Cerebrovascular accidents associated with aortic manipulation during cardiac surgery

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“Science grows step by step and every man depends on the work of his predecessors. Inevitably, the monuments of success have been built on the rubble of failure, rubble which nevertheless plays its part in the foundation of the subject.”

Sir Ernest Rutherford (1871-1937)
Cerebrovascular accidents associated with aortic manipulation during cardiac surgery
ABSTRACT

**Background:** Despite the successful development in cardiac surgery, cerebrovascular accidents (CVA) remain a devastating complication. Aortic atherosclerosis has been identified as a major risk factor for CVA. The present thesis addresses this question in relation to aortic manipulation during cardiac surgery, being divided into a clinical (I-II) and an experimental part (III-V).

**Material and methods:** Consecutive cardiac surgery cases (n=2641) were analyzed. Patients with CVA were extracted from a database designed to monitor clinical symptoms. Patient records were used to confirm clinical data and diagnosis. Subdivision was made into three groups: control subjects, immediate, and delayed CVA, being analyzed for neurological symptoms (I). Patients with CVA who also had been investigated with computer tomography (CT) (n=77) were further evaluated in terms of hemispheric and vascular distribution of lesions. The CT-findings were compared with CVA symptoms (II). An aortic perfusion model was developed using cadaver aorta onto which multiple cross-clamp manipulations were applied (III). Washout samples of perfusate were analyzed by computerized image processing and with subdivision into different particle spectra. The model was further developed with the introduction of intraluminal manipulation from cannula and intra-aortic filter (IV). A technique for macro-anatomic mapping of plaque distribution of cadaver thoracic aorta was developed (V). Variation in plaque density was analyzed in different anatomical segments, monitored by digital image analysis. Hazards associated with surgical manipulation were studied by superimposing cannulation and cross-clamp sites onto the aortic maps in a blinded fashion.

**Results:** The incidence of immediate and delayed CVA was 3.0% and 0.9%, respectively. Aortic quality was strongly associated with immediate but not delayed CVA. Left-sided symptoms of immediate CVA were significantly more frequent than of the contra-lateral side. Positive signs on CT were seen in 66% of the CVA patients. Right-hemispheric lesions were more frequent compared with the contra-lateral side and the middle-cerebral artery territory dominated. Aortic cross-clamping produced a substantial output of particulate matter. Manipulation by intra-aortic filter produced a significant washout of embolic particles that escaped the filter, although some particles were captured. Cannulation was an additional source of embolic material. In terms of plaque distribution was the anterior wall of the ascending part and arch of the aorta more affected than its posterior side. However, observing a plaque in the anterior wall of this aortic segment predicted to 83% a concomitant plaque in the posterior wall. Increased age correlated positively with plaque density. The theoretical chance of interfering with a plaque during cannulation and/or clamp positioning was 45.8%.

**Conclusions:** Both CT scans and clinical symptoms confirmed that CVA after cardiac surgery had a right-hemispheric predominance. The perfusion model resulted in a profound output of material during cross-clamp maneuvers. The intra-aortic filter successfully collected particles but also generated embolic debris on its own. Aortic cannulation was an additional source of embolic debris. Plaques were frequently found in the cadaveric aorta, and there was a high risk of plaque interference during surgical manipulation. As expected, plaque density was age-dependent.

**Key words:** Aortic atherosclerosis, aortic cannulation, aortic cross-clamp, cardiac surgery, cerebral protection, cerebrovascular accidents, epiaortic ultrasound, intra-aortic filter.
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ORIGINA L PAPERS

The thesis is based on the following papers that are referred to by their roman numerals I-V:

I. **Boivie P**, Edström C, Engström KG.
   Side differences in cerebrovascular accidents after cardiac surgery: A statistical analysis of neurologic symptoms and possible implications for anatomic mechanisms of aortic particle embolization.

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

III. **Boivie P**, Hansson M, Engström KG.
    Embolic material generated by multiple aortic cross-clamping: A perfusion model with human cadaveric aorta.

IV. **Boivie P**, Hansson M, Engström KG.
    Intraluminal aortic manipulation by intra-aortic filter, cannulation and external clamp maneuvers evaluated versus dislodged embolic material.

V. **Boivie P**, Hansson M, Engström KG.
    Aortic plaque distribution in relation to cross-clamp and cannulation procedures during cardiac surgery.
    *Manuscript.*
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<td>ACA</td>
<td>anterior cerebral artery</td>
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<tr>
<td>ACC</td>
<td>aortic cross-clamp</td>
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<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<td>CPB</td>
<td>cardiopulmonary bypass</td>
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<td>CT</td>
<td>computer tomography</td>
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<td>CVA</td>
<td>cerebrovascular accidents</td>
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<td>IAF</td>
<td>intra-aortic filter