Stroke during cardiac surgery; risk factors, mechanisms and survival effects

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To my family
ABSTRACT

Introduction: Neurological complications and stroke in association with cardiac surgery is a serious problem. The stroke event can occur during surgery (early stroke) or in the postoperative period with a symptom free interval (delayed stroke). Particle embolization due to aortic manipulation during surgery has been suspected as a mechanism for early stroke. The present thesis address mechanisms and survival effects of stroke both clinically (I-III) and experimentally (IV-V).

Methods: Study I) Within a cohort of 2641 consecutive cases, a group of cardiac surgery patients with stroke and evaluated by computed tomography (CT) were studied (n=77). CT-findings were analyzed in relation to stroke symptoms. Study II) Data from 9122 patients undergoing coronary surgery were analyzed. Records of patients with any signs of neurological complications were reviewed to extract 149 subjects with stroke at extubation (early, 1.6%) versus 99 patients having a free interval (delayed, 1.1%). Early and delayed stroke were evaluated separately. Independent risk factors for stroke were analyzed by logistic regression and survival by Cox regression (9.3 years median follow-up). Study III) Patients with early (n=223) and delayed stroke (n=116) were identified among 10809 patients undergoing cardiac and aortic surgery, both groups exposed to cardiopulmonary bypass. Stroke patients were subdivided by the hemispheric location of lesions. Subgroups were compared and their associated pre- and peroperative variables and survival were analyzed. Study IV) Aortic cross-clamp manipulation was studied in a human cadaveric perfusion model. The pressurized aorta was repeatedly cross-clamped and washout samples were collected before and after clamp maneuvers. Particles in the washout samples were evaluated by microscopy and by digital image analysis. Study V) Pig aortas were pressurized and cannulated. Washout samples were collected before and after cannulation (n = 40). Particles were deposited onto a 10-μm filter to be evaluated by microscopy and digital image analysis.

Results: Study I) In the group of patients exposed to routine cardiac surgery (i.e., clamping and cannulation) and with early stroke, right-hemispheric lesions were more frequent than of the contra-lateral side (P=0.005). Patients with aortic dissections had a strong dominance of bilateral findings, which was different from the unilateral pattern in the routine-surgery group (P<0.001). Study II) Early and delayed stroke did not share any risk factors. Both early and delayed stroke explained mortality in the early postoperative period (P<0.001, P<0.001 respectively) but also at long term follow-up (P=0.008, P<0.001 respectively). For patients surviving their first postoperative year, delayed but not early stroke influenced long-term mortality (P=0.001 and P=0.695, respectively). Study III) Stroke lesions in association to cardiac surgery were near exclusively ischemic. Early stroke had a preponderance for right-hemispheric lesions (P=0.009). In contrast, patients with early stroke that had undergone surgery of the aorta with circulatory arrest showed a pattern with more bilateral lesions compared to 'cardiac-type' operations (P<0.001). Patients with bilateral lesions had a dramatically impaired survival compared to those with unilateral lesions (P<0.001). Study IV) In the cadaveric perfusion model, cross-clamping produced a significant output of particles, which was seen for size intervals of 1 mm and smaller (P=0.002 to P=0.02). In all size intervals the particle output correlated with the degree of overall aortic calcification (P =0.002 to P=0.025). Study V) At cannulation of the pig aorta, more particles were noted after cannulation compared to before the maneuver (P<0.001). This increase included small (<0.1 mm, P<0.001) and intermediate-size particles (0.1-0.5 mm, P< 0.001). Particles above 0.5 mm were few and were not associated with cannulation.

Conclusions: The influence of stroke on mortality was devastating, for both early and delayed stroke. These two stroke groups had obvious differences in both their risk factors and their hemispheric distribution. It is here emphasized that early and delayed stroke should be considered as two separate entities with suggested mechanistic differences. Ischemic lesions accounted for near all stroke events seen in association to cardiac surgery. For early stroke, these were mostly located within the right hemisphere. Results from the experimental studies underscore microembolic risks associated with aortic manipulation.

Key words: stroke; cardiac surgery; adult; risk factors; mortality; embolism; aortic cross-clamp; aortic cannulation.
Stroke during cardiac surgery; risk factors, mechanisms and survival effects

**POPULÄRVETENSKAPLIG SAMMANFATTNING På SVENSKA**

**Stroke i samband med hjärtkirurgi; riskfaktorer, mekanismer och effekter på överlevnad**

**Bakgrund:** Hjärnskador är en fruktad komplikation till hjärtkirurgi. Skadorna omfattar allt från milda kognitiva nedsättningar till omfattande stroke och hjärnödem. Stroke kan inträffa i samband med operationen och noteras då patienten väcks (tidig stroke) eller uppträda senare i förloppet (sen stroke). Mekanismerna bakom stroke är ännu inte helt kända men partikelfrisättning från aorta under operationen tros vara en viktig faktor. Vid ingreppet utsätts aortan för en förhållandevis brutal manipulation dels då kirurgen kanalerar aortan för att koppla in hjärt-lungmaskinen men även då cirkulationen till hjärtat stängs av med en tång på aorta. Denna avhandling syftar till att analysera mekanismer och överlevnadseffekter av stroke i både kliniska (I-III) och experimentella studier (IV-V).

**Metod:**

*Delarbete I)* Bland 2641 hjärtopererade patienter identifierades de som drabbats av stroke och som utretts med en datortomografi (DT) av hjärnan (n=77). DT-fynd och symtom analyserades.

*Delarbete II)* Data från 9122 patienter som genomgått kranskärlskirurgi utvärderades. Journaler från patienter med postoperativ neurologisk avvikelse granskades. Man fann 149 patienter med tidig stroke (1.6%) och 99 patienter med sen stroke (1.1%). Tidig och sen stroke utvärderades separat för riskfaktorer samt effekter på kort- och långtidsöverlevnad (i medeltal 9.3 års uppföljning).

*Delarbete III)* Patienter med tidig stroke (n=223) och sen stroke (n=116) identifierades i en grupp av 10809 patienter som genomgått hjärtkirurgi eller kirurgi på brö斯塔orta. Patienterna delades in i grupper beroende på vilken/vilka delar av hjärnan som drabbats och grupperna jämfördes för att hitta eventuella skillnader i bakomliggande faktorer.


**Resultat:**

*Delarbete I)* Hos patienter som genomgått rutinmässig hjärtkirurgi och som drabbats av tidig stroke var skador i höger storhjärnshalva vanligare jämfört med skador på vänster sida (P=0.005). Patienter opererade för en aortadissektion hade vanligen skador i båge storhjärnshalvorna. *Delarbete II)* Tidig och sen stroke skiljde sig åt genom att inte ha några gemensamma riskfaktorer. Både tidig och sen stroke ökade risken för att avlida på såväl kort (P<0.001, P<0.001) som lång sikt (P=0.008, P<0.001). För patienter som överlevde det första året hade dock endast de med sen stroke en fortsatt ökad dödlighet. *Delarbete III)* Patienter med tidig stroke hade en dominans av skador i höger storhjärnshalva (P=0.009). Hos patienter opererade i cirkulationsstillestånd sågs en större andel med skador i båge storhjärnshalvorna jämfört patienter med genomgått rutinmässig hjärtkirurgi (P<0.001). Patienter med skador i båge storhjärnshalvorna hade kraftigt försämrad överlevnad (P<0.001). *Delarbete IV)* Tångmanipulation av aorta frisatte en betydande mängd partiklar, men av liten storlek (1 mm och mindre). Antalet frisatta partiklar stod i proportion till grad av aortaförkalkning.

*Delarbete V)* Kanylering av grisaorta frisatte små (<0.1 mm, P<0.001) och mellanstora partiklar (0.1 -0.5 mm, P<0.001). Partiklar större än 0.5 mm var få och hade ingen relation med kanylering.

**Konklusioner:** Patienter som drabbas av såväl tidig som sen stroke i samband med hjärtkirurgi har kraftigt försämrad överlevnad. Dessa två grupper av stroke har påtagliga skillnader vad gäller riskfaktorer, DT-fynd och symtommönster. Tidig och sen stroke bör därför betraktas som två olika företeelser. Resultaten från de experimentella studierna framhåver de mikroembolisiska risker som förknipps med aortamanipulering.
This thesis is based on the following papers that are referred to by their roman numerals I-V:

I. Hedberg M, Boivie P, Edström C, Engström KG.
Cerebrovascular accidents after cardiac surgery: An analysis of CT scans in relation to clinical symptoms.

II. Hedberg M, Boivie P, Engström KG.
Early and delayed stroke after coronary surgery - an analysis of risk factors and the impact on short and long-term survival.
*Manuscript, submitted.*

III. Hedberg M, Engström KG.
Hemispheric distribution of stroke after cardiac surgery – patient characteristics and survival impact.
*Manuscript, submitted.*

IV. Boivie P, Hedberg M, Engström KG.
Size distribution of embolic material produced at aortic cross-clamp manipulation.

V. Hedberg M, Funck B, Engström KG.
Cannulation of the Noncalcified Aorta Generates Particles of Microembolic Nature: An Experimental Study Using Pig Aorta.
ABBREVIATIONS

TIA  transient ischemic attack
CT   computed tomography
MRI  magnetic resonance imaging
CPB  cardiopulmonary bypass
CABG coronary artery bypass grafting
OPCAB off-pump coronary artery bypass
COMB coronary surgery in combination with aortic and/or mitral valve procedures
ROC  receiver operating characteristics
AUC  area under curve
HR   hazard ratio
CI   confidence intervals
MCA  middle cerebral artery
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INTRODUCTION

The era of modern cardiac surgery began in the 1950s when the cardiopulmonary bypass technology was developed. Since then, an astonishing evolution of methods has been seen in the field of cardiac surgery and with improved results. Each year, hundreds of thousands of patients undergo cardiac procedures worldwide and about 7,000 are performed in Sweden. Neurological complications were early recognized as a problem. Despite advances in operative techniques and cardiac anesthesia, neurological complications remain an important cause of mortality and morbidity.

