderna förbättrade CPP och hjärnans syresättning, vilket visar på en åtminstone kortsiktig möjlighet att förbättra hjärnans cirkulation vid denna typ av problem vid ECC.

I det tredje arbetet beskrivs effekterna av pulserande och icke-pulserande flöde under ECC hos 20 patienter som fått båda varianterna underst sin hjärtoperation. Hos hälften av patienterna fanns en känd förträngning av någon halsartär och hos den andra hälften fanns ingen känd sådan förträngning. Resultatet visade att pulserande flöde var associerat med lägre artärblodtryck. Det anges i viss litteratur att pulserande flöde kan ha gynnsamma effekter på cirkulationen, men inga sådana effekter på hjärnans syresättning kunde iakttas.

I det fjärde arbetet studerades experimentellt blodflödet i hjärnan i den situation där kroppen har kylts till 20°C, cirkulationen stängts av till övriga kroppen (hypoterm cirkulationsarrest, HCA) och endast huvudet försörjs med blod (selektiv antegrad cerebral perfusion, SACP). Mätningarna utfördes med positron-emissionstomografi (PET) på grisar. Cirkulationen visade sig kunna anpassa hjärnans blodflöde till en lägre nivå (0,10 ml/cm³/min) vid 20°C och
ECC. Därefter gavs grisarna antingen SACP på en flödesnivå som tidigare visat sig ge skydd mot ischemi, alternativt var cirkulationen helt avstängd under motsvarande tid; ca 45 min. Flödet under SACP visade sig ligga stabilt på samma nivå (0,10 ml/cm³/min) utan tecken på försämrad syresättning i hjärnan. Därefter värmdes grisarna till 37°C och ämnesomsättningen studerades i form av hjärnans upptag av fludeoxyglukos (FDG). Inga säkra skillnader kunde påvisas mellan HCA och HCA+SACP.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)