Stroke definitions

The World Health Organization defines stroke as; suddenly (within seconds), or at least rapidly (within hours), developing clinical signs of focal or global disturbance of cerebral functions, with symptoms lasting for 24 hours or longer or leading to death, with no apparent cause other than of vascular origin. If the symptoms and signs completely disappear within 24 hours the event is defined as a transient ischemic attack (TIA). Symptoms and signs of stroke are caused by the interrupted brain perfusion leading to tissue damage.

Stroke in the general population

In the general population, 80% of all stroke events are ischemic whereas intracerebral and subarachnoid hemorrhages account for 20% together. Ischemic strokes are caused by thrombi or by emboli from the carotid arteries or the heart. Computed tomography (CT) is the main diagnostic tool in acute stroke and is very reliable in distinguishing between ischemic and hemorrhagic lesions. However, despite advances in CT technology this method has limitations in detecting early ischemic lesions, especially in the posterior circulation. Magnetic resonance imaging (MRI) and diffusion-weighted MRI has been shown to be more sensitive tools for detection of early and small ischemic changes.

Stroke in conjunction with other procedures than cardiac surgery

Patients undergoing non-cardiovascular procedures are also at risk of stroke. The rate of perioperative ischemic stroke after non-cardiovascular surgery has been reported to be in the range of 0.2% and 0.7%. Stroke is also an identified complication to cardiac catheterizations with rates of 0.10% for diagnostic catheterizations and between 0.12% and 0.38% for interventional procedures. After pulmonary vein ablations, stroke rates between 1% and 5% have been reported.

Stroke and other neurological complications in cardiac surgery

Neurological complications after cardiac surgery vary from mild cognitive decline to fatal stroke. According to the American Heart Association and American College of Cardiology, postoperative neurological deficits can be subdivided into two categories. Type I deficits are associated with major, focal deficits, stupor and coma. Type II deficits are without detectable focal lesions but are instead associated with diffuse symptoms in terms of confusion, agitation, memory deficits and deterioration in intellectual function. Type I deficits have reported frequencies in between 1.6% and 8.4%, whereas type II deficits are more common. Depending on diagnostic methods and when type II symptoms are studied, the frequency ranges between 15% and 66%.

Patients undergoing cardiac surgery are not only at risk of stroke during the procedure but also in the postoperative period. In the majority of previous studies, stroke has been investigated without considering the timing details. With these merged together, potential mechanistic differences between strokes occurring during surgery and in the postoperative period cannot be explored. Only a few reports are available which address to what extent early and delayed stroke differ in risk factors and in hemispheric distribution.

Risk factors for stroke in cardiac surgery

Previous studies have recognized several risk factors for stroke. Commonly reported preoperative risk factors are; advanced age, female gender, history of cerebrovascular events, history of diabetes mellitus, impaired left ventricular function, history of hypertension and peripheral vascular disease. Identified intra- and postoperative risk factors are; extensive aortic atherosclerosis, prolonged time on cardiopulmonary bypass (CPB), atrial fibrillation and prolonged inotropic need.
Stroke mechanisms in cardiac surgery
Among suggested mechanisms behind neurological complications are; cerebral hypoperfusion during CPB,27-29 air embolism,30,31 inflammatory mechanisms32 and fat microembolism from retrieved pericardial suction blood.33,34 However, embolization from the ascending aorta is considered as the major cause of stroke.23 Aortic manipulation is believed to cause the embolization by different mechanisms; aortic cannulation, cross-clamping, and aortic cannula stream jets.35,36 From intraoperative use of transcranial Doppler ultrasound, embolic risks at aortic cannulation and at cross-clamping have been identified.36-38 In general, Doppler measurements report the number of recorded signals, but have limitations in terms of distinguishing between gaseous and solid particles, and to measure particle size.39 While Doppler-studies are numerous there are few in vitro studies on aortic manipulation and embolic particles.

Hemispheric distribution of stroke
The anatomical distribution of stroke may have importance for the understanding of stroke mechanisms. In a previous study at our institution, symptoms of stroke were analyzed and a dominance of left-sided symptoms (right hemisphere) was found for early stroke.21 It was suggested that the predominance of lesions within the right hemisphere is caused by emboli being expelled into the brachiocephalic trunk. High-density emboli are subject to centrifugal force during their passage into the aortic arch. A few other studies have also reported a dominance for right hemispheric lesions.5,6,40-41 However, none of these studies have separated stroke into early and delayed forms for their analysis of hemispheric distribution. A contradictory report stated a dominance of left hemispheric lesions, assumed to be caused by cannula stream jets directing particles to the left common carotid artery.42

Survival after stroke
Stroke in conjunction with cardiac surgery is associated with poor outcome. Many studies have reported a highly impaired short-term survival for stroke patients, with an inhospital mortality ranging between 17% and 24%, to be compared with 1.5%-to-4.6% for non-stroke patients.5,4 The knowledge about the long-term survival effects of stroke is limited, especially beyond 10 years of follow-up. Dacey and coworkers analyzed coronary artery bypass grafting (CABG) and concluded that the greatest risk of death was within the first postoperative year, but, with a sustained mortality effect during the following 10-year follow-up.43 None of these studies have separated early and delayed stroke in their survival analyses.

Surgical strategies to avoid cerebral embolization
The area of cerebral protection during cardiac surgery includes a wide range of various protective methods. A subset of methods to avoid cerebral embolization is here referred. Off-pump coronary artery bypass (OPCAB) has been suggested to have less cerebral complications compared to conventional on-pump techniques.44,45 Other studies have failed to prove this advantage with OPCAB in terms of neurological outcome.46-47 In a recent randomized trial, on-pump CABG was found to be superior to OPCAB with respect to survival and graft patency and with no differences in neurologic outcome.48 Off-pump techniques can be combined with methods to avoid aortic manipulation from proximal anastomoses (no touch technique), and thereby reducing the risk of cerebral embolization.49 The use of a side-biting clamp can also be avoided by means of a membrane-sealing device while suturing the proximal anastomoses. Another example is the use of automatic anastomotic devices for the aorto-saphenous vein connections. Repetitive clamping can be avoided by a single-clamp approach during on-pump CABG, with potential benefits.50 Another approach to protect against emboli is by using an intra-aortic filter.51 Moreover, the usage of side-hole instead of end-hole cannulas have been suggested to decrease cerebral embolization by avoiding unfavorable stream jets from damaging the aortic wall.35
AIMS

The aims of the thesis were:

Study I  To evaluate CT-findings and symptoms of stroke in association with cardiac surgery, in terms of hemispheric and vascular distribution.

Study II  To separately evaluate early and delayed stroke for risk factors and to analyze their individual impact on short and long-term survival.

Study III  To analyze differences between bilateral, right and left hemispheric stroke in terms of patient characteristics and survival.

Study IV  To analyze the size distribution of particles produced at cross-clamp manipulation of the ascending aorta in a human cadaveric perfusion model.

Study V  To evaluate the embolic risks associated with cannulation of the non-calcified aorta in a pig aortic perfusion model.
MATERIAL AND METHODS

Study I-III

Patient cohorts

In study I, consecutive cardiac surgery patients operated at the Cardiothoracic Department/Heart Center of Umeå University Hospital between January 1999 and May 2001 were analyzed (n=2641). This patient cohort had history from a previous study with focus on stroke symptoms but was here reevaluated to review cerebrovascular events in perspectives of CT findings. CT scans were available in 77 patients with stroke or with TIA (Figure 1). Patients were stratified by the type of surgery performed. The group ‘cardiac type’ included all procedures employing CPB but excluded surgery due to aortic dissections. Aortic dissections were separately studied. Isolated CABG procedures were also extracted for a separate analysis among the ‘cardiac type’ procedures.

In study II-III the patient inclusion was expanded to incorporate patients operated between January 1994 and December, 2004 (n=11342). Some patients undergoing re-do procedures reoccurred in the dataset and were handled as separate cases in the analysis. In study II, three surgical groups were extracted, all sharing CABG; isolated on-pump CABG, OPCAB, and coronary surgery in combination with aortic and/or mitral valve procedures (COMB, Figure 2). Two surgical groups were extracted for study III, all sharing CPB. Aortic aneurysm or dissections operated on using circulatory arrest and deep hypothermia (25°C or colder) constituted the ‘vascular’ group (Figure 3). Eight patients undergoing deep hypothermia for other reasons than aortic procedures were excluded. All remaining procedures were included in the other group, referred to as ‘cardiac type’.

Patients with foreign citizenship were not available to survival follow-up and were omitted (n=5, n=14). The analyses in study II and III aimed at evaluating stroke, and therefore, a post-operative evaluation was required. Patients dying in the operating theatre or within the first 24 hours could not be diagnosed with stroke and were therefore excluded (n=50, n=118, in study II and III, respectively). In order to avoid uncertain stroke diagnosis patients with short episodes of neurological symptoms (i.e., TIA) were excluded (n=28, n=28). Some patients had neurological deficits explained by other etiologies (e.g., spinal cord ischemia, preoperative symptoms, or global ischemia due to heart-lung resuscitation) and were also excluded (n=30, n=64). In total, 9122 patients were analyzed in study II, subdivided into 7839 CABG, 297 OPCAB and 986 COMB procedures (Figure 2). A total of 10809 patients were analyzed in study III, subdivided into 10642 ‘cardiac-type’ and 167 ‘vascular’ procedures (Figure 3).
Clinical database 1994-2004 
(n=11 342)

OPCAB
(n=301)

Surgery in DHT but 
not ‘vascular’
(n=8)

Dead <24 h or foreign 
citizen (n=132)

‘Cardiac type’/’Vascular’
(n=10 901)

Neurological deviation 
in database (n=720)

Stroke 
(n=339)

None-verified 
neurological 
deviation (n=289)

Early stroke (n=223)

Delayed stroke (n=116)

Hemispheric early 
stroke (n=171)

Hemispheric delayed 
stroke (n=97)

Control group 
(n=10470)

STUDY III
(n= 223+116+10470 = 10809)

TABLE 1. Variables in the database regarding neurological symptoms

<table>
<thead>
<tr>
<th>Neurological deviation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced level of consciousness</td>
<td>153 (1.3%)</td>
</tr>
<tr>
<td>Unconsciousness</td>
<td>50 (0.44%)</td>
</tr>
<tr>
<td>Paresis right leg</td>
<td>88 (0.77%)</td>
</tr>
<tr>
<td>Paresis left leg</td>
<td>121 (1.0%)</td>
</tr>
<tr>
<td>Paresis right arm</td>
<td>89 (0.78%)</td>
</tr>
<tr>
<td>Paresis left arm</td>
<td>143 (1.2%)</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>26 (0.22%)</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>88 (0.77%)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>78 (0.68%)</td>
</tr>
<tr>
<td>Balance problem</td>
<td>237 (2.0%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>27 (0.23%)</td>
</tr>
<tr>
<td>Blindness</td>
<td>4 (0.035%)</td>
</tr>
<tr>
<td>Visual field loss</td>
<td>66 (0.58%)</td>
</tr>
<tr>
<td>Impaired visual focus</td>
<td>41 (0.36%)</td>
</tr>
<tr>
<td>Moderate delirium*</td>
<td>760 (6.7%)</td>
</tr>
<tr>
<td>Severe delirium*</td>
<td>190 (1.6%)</td>
</tr>
<tr>
<td>Other neurological deviation</td>
<td>193 (1.7%)</td>
</tr>
<tr>
<td>Total with neurological symptoms except delirium</td>
<td>734 (6.4%)</td>
</tr>
</tbody>
</table>

*Variables not used for the extraction of patients with possible stroke.


data accuracy was presumed, and the exact day of death was provided.

Protocol for stroke evaluation

The database contained 17 variables describing different postoperative neurological symptoms (Table 1). These included two variables referring to postoperative delirium which was beyond the scope of the present analyses but served as background information in the review of patient records. The search for neurological symptoms extracted 734 patients from the analyzed cohort (n=11342, Table 1). The records for these patients were reviewed for the different studies (Figures 1-3).

In the review of patient records a protocol was used to confirm the diagnosis of stroke and to separate the patients into early and delayed stroke groups. For most patients the diagnosis was obvious at the time of the event. However, for patients with uncertain diagnosis the symptom patterns, neurologist reports, and/or CT findings were evaluated to confirm the stroke. Stroke definitions were according to routine guidelines. Patients with neurological deficits explained by other etiologies (exemplified by acute preoperative stroke, global ischemia following heart and lung resuscitation, and spinal cord ischemia) were excluded from the analysis. Other patients not fulfilling the stroke criteria were grouped together with the control subjects. Early stroke was defined as symptoms observed at extubation whereas delayed stroke followed a symptom-free interval after extubation.

Anatomical subdivision of stroke

In study I, reports from CT scans were systematically reviewed in detail according to a protocol. Ischemic and/or hemorrhagic lesions were categorized with respect to anatomical level (cerebrum, cerebellum, and brainstem), size (lacunar/territorial), hemispheric side, and vascular territories. The protocol also separated acute from old lesions, handled separately. Definitions of vascular territories were according Osborn’s Diagnostic Neuroradiology.58

In study III cerebral stroke was evaluated and subdivided into hemispheric right/left or bilateral lesions. This
subdivision considered both symptoms and CT-findings. Some of the patients with stroke could not be classified as hemispheric, exemplified by patients with cerebellar or brain-stem lesions. These patients were not included in the analysis.

Peroperative management
Surgical procedures and anesthetic management were according to routine and contemporary methods. Anesthesia was generally induced with propofol, fentanyl and/or midazolam. Pancuronium was used for muscle relaxation in most cases. Anesthesia was maintained with a combination of fentanyl boluses, continuous infusion of propofol and/or isoflurane.

The great majority of on-pump CABG procedures used standard aortic cross-clamping followed by partial clamping of the aorta for proximal anastomoses. In most cases the aortic quality was assessed by palpation only, otherwise by aortic scanning. The standard CPB set-up included; moderate hypothermia, cardioplegic arrest, using a curved-tip/end-hole aortic cannula, and with recycling of pericardial suction blood. Open-heart procedures comprised routine venting via the apex, pulmonary vein, or the pulmonary artery. Carbon dioxide wound flushing was introduced at the end of the study period. For most procedures involving circulatory arrests and deep hypothermia no cerebral perfusion was used. In some operations retrograde cerebral perfusion was applied whereas antegrade cerebral perfusion was introduced in more recent years of the study period. Unfortunately, use of carbon dioxide or methods for cerebral perfusion was not recorded in the database.

Study IV
Perfusion model
Embolism associated with aortic cross-clamping was studied in a perfusion model using human cadaveric aorta. The study reevaluated microscopic slides with particulate matter derived from two previous studies. In total, experimental data from 27 subjects undergoing autopsy were analyzed. Both these studies (10 and 17 subjects, respectively) analyzed particle debris generated at aortic cross-clamping and shared the same perfusion model and the initial procedures of aortic manipulation. The aorta (ascending aorta, aortic arch, and part of the descending aorta) was freed from surrounding connective tissue, branches and small vessels were sealed, and a perfusion cannula was connected to the descending part. The cannula delivered perfusion medium (9 g/L NaCl in pre-filtered deionized water) at a constant hydrostatic pressure of 60 mmHg. The aorta was flushed to remove debris. The procedure followed a standardized protocol. A baseline sample was collected in a 50-mL test tube prior to manipulation. The ascending aorta was clamped (standard 70-mm aortic cross-clamp, Pilling Co, Fort Washington, PA, USA) and the clamp jaws were sutured to the adventitia to allow repeated clamping at the same location. The clamp was closed to half of its range of cogs. The cross-clamp was opened and closed under pressure to stepwise collect washout samples. The procedure was repeated 10 cycles.

The aorta was cut open after the perfusion experiment. The magnitude of overall calcifications was graded using a semi quantitative scale (0 = normal to 4 = porcelain aorta). The characteristics of plaques and the aortic dimensions were recorded.

Sample processing
Washout samples were centrifuged. In each sample the supernatant was aspirated leaving the deposit in the test tube. The particle deposit was resuspended in deionized and filtered water to lyze remaining erythrocytes. After a repeated centrifugation the deposit was fixed for 10 minutes in 4% formaldehyde in phosphate buffer. Fixation was ceased by another set of centrifugation and water resuspension, followed by staining (both Cresyl-Violet and Giemsa were used) and with two additional washing/centrifugation cycles. The deposit was spread onto a microscope slide and left to dry at room temperature. If heavily condensed, the sample was separated onto additional slides to enable reliable image analysis.

Image analysis
Deposits from the two previous studies were here merged and reevaluated according to a new protocol and with the aim of subdividing particles by size. Slides with particle deposits were analyzed both macroscopically (Sony DXC-101P, Tokyo, Japan) and microscopically (Olympus CK40-F200, Olympus Optical Company Ltd, Tokyo, Japan, and camera C5405-01 Hamamatsu Photonics, Hamamatsu City, Japan). The microscope was of inverted type and was equipped with a CDPlan x10-FPL objective lens. The digital analysis (Zeiss KS 300, version 3.0, Carl Zeiss Vision GmbH, Hallbergmoos, Germany) was based on grayscale images with a x 327 magnification within the frame grabber. The resolution was 1.1 µm/pixel whereas a digital filter was
applied to count particles having a minimum size of 2x2 pixels (3.1 µm diagonal). Essentially, the analysis followed similar routines to that previously described. However, the image analysis was here refined. Focus was on solid particles with an embolic potential and the settings of the image analysis were adjusted thereby. Results from the macroscopic and microscopic evaluation were also merged to form a continuous diameter span for the identified particles rather than evaluating the two methods separately.

At macroscopic evaluation the entire deposit was scanned in one view. When washout samples were deposited onto more than one slide, each slide was scanned and the particle results were merged. The microscopy analysis did not cover the entire area of the deposit. Three views were randomly selected by arbitrarily changing the coordinates of the microscope stage. This routine reduced the influence from unevenly distributed particles within the deposit. From these three measurements the overall particle output was calculated. This procedure was made possible by measuring the area of the particle deposit on each slide, in relation to the area of the three recorded microscopic views. The type of sample was unknown to the investigator during analysis to avoid bias. Microscope and image-analyzer settings were adjusted to avoid duplicate measurements between the macroscopic and microscopic approaches. This becomes relevant when the results from the two methods are merged into a continuum of particle diameters. Particle counts and their individual maximum diameter were recorded and the particles were categorized by diameter size. The experimental steps described above, and to calculate the absolute number of particles, are new to this study compared with the underlying reports.

Study V
Perfusion model
It was hypothesized that the sharp tip of the aortic cannula may shear off aortic-wall tissue which becomes expelled into the lumen. A perfusion model was developed to test this hypothesis (Figure 4). The model had similarities to the one described in study IV. However, the present model used antegrade perfusion and non-calcified aortas. Aortas were obtained from freshly sacrificed pigs (6 months of age and weighing approximately 120 kg). The heart, lungs and great vessels were removed en block and immediately refrigerated before transportation to the laboratory.

The aorta was cannulated, which due to technical reasons was performed on the thoracic part of the descending aorta rather than the ascending counterpart. This part of the aorta also allowed repetitive cannulations to be stepwise performed. The aorta was freed from surrounding tissue and branches were sealed. Antegrade perfusion was provided via a modified venous-return cannula (28F model 69428, DLP Inc., Grand Rapids, MI, USA) connected in the aortic root (Figure 4). The perfusion had a feeding pressure of 77 mmHg delivered from an elevated medium reservoir. The perfusion medium consisted of filtered de-ionized water with 9 g/L NaCl added. The temperature was found to influence the aortic tissue compliance. To more realistically simulate surgical conditions the perfusion medium was heated to 37°C in a blood-cardioplegia heat exchanger (COBE Cardiovascular, Inc. Arvada, Colorado USA). The aorta was carefully flushed prior to the series of repeated experiments in order to remove luminal debris.

Aortic cannulation and washout sampling
The cannulation required a pressurized aorta, similar to the surgical conditions, and which necessitated a cross-clamping to be positioned distally (standard 70-mm aortic clamp, Pilling Co, Fort Washington, Pa). As demonstrated in study IV with human cadaveric aorta, cross-clamp manipulation dislodged intimal particles. However, the amount of particles declined towards the baseline after five repeated clamp maneuvers. In line with this knowledge, the protocol included five repeated clamp and flush maneuvers prior to the cannulation. A washout sample was collected at the final
clamp release in a 50-mL Falcon test tube (sample denoted ‘before cannulation’).

A modified aortic cannula was used (24F curved tip end-hole cannula, Medtronic, Inc., Minneapolis, MN, USA). The cylindrical tube had been removed and the cannula top section was attached to a 5-mL syringe. This modification minimized the dead space, and allowed flushing of the cannula while in position. The flushing maneuver was performed to avoid particles from being entrapped inside the cannula and instead being forced back into the aortic lumen. After the cannulation maneuver the aortic clamp was released to collect a washout sample from this procedure (denoted ‘after cannulation’). The cannulated section of the aorta was then cut away and the experiments were repeated in a proximal direction along the aorta until the subclavian artery was reached.

The perfusion medium was analyzed for the presence of background-noise particles and for methodological validation (sample denoted ‘input perfusate’). Input perfusate samples were collected from the aortic feeding line (n=12).

Sample processing
Collected washout samples were fixed by adding 5 mL of 4% formaldehyde in phosphate buffer, and were refrigerated until further processing. A new method for particle analysis was designed. The particles were deposited and condensed onto a filter which could be viewed and analyzed microscopically. A 10-µm Nuclepore® filter (Corning Costar, Coming, NY, USA) was mounted in a specially manufactured filter holder which had flow channels of 3-mm diameter. The wash-out sample was allowed to pass through the filter and particles were deposited onto the membrane. Particles smaller than 10 µm passed through the filter pores. After filtration, 2 mL of 99% ethanol was flushed through the filter for additional fixation and which also enabled a more efficient filter drying. The filter was dried at room temperature and mounted onto a microscope slide.

Image analysis
The deposits from before and after cannulation were randomized and the sample identity was kept unknown to the observer. The image analysis was similar to that described above for study IV, using the same microscope and digital image analyzer. Because the particle deposit was restrained to a 3-mm diameter it fitted inside a single microscopic view (objective lens Plan x1.25). This method was different from that described above (study IV), and the image analysis followed an upgraded protocol. Images were corrected for skewed illumination by background subtraction. Particle identification was accomplished by a manual threshold setting. The image analyzer was set to identify particles larger than 121 µm² (above 10-µm diameter) whereas smaller particles were omitted. With this cut-off area the filter pores were disregarded in the analysis (Figure 5). Maximum particle diameter, shape factor and area were recorded and transferred to an Excel spreadsheet. Particles were subdivided into three diameter intervals; small <0.1 mm, intermediate 0.1-0.5 mm, and large >0.5 mm. This diameter subdivision was selected with reference to known intervals within the arterial circulation, with arterioles having diameters in the range of 0.1 mm to 0.5 mm.55

Statistics
Data in all studies were tabulated using Microsoft Excel (Microsoft Corp, Redmond, WA). Statistica (Stat-Soft Tulsa, OK, USA) version 6.1 was used for statistical analyses in study I and V. In study II and IV analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, IL), and for study III SPSS version 18.0 was used. In all studies a P-value above 0.05 was considered non-significant.

Study I
Cross tabulations were used and evaluated by Fisher’s exact, McNemar, Cohen’s Kappa, and Sign tests, as well as by exact probability calculation. Univariate factorial analysis was performed by logistic regression. Numerical
data were presented with mean values ± standard deviation and nominal data by frequencies.

**Study II–III**

The data and variables in study II and III were in many aspects similar but the analyses had different hypotheses and therefore different statistical approaches. The number of analyzed variables differed between the two studies due to the different types of surgery included. Continuous variables were categorized into multiple levels. This was in order to avoid identified non-linear characteristics. The continuous variables of study II and III had different spread and range due to the different inclusion criteria. The cut-off values for categorization were therefore updated for study III. Study II and III had an 11-year period of inclusion. Period of surgery was added as a variable to compensate for possible variation in surgical management and care during this time period. Type of surgery was treated as a predictor variable rather than analyzing the surgery-groups separately.

Univariate predictors were assessed in study II using Chi-square or Fisher’s exact test. The multivariable logistic regression performed in study II included all variables having a P-value ≤0.15 at univariate testing. Added for the present thesis, the variables significant at multivariable level are also presented by their receiver operating characteristics (ROC) curve and with the area under curve (AUC) calculated. For the factor analyses in study III, logistic regression was used at univariate level only. Deviation from equal distribution between left and right hemispheric stroke was tested using the binominal test.

Missing observations were given a separate category in the analyses rather than applying case-wise deletion. If the missing-data category had a significant influence at multivariable testing, then, subjects with missing data were omitted by case-wise deletion.

For survival analyzes, the starting point of follow up was the time of the stroke event, and for non-stroke subjects the day of surgery. Kaplan-Meier estimates and log-rank tests were performed for mortality-rate comparisons. Survival was further evaluated in study II using Cox regression models. The assumption of proportionality was confirmed for the included variables. The Cox regressions were further explored by repeating the analyses with different time periods of follow-up.

In both study II and III, data were presented as; median values with quartile range, odds ratio, or hazard ratio (HR) with 95% confidence intervals (CI).

**Study IV**

Particle counts showed a skewed distribution, both within and between subjects, and were therefore logarithmically transformed (Log10). Samples without recorded particles were at logarithmic transformation given a value of 0.1 that logarithmically equals −1. Data showed a reasonable normal distribution after logarithmic transformation and were presented as mean values ± standard error. The logarithmically transformed data were analyzed by Wilcoxon matched pairs test for comparison of particle counts from before and after cross-clamping. Spearman’s test was used for correlation analyses. The particle counts for the repetitive clamp maneuvers were plotted and the slope value for each experiment was calculated. Differences from horizontal slope (zero values) were analyzed by Wilcoxon matched pairs test.

**Study V**

Data are presented as median values with 15/85 percentiles. Wilcoxon matched pairs test was applied for comparison of washout samples from before and after cannulation. Mann-Whitney U test was used for the unpaired comparison of input perfusate versus samples before cannulation.

**Ethics**

All studies had ethical approval. Study I and IV were approved by the Umeå University ethical committee (study I: Dnr 01-145, study IV: Dnr 01-142). Study II and III were approved by the Regional Ethical Review Board (Dnr 07-078M). The use of retrieved animal organs for study V was approved by the Swedish Board of Agriculture (Dnr 38-2537/06).
RESULTS

Stroke rate
The cohorts in study II and III differed by the types of procedures included. The overall stroke rate in study II was 2.7%, which subdivided into 1.6% early stroke and 1.1% delayed stroke. The corresponding figures in study III were 3.1%, 2.1% and 1.1%, respectively. The rate of early stroke varied considerably between different types of procedures ($P<0.001$ study II and III). The highest rate of early stroke was 17.4% for the group of patients undergoing vascular procedures with circulatory arrest. The other extreme was OPCAB procedures with only 0.3% of early stroke. The rate of delayed stroke showed less variation between surgery groups, with a range from 1.8% for vascular procedures (study III) to 1.1% for CABG procedures (study II). In the small group of OPCAB procedures the corresponding rate was 0% (study II).

Risk factors
Risk factors for early and delayed stroke were analyzed separately in study II. Variables with $P<0.15$ were included in a multivariable logistic regression (29 and 25 variables for early and delayed stroke, respectively). The results of the logistic regressions are presented in Table 2. Early and delayed stroke did not share any risk factors. The two groups of stroke were compared to each other in a univariate analysis and the results confirm that the two groups had significant differences. The predictive value of each variable was further analyzed. The ROC curves for the individual risk factors of early and delayed stroke are presented in Figure 6 and 7. Their corresponding AUC values are presented in Table 3.

TABLE 2. Study II: Multivariable predictors of stroke

<table>
<thead>
<tr>
<th></th>
<th>Early stroke (n=149) vs controls (n=8874)</th>
<th>95% CI</th>
<th>OR Lower Upper P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60-70</td>
<td>3.99 1.56 10.21</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>≥70-80</td>
<td>6.94 2.78 17.33</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>5.63 1.92 16.50</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, µmol/L</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-200</td>
<td>2.35 1.63 3.38</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>&gt;200</td>
<td>4.90 2.52 9.50</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Aortic wall quality</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately</td>
<td>2.04 1.37 3.05</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Severely</td>
<td>5.32 3.44 8.22</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CPB time, min</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>&lt;90 (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-150</td>
<td>1.47 0.990 2.18</td>
<td>0.056</td>
<td></td>
</tr>
<tr>
<td>&gt;150</td>
<td>2.96 1.89 4.62</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Delayed stroke (n=99) vs controls (n=8874)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (Male as reference)</td>
<td>2.18 1.46 3.27</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.86 1.24 2.80</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Previous cerebrovascular accident</td>
<td>2.16 1.21 3.48</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Inotropic support</td>
<td>2.17 1.45 3.25</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Postoperative atrial fibrillation</td>
<td>2.56 1.71 3.84</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

OR: Odds ratio; CI: Confidence interval; CPB: cardiopulmonary bypass.
Stroke during cardiac surgery; risk factors, mechanisms and survival effects

Symptoms and CT-findings
Stroke in association with cardiac surgery was found to almost exclusively be an ischemic phenomenon. No hemorrhages were found among the CT findings analyzed in study I. In the larger cohort of study III only three patients with signs of hemorrhage were added to this finding. However, two of these added patients, both with early stroke, had small cerebellar bleedings whereas their neurologic symptoms were more likely explained by concurrent ischemic lesions located in the cerebrum. The third patient had an intracerebral hemorrhage 18 days after surgery which occurred during treatment with extracorporeal membrane oxygenation and during continuous heparin treatment.

The results in study I and III showed an obvious side difference in the distribution of ischemic lesions between the right and left hemispheres. There was a strong dominance for left-sided symptoms (P=0.023, study I) which was confirmed by a corresponding dominance for right hemispheric lesions visualized by CT scans (P=0.005, study I). In study I, 66% of the patients had signs of acute ischemic lesions on their CT. There was a good correlation between CT-findings and symptoms, confirmed by a Cohen’s Kappa value of 0.824.

Vascular distribution of stroke
In terms of vascular distribution there was an overweight of stroke lesions within the territory of the middle cerebral artery (MCA), seen for both early and delayed stroke (study I). For early stroke, there was a significant overweight of right-sided lesions within the MCA territory compared to left-sided lesions (P=0.022). For the other vascular territories there was a more uniform distribution between the left and right hemispheres (Figure 8).

In study III both symptom data and CT findings was used to subdivide patients into hemispheric groups. The overweight for right hemispheric lesions was again confirmed significant for the groups of all patients and for cardiac type procedures (Table 4). A similar trend was seen for the vascular group but the number of unilateral events was few and without statistical power. In the small group of aortic dissections analyzed in study I, no unilateral findings were observed among these patients. Instead, all observed lesions were bilateral for this patient group, which represented a difference compared with the unilateral dominance in the cardiac-type group (P=0.001). In study III, the presence of bilateral findings were also more frequent in the vascular group compared to the cardiac-type group (P=0.039). The number of bilateral lesions for delayed stroke was few which differed from the pattern for early stroke (P=0.001, study III, all patients).

Neither study I nor study III presented a significant hemispheric side difference for delayed stroke. To explore the effect of subdividing stroke into early and delayed forms, side differences were also analyzed with early and delayed stroke grouped together (study III). No significant side difference was achieved in this analysis.

### TABLE 3. Area under the ROC curve

<table>
<thead>
<tr>
<th></th>
<th>Early stroke</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Area</td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
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<tr>
<td>Serum creatinine</td>
<td>0.592</td>
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<td></td>
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<tr>
<td>Aortic wall quality</td>
<td>0.710</td>
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<tr>
<td>CPB time</td>
<td>0.645</td>
<td></td>
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<tr>
<td>Delayed stroke</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.595</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Unstable angina</td>
<td>0.573</td>
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<td></td>
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</tr>
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<tr>
<td>Inotropic support</td>
<td>0.609</td>
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<td></td>
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<td>Postoperative atrial fibrillation</td>
<td>0.624</td>
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</table>

### TABLE 4. Study III: Hemispheric distribution of stroke

<table>
<thead>
<tr>
<th></th>
<th>Total events n (%)</th>
<th>Right hemisphere n (%)</th>
<th>Left hemisphere n (%)</th>
<th>P-value*</th>
<th>Unilateral (merged) n (%)</th>
<th>Bilateral n (%)</th>
<th>Not classified hemispheric n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>223 (100)</td>
<td>86 (38.6)</td>
<td>54 (24.2)</td>
<td>0.009</td>
<td>140 (62.8)</td>
<td>31 (13.9)</td>
<td>52 (23.3)</td>
</tr>
<tr>
<td>Cardiac type surgery</td>
<td>194 (100)</td>
<td>77 (39.7)</td>
<td>48 (24.7)</td>
<td>0.012</td>
<td>125 (64.4)</td>
<td>23 (11.9)</td>
<td>46 (23.7)</td>
</tr>
<tr>
<td>Dissections/aneurysm in DHT</td>
<td>29 (100)</td>
<td>9 (31.0)</td>
<td>6 (20.7)</td>
<td>0.607</td>
<td>15 (51.7)</td>
<td>8 (27.6)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td><strong>Delayed stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>116 (100)</td>
<td>41 (35.3)</td>
<td>52 (44.8)</td>
<td>0.300</td>
<td>93 (80.2)</td>
<td>4 (3.4)</td>
<td>19 (16.4)</td>
</tr>
<tr>
<td>Cardiac type surgery</td>
<td>113 (100)</td>
<td>41 (36.3)</td>
<td>50 (44.2)</td>
<td>0.402</td>
<td>91 (80.5)</td>
<td>4 (3.5)</td>
<td>18 (15.9)</td>
</tr>
<tr>
<td>Dissections/aneurysm in DHT</td>
<td>3 (100)</td>
<td>0 (0)</td>
<td>2 (66.7)</td>
<td>0.500</td>
<td>2 (66.7)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
</tr>
</tbody>
</table>

DHT; Deep hypothermia <25°C. *Binomial comparison (exact test) assuming equal distribution between right versus left hemisphere.
Factors associated with hemispheric differences

Stroke was separated by hemispheric side and the associated variables were analyzed in study III. These analyses were restricted to early stroke only because delayed stroke had no significant side difference. When tested against non-stroke subjects, many of the univariate variables were shared between the groups; left hemispheric, right hemispheric and bilateral stroke. Of particular interest, both impaired aortic quality and vascular type surgery were found to have a strong influence on stroke occurrence in each subgroup (see Table 3 of study III).

Bilateral lesions were compared against those unilateral, and right-hemispheric lesions were compared against those on the contralateral side (Table 5). Impaired aortic quality was highly linked with bilateral lesions. A number of other variables were also associated with bilateral lesions, exemplified by: vascular type surgery, variables related to bleeding problem and prolonged CPB time (Table 5). In the comparison of hemispheric sides, two variables showed association with right-hemispheric lesions; large volume of infusion at surgery and the use of tranexamic acid.

### TABLE 5. Study III: Univariate analysis of hemispheric differences for early stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bilateral vs. Unilateral</th>
<th>Right vs. Left hemispheric</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>OR Lower Upper P-value</td>
<td>OR Lower Upper P-value</td>
</tr>
<tr>
<td>Type of procedure; cardiac type as reference</td>
<td>2.90 1.10 7.62 0.031</td>
<td>2.90 1.10 7.62 0.031</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.78 1.21 6.40 0.016</td>
<td>2.78 1.21 6.40 0.016</td>
</tr>
<tr>
<td>Aortic wall quality/calcification*</td>
<td>Normal 7.17 0.824 62.32 0.074</td>
<td>Normal 7.17 0.824 62.32 0.074</td>
</tr>
<tr>
<td></td>
<td>Moderately 15.64 1.93 126.4 0.010</td>
<td>Moderately 15.64 1.93 126.4 0.010</td>
</tr>
<tr>
<td>Aortic wall quality/calcification*</td>
<td>Severely 15.64 1.93 126.4 0.010</td>
<td>Severely 15.64 1.93 126.4 0.010</td>
</tr>
<tr>
<td>No. of anastomoses*</td>
<td>&lt;3 0.411 0.119 1.42 0.160</td>
<td>&lt;3 0.411 0.119 1.42 0.160</td>
</tr>
<tr>
<td></td>
<td>3-4 2.05 0.547 7.70 0.286</td>
<td>3-4 2.05 0.547 7.70 0.286</td>
</tr>
<tr>
<td></td>
<td>&gt;4 2.05 0.547 7.70 0.286</td>
<td>&gt;4 2.05 0.547 7.70 0.286</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>&lt;80 1.10 0.206 5.84 0.914</td>
<td>&lt;80 1.10 0.206 5.84 0.914</td>
</tr>
<tr>
<td></td>
<td>80-110 3.78 1.07 13.38 0.039</td>
<td>80-110 3.78 1.07 13.38 0.039</td>
</tr>
<tr>
<td></td>
<td>&gt;110 3.78 1.07 13.38 0.039</td>
<td>&gt;110 3.78 1.07 13.38 0.039</td>
</tr>
<tr>
<td>Total volume given, mL</td>
<td>&lt;3000 2.85 1.09 7.45 0.033</td>
<td>&lt;3000 2.85 1.09 7.45 0.033</td>
</tr>
<tr>
<td></td>
<td>3000-4000 2.19 1.01 4.77 0.047</td>
<td>3000-4000 2.19 1.01 4.77 0.047</td>
</tr>
<tr>
<td></td>
<td>&gt;4000 2.19 1.01 4.77 0.047</td>
<td>&gt;4000 2.19 1.01 4.77 0.047</td>
</tr>
<tr>
<td>Erythrocyte transfusion required</td>
<td>2.99 1.28 6.95 0.011</td>
<td>2.99 1.28 6.95 0.011</td>
</tr>
<tr>
<td>Plasma transfusion required</td>
<td>2.92 1.31 6.53 0.009</td>
<td>2.92 1.31 6.53 0.009</td>
</tr>
<tr>
<td>Platelet transfusion required</td>
<td>4.65 2.05 10.52 0.000</td>
<td>4.65 2.05 10.52 0.000</td>
</tr>
<tr>
<td>Total bleeding, mL</td>
<td>&lt;400 2.33 0.638 8.53 0.200</td>
<td>&lt;400 2.33 0.638 8.53 0.200</td>
</tr>
<tr>
<td></td>
<td>400-600 5.31 1.69 16.63 0.004</td>
<td>400-600 5.31 1.69 16.63 0.004</td>
</tr>
<tr>
<td></td>
<td>&gt;600 5.31 1.69 16.63 0.004</td>
<td>&gt;600 5.31 1.69 16.63 0.004</td>
</tr>
<tr>
<td>Inotropic requirement</td>
<td>4.02 1.46 11.07 0.007</td>
<td>4.02 1.46 11.07 0.007</td>
</tr>
<tr>
<td>Tranexamic acid given</td>
<td>4.43 1.75 11.23 0.002</td>
<td>4.43 1.75 11.23 0.002</td>
</tr>
</tbody>
</table>

Univariate logistic regression were used to calculate OR, CI values and P-values. First categorization level is used as reference. Only variables significant at p<0.05 on group level are presented. Left/Right/Bilateral hemispheric: Patients with lesions located in the left/right/both hemispheres; Unilateral: Patients with lesions in either left or right hemisphere; NYHA: New York Heart Association; CPB: cardiopulmonary bypass. * Variable available only for coronary artery bypass grafting procedures.
In study III a few variables were added to the analysis compared with those in study II, such as the intraoperative use of hemostatic drugs. Among these, tranexamic acid was found to be associated with a hemispheric side difference of stroke (study III) whereas its underlying relationship to stroke remained unexplored. For comparison, the variable tranexamic acid was here tested as a potential risk factor for stroke with reference to the groups analyzed in study II. However, this variable was found without significant impact on neither early nor delayed stroke at univariate analysis.

**Survival**

**Study II**

Survival data was complete for all included patients with a follow-up time of up to 16.3 years. The 30-day mortality was 1.1% for the entire group of analyzed patients. The 30-day mortality for early stroke was 14.1% and for delayed stroke 8.1%, which contrasted to 0.8% among control subjects (group $P<0.001$). Further analyses focused on CABG patients only.

The Kaplan-Meier survival curves for the two stroke groups and control subjects are presented in Figure 9. At log-rank testing, both early and delayed stroke demonstrated a significantly shorter survival compared to controls ($P<0.001$). No significant difference was found between early and delayed stroke. A total of 44 variables were included in a Cox regression analysis and the entire follow-up was used. Both early and delayed stroke were found to be independent predictors of mortality with HR of 1.44 (CI 1.10/1.89) and HR 1.85 (CI 1.39/2.46), respectively. Other variables predicting long-term survival are presented in study II.

The hazard ratios for stroke were dependent on the follow-up time. This phenomenon was explored by repeating the Cox analyses and by stepwise expanding the follow-up. At six-month follow up the HR was 12.26 (CI 6.27/23.97) and 6.53 (CI 2.73/15.63) for early and delayed stroke, respectively. The corresponding figures at 1-year follow-up was 5.46 (CI 3.13/9.53) and 3.76 (CI 1.82/7.75). As the follow-up was further prolonged to approach the entire follow-up, the HR reached the values referred above. This phenomenon is illustrated in Figure 10.

To analyze survival beyond the acute phase, the Cox regression was repeated to only include patients who survived their first postoperative year. In this cohort, delayed stroke remained an independent predictor of mortality with HR 1.71 (CI 1.24/2.36, $P=0.001$). In contrast, early stroke did not yield a significant difference compared to the control group.

**Study III**

Survival differences between hemispheric groups of early stroke were investigated. Figure 11 shows the Kaplan-Meier survival curves for left hemispheric, right hemispheric and bilateral stroke in comparison to control subjects. The mortality for patients with bilateral stroke was considerably higher compared those with unilateral stroke ($P<0.001$). This difference occurred in the acute phase. On the other hand, for patients surviving their first postoperative year no difference was verified between unilateral and bilateral stroke ($P=0.630$). No significant survival difference was revealed between left and right-hemispheric stroke ($P=0.627$).
Particles generated at aortic cross-clamping

Aortic cross-clamping dislodged a median number of $81.7 \times 10^3$ particles (quartile range $7.21 \times 10^3 - 303 \times 10^3$), including particles of all sizes. Because of the wide spread and a skewed distribution, particle counts were logarithmically transformed. Particle counts from baseline samples and after the repetitive clamp maneuvers are presented in Figure 12ab. The number of particles dislodged by the cross-clamp was analyzed by a pair-wise comparison between baseline and the first cross-clamp measurement. Significant outputs of particles were observed in all diameter intervals of 0.5-1 mm and smaller (Table 6). There was a significant correlation, in all diameter intervals, between the overall magnitude of aortic calcifications and the number of particles generated by cross-clamp manipulation. Repeated clamping continued to generate particles. The output of small-size particles (<0.5 mm) remained significant for the second and third clamp maneuver, but then reached baseline with further maneuvers.

Table 6. Study IV: Statistical output

<table>
<thead>
<tr>
<th>Diameter interval</th>
<th>C1 vs Baseline* (P-value)</th>
<th>Baseline vs Calcification score† (P-value)</th>
<th>C1 vs Calcification score† (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 mm</td>
<td>0.760</td>
<td>0.603</td>
<td>0.016</td>
</tr>
<tr>
<td>1-2 mm</td>
<td>0.053</td>
<td>0.804</td>
<td>0.022</td>
</tr>
<tr>
<td>0.5-1 mm</td>
<td>0.022</td>
<td>0.351</td>
<td>0.025</td>
</tr>
<tr>
<td>0.1-0.5 mm</td>
<td>0.000</td>
<td>0.226</td>
<td>0.003</td>
</tr>
<tr>
<td>10-100 µm</td>
<td>0.011</td>
<td>0.185</td>
<td>0.008</td>
</tr>
<tr>
<td>50-100 µm</td>
<td>0.006</td>
<td>0.371</td>
<td>0.000</td>
</tr>
<tr>
<td>&lt;5 µm</td>
<td>0.000</td>
<td>0.665</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 6. Study IV: Statistical output

* Differences analyzed by Wilcoxon matched pairs test. † Spearman's test was used for correlation analyses. All correlations were of positive sign.
Particles generated at aortic cannulation
Washout samples after cannulation contained significantly more particles compared to samples from before cannulation (Table 7). The cannulation procedure generated particles within the small and intermediate size intervals, <0.1 mm and 0.1-0.5 mm diameter. Large-size particles were overall few and their frequency did not increase after cannulation. In one of the cannulation experiments a particle was visually observed, having a diameter of 0.78 mm. This was a single observation among the 40 experiments and without statistical impact.

**TABLE 7. Study V: Particle washout in response to cannulation**

<table>
<thead>
<tr>
<th></th>
<th>Before cannulation (n=40)</th>
<th>After cannulation (n=40)</th>
<th>Input perfusate (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median p15 / p85</td>
<td>P-value*</td>
<td>median p15 / p85</td>
</tr>
<tr>
<td>Number of particles</td>
<td>120 0 / 0</td>
<td>&lt;0.001</td>
<td>175 0 / 0</td>
</tr>
<tr>
<td>Number of particles &lt;0.1 mm</td>
<td>76 36 / 143</td>
<td>&lt;0.001</td>
<td>125 71 / 233</td>
</tr>
<tr>
<td>Number of particles 0.1-0.5</td>
<td>39 16 / 75</td>
<td>&lt;0.001</td>
<td>68 39 / 136</td>
</tr>
<tr>
<td>Number of particles &gt;0.5 mm</td>
<td>4.0 1.0 / 9.3</td>
<td>0.468</td>
<td>4.0 1.0 / 7.2</td>
</tr>
<tr>
<td>Total particle area (mm²)</td>
<td>0.68 0.26 / 1.6</td>
<td>0.216</td>
<td>0.95 0.50 / 2.2</td>
</tr>
<tr>
<td>Sample volume (mL)</td>
<td>37 32 / 43</td>
<td>0.839</td>
<td>37 33 / 41</td>
</tr>
</tbody>
</table>

*Wilcoxon matched-pairs test between Before and After Cannulation.
†Mann-Whitney U test versus before cannulation.

Data describe particle counts of each washout sample. p15 and p85 denotes the 15 and 85 percentiles.
GENERAL DISCUSSION

Stroke remains a worrisome complication in cardiac surgery. Increased knowledge regarding this complication is essential to develop preventive strategies. Stroke mechanisms are complex and difficult to study. Fortunately, stroke is a rather rare complication and therefore it often seems to occur at random. Conclusions regarding stroke mechanisms are often made from indirect findings in view of risk factor analyses, histological studies, Doppler ultrasound measurements, and radiological interpretations. Embolization is generally believed to be a major cause of stroke. The present thesis addresses the clinical problem of stroke in cardiac surgery by analyzing risk factors, anatomical features of lesions, and effects on survival. Potential embolic mechanisms are also experimentally investigated.

Risk factors for stroke

Stroke in association with cardiac surgery may occur during surgery, evidenced at extubation, or occur after a stroke-free interval in the postoperative period. Most previous studies of risk factors have considered stroke as a single entity and without temporal subdivision. In the present thesis, early and delayed types of stroke were anticipated to express differences in underlying mechanisms, risk factors and survival effects. Therefore, early and delayed stroke were analyzed separately. It was here shown (study II) that the two stroke groups did not share any of their independent risk factors. The differences were statistically confirmed when the two groups were tested against each other. The observed discrepancy in risk factors between early and delayed stroke finds support in a few other studies with similar subdivision.

Advanced age was found to predict early stroke. With increased age the brain is known to become more vulnerable and susceptible to ischemic lesions. Advanced age might also reflect general atherosclerosis and various comorbidities. Regardless of age, high preoperative creatinine was identified as an independent predictor of early stroke. This variable may also reflect the presence of general atherosclerosis. In the present study, atherosclerosis was most obviously reflected by the surgeon’s evaluation of the aortic quality. Impaired aortic quality was found independently associated with early stroke, which confirms previous knowledge. The impact of aortic atherosclerosis was further noticed in the experimental study IV with a significant correlation between the degree of aortic calcification and the number of dislodged particles from cross-clamp manipulation.

Delayed stroke was predicted by both demographic and postoperative variables (study II). Interestingly, females had a doubled risk for delayed stroke compared to males, an observation that is in line with previous reports. Females have been suggested to more frequently develop perioperative hypercoagulability which might explain their higher risk of delayed stroke. Hypercoagulability may possibly also explain the role of unstable angina emerging as a risk factor in the present analysis. It can be speculated that anticoagulation-therapy withdrawal may have rebound effects during the postoperative period with thrombotic complications.

Atrial fibrillation was found to predict delayed stroke and this finding is intuitively understood as an embolic mechanism. Inotropic requirement was also demonstrated as a risk factor for delayed stroke. Inotropic drugs have been reported to induce atrial fibrillation. Nevertheless, it was here found that inotropic requirement was statistically independent from atrial fibrillation. Inotropic requirement may reflect periods of hypotension after CPB and by this mechanism contribute to cerebral ischemia. Impaired left ventricular function did not evolve as a risk factor in the present study (II). This parameter describes the preoperative state whereas the postoperative function was unknown. From other fields of medicine, impaired left ventricular function is known to increase the risk of stroke via embolic mechanisms, both for patients with and without concomitant atrial fibrillation. In the present analysis inotropic requirement may have reflected a postoperative impaired left ventricular function and hereby explaining the observed relationship between inotropic need and delayed stroke.

Survival after stroke

Survival after CABG was analyzed in study II. In the multivariable analysis considering the entire follow-up, patients with both early and delayed stroke had a significantly impaired survival. However, in this long-term perspective the HR levels referring stroke,
and hence their impact, were rather moderate. The increased mortality due to stroke was mainly observed in the early postoperative period. Within a 6-month follow-up, the corresponding HR levels indicated a twelve-fold and near seven-fold increased risk of death for early and delayed stroke, respectively. This illustrated how the HR values are dependent on the follow-up time; a short follow-up together with a high early mortality generates a high HR. This effect must be considered when the results are compared to other studies. For example, Dacey et al reported a hazard ratio of 3.2 at 10-year follow-up although early and delayed stroke were not subdivided in their analysis. The survival knowledge beyond 10-years of follow-up after stroke in cardiac surgery is extremely limited, a gap filled by this thesis.

The devastating mortality-effect due to stroke diminished for patients who survived their first postoperative year. For these surviving patients, early stroke did not influence long-term mortality. In contrast, the corresponding delayed-stroke patients continued to have a higher long-term mortality compared to stroke-free controls. It can be speculated that this difference between early and delayed stroke is related to the underlying stroke mechanisms. Acute mortality is most likely caused by the brain injury itself and its adverse effects. In theory, mechanisms underlying delayed stroke can reoccur after discharge and cause late mortality. On the other hand, early stroke may largely be reflected by surgical events to which the patient is not further exposed.

Mortality after stroke in the general population is substantial, especially in the early period. In one study, the 28-day mortality was 9.7%, at one year 19.6%, and at three years 32.1%. In another study a 17% mortality at 7 days was reported which accumulated to 74% at 10 years. These figures are in line with the mortality reported herein, referring to stroke after cardiac surgery.

In terms of hemispheric subdivision of early stroke (study III) no survival difference was confirmed between unilateral lesions of the left and right side. The survival for patients with bilateral lesions differed significantly from those with unilateral lesions. Patients with bilateral lesions had a remarkably poor survival in the acute phase. However, those patients surviving the acute period had a long-term life expectancy similar to non-stroke subjects.

**Hemispheric distribution of stroke**

Stroke was near exclusively ischemic, which supports previous reports. It is noteworthy that hemorrhagic lesions were rare, despite a full heparinization during CPB and the frequent use of anticoagulants in the postoperative period.

The anatomical distribution of lesions was explored in study I and III. There was preponderance for lesions in the right hemisphere for early but not delayed stroke. This is in line with previous observations within the research group. The difference in hemispheric distribution between early and delayed stroke may reflect mechanistic details. An overweight for right hemispheric stroke after cardiac surgery has been reported by others, but without stroke being subdivided into early and delayed forms. It is notable that a significant hemispheric side difference was only statistically confirmed in one of the referred studies. The latter issue is interesting in view of the present thesis. If early and delayed stroke were grouped together no significant side difference was achieved. This detail supports the necessity to separate the two stroke groups.

The interpretation of the observed right-hemispheric overweight of lesions is presently unknown. It is here speculated that embolic particles are expelled by centrifugal force into the brachiocephalic trunk and subsequently into the right hemisphere. Variables associated with the right-to-left hemispheric difference were investigated in study III. In this analysis only increased volume requirement during surgery and the use of tranexamic acid were found associated with right hemispheric stroke. The volume requirement is difficult to explain but possibly represents a surrogate variable for factors not accounted for. Tranexamic acid may contribute to embolic intracardiac blood-clots that are similarly expelled with a preference for the right hemisphere. It must be kept in mind that tranexamic acid was not statistically confirmed as a risk factor behind overall stroke. Moreover, no other published studies have been found that report a possible linkage between stroke and tranexamic acid.

The impact of poor aortic quality may reflect an embolic mechanism. As hypothesized, these emboli reach the right hemisphere via the brachiocephalic trunk. However, this hypothesis was weakly supported by this variable. Although poor
aortic quality showed a trend to suggest a right-to-left hemispheric difference this finding was not statistically proven.

As seen in both study I and III, the occurrence of bilateral lesions was more common in the group of early stroke compared to its delayed form. In study III, the mechanistic distinction between bilateral and unilateral stroke was further explored. It was found that the type of surgical procedure clearly affected the distribution between bilateral and unilateral stroke. Bilateral stroke was more common after vascular type compared with cardiac-type procedures. In this perspective, ischemic injuries due to a circulatory arrest may have a more general effect and consequently more often cause bilateral lesions. The vascular-procedure group is also affected by the influence from its underlying vessel disease (including dissections) which must also be considered. Moreover, hemodynamic details are important in the interpretation of factors separating bilateral versus unilateral lesions. Some of the extracted significant variables connected with bilateral lesions may reflect periods of low blood pressure and hence cerebral hypoperfusion. Bilateral lesions may also be the effect from multiple emboli. This assumption finds support in the finding that patients with impaired aortic quality more often had bilateral findings compared to unilateral lesions. Furthermore, the correlation between a poor aortic quality and large numbers of embolic particles was experimentally demonstrated in study IV.

The uneven hemispheric distribution of lesions is to be compared with the knowledge from stroke in the general population. A slight but significant overweight for left hemispheric lesions has been reported for ischemic strokes in the general population (56% left versus 44% right). However, rather than being a true overweight for left hemispheric lesions, Foerch et al explained the uneven distribution as a recognition artifact. Lesions in the dominant left hemisphere are usually more easily recognized. If this applies to the patients studied in the present thesis, some right-hemispheric stroke events may have escaped detection. Possibly therefore, the right hemispheric predominance was here underestimated.

**Particles generated by aortic manipulation**

Embolization from the ascending aorta is considered to be a major cause of stroke. In the present thesis, aortic cross-clamping and cannulation were analyzed experimentally. Both these maneuvers are known to generate embolic particles visualized by Doppler ultrasound. However, Doppler measurements have methodological weaknesses. Moreover, the correlation between the number of Doppler-identified particles and cognitive decline remains unclear. Rodriguez et al could not confirm a correlation between microembolization and postoperative cognitive decline. This is in opposition to previous reports. Of interest in these aspects is the potential difference in clinical impact of various forms of emboli, comparing air microemboli to solid particles. In view of these difficulties, aortic manipulation was here analyzed in experimental models.

Particles generated by aortic cross-clamping were analyzed in study IV. The study was based on a human cadaveric perfusion model and with focus on particle counts in various size intervals. From these experiments clamp maneuvers were confirmed to generate embolic particles smaller than 1 mm. Large-size particles were also observed but did not reach significance from the limited number of experiments. The number of particles correlated with the degree of aortic calcifications.

Another aspect of aortic manipulation at surgery is the insertion of the aortic cannula. This may involve several embolic mechanisms, most obviously exemplified by dislodged intimal calcifications. In addition, the sharp edge of the cannula tip may shear-off adventitial tissue during its passage through the vessel wall. The latter of these mechanisms was analyzed in study V. For this hypothesis an experimental perfusion model was developed using non-calcified pig aortas. These experiments did not generate large-size particles, as hypothesized, whereas aortic cannulation instead was found to produce substantial numbers of small and intermediate size particles.

The clinical interpretation of the numerous emboli generated at aortic manipulation is challenging. It is here believed that the large number of observed small-size particles may contribute to neurocognitive decline (type II injury) rather than to stroke (type I injury). However, an isolated ischemic lesion is not obviously caused by a single embolus. The result of multiple emboli has been studied in different animal models. Rapp et al managed to induce brain infarctions by atherosclerotic particles as small as 60 to 100 µm which were injected into the carotid artery of rats.
The lesions were identified by magnetic resonance and by microscopy. The particles demonstrated in study IV and study V may in theory aggregate to form ischemic lesions of stroke character, similar to that demonstrated by Rapp et al, although this remains speculative. Further, a small lesion may affect the patient more than a large lesion, depending on its cerebral location.70,71 The effect of an ischemic lesion also depends on the cerebral vulnerability being amplified by comorbidities,98 which must be considered.

Limitations
Studies I, II, and III were limited from their retrospective design. Database studies do not reach beyond the quality of its documented data. This was partly compensated for by reviewing clinical records and CT reports for all patients with neurological complications extracted from the database. The studies only included events occurring during the period of hospitalization. Neurological evaluations and CT scans were performed according to contemporary clinical routines and were not determined by a study protocol. The database had missing observations. However, the statistical methods compensated for this lack of data by giving missing observations a separate category in the calculations. If the category of missing data had a significant impact, case-wise deletion was applied for this variable. In overview, the category of missing data had no influence on any of the independent risk-factor variables reported. Unfortunately the variable aortic quality was only available for coronary surgery and their combination procedures, a limitation which influenced study III.

Stroke is a rare complication. Despite a large number of patients included the statistical power becomes limited, in particular at open-heart surgery. For these analyses only univariate methods were applied. Another reflection refers to OPCAB procedures in study II, with few available patients. No major conclusions can be drawn from this small group.

The only outcome variable available was survival whereas the analyses had no information regarding functional outcome or quality of life. Moreover, survival analyses referred to all-cause mortality. Additional interpretations may have been derived from information about the causes of death. In both of the experimental studies (IV and V) a substantial background noise of particles was seen in the washout samples. This can partly be the effect of post mortem intimal changes with cellular debris in both the human cadaver aortas and the pig aortas. In study V, the necessity of a cross-clamp and its manipulating influence may have contributed to the noise. However, this artifact was presumably reduced because of the repeated clamping in order to clear the clamp site from particles. This routine was in line with experiences from study IV. In study V, the input perfusate was also evaluated separately for background noise. The perfusate was found to contain small-size particle. This was despite efforts to filter the medium before the experiments. Their origin remains unknown, although the particles most likely represent dust caught during sample processing. Nevertheless, pair-wise comparisons were used in the statistical analysis in both study IV and V, which reduce the influence from background noise and potential post-mortem changes.

Study V is also limited by the use of pig aortas and that cannulations were performed on the descending part. The pig aorta was examined histologically and roughly was without differences compared to sections of the human aorta.72 The descending aorta is in many aspects similar to the ascending part although there are some known histological differences. The descending aorta consists of less elastin and collagen and has a thinner medial layer compared to the ascending part.73

Neither cross-clamp manipulation nor cannulation was found to generate large particles with obvious stroke potential. However, the tested types of aortic manipulation cannot be disregarded in these perspectives. In view of the low frequency of early stroke (about 2%, study III), and also, the multiple mechanisms encountered among which embolization is one, the experiments performed in study II and III might have been too few to generate sufficient statistical power.

Clinical implications
Because of its disastrous nature, stroke risks should be considered in the decision-making prior to surgery. The clinical benefits from surgery are to be balanced against potential risks, including stroke. In fact, for certain patients a high stroke risk may exceed these benefits. For high-risk patients, the surgical technique and the perioperative management can be modified to reduce the risk of stroke. The impact of poor aortic quality is emphasized in the present thesis. Potential advantages with the use of epiaortic scanning are tempting to suggest.74 Unfortunately, the handling of the diseased aorta is problematic, in particular at open-heart surgery. For
CABG procedures OPCAB is an option with suggested benefits. However, the present results did not support these assumptions although it must be recognized that this statement is severely limited from the few OPCAB observations. Another protective routine is the use of single clamp techniques to avoid unnecessary aortic manipulation. Although this approach increases the clamp time the potential benefits with this routine in high-risk patients is possibly underestimated, an assumption supported by study IV.

Stroke was found to be near exclusively ischemic. This finding may have clinical implications. Presumable benefits are seen with an immediately initiated anticoagulation therapy instead of awaiting a CT scan to be performed for the exclusion of hemorrhage. However, the risk-benefit balance from overlooking cerebral hemorrhage must be considered. Rapidly initiated anticoagulation therapy is mostly relevant for the group with delayed stroke whereas for early stroke the recovery period of cerebral ischemia may have expired.

In terms of stroke-preventive strategies, the preoperative conditions are to be considered for the indication to perform surgery. The intraoperative conditions may partly be compensated for by modified routines. In the postoperative scenario of delayed stroke, the risks associated with atrial fibrillation can be reduced. Close attention and strict treatment for postoperative atrial fibrillation together with a liberal use of anticoagulants may pose a preventive effect.

The patients with stroke had a poor prognosis with a one-year mortality of about 20% for early stroke and 13% for delayed stroke, respectively. Patients with bilateral stroke were at particularly high risk with a one-year mortality of about 60%. Nevertheless, for early-stroke patients surviving their acute event there is reason to be more optimistic about their future life expectancy. In contrast, the delayed-stroke group demonstrated an added but modest long-term mortality effect.
CONCLUSIONS

The conclusions of the thesis were:

Study I  Early stroke, in association to cardiac surgery, had a right hemispheric predominance and with lesions overrepresented in the domain of the middle cerebral artery.

Study II  Early and delayed stroke differed in terms of risk factors. The acute-phase mortality in association with stroke was high, and delayed stroke continued to affect mortality beyond the first post-operative year. Early and delayed stroke should be considered as two separate entities.

Study III  Bilateral stroke was more frequent after vascular than after cardiac-type procedures. Mortality after bilateral stroke was substantial. The predominance of right-hemispheric lesions for early stroke was confirmed. Delayed stroke had a more uniform hemispheric distribution. Stroke lesions were near exclusively ischemic.

Study IV  Aortic cross-clamping was verified to dislodge aortic debris which correlated with the degree of aortic calcifications. Cross-clamping produced substantial numbers of small-size particles.

Study V  Cannulation was a source of embolic material in the non-calcified aortic model and generated particles of less than 0.5 mm in diameter. These findings underscore microembolic risks associated with aortic manipulation.
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Stroke during cardiac surgery: risk factors, mechanisms and survival effects


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Early and delayed stroke after coronary surgery - an analysis of risk factors and the impact on short and long-term survival.

Manuscript, submitted.
Hedberg M, Engström KG.

Hemispheric distribution of stroke after cardiac surgery – patient characteristics and survival impact.

Manuscript, submitted.
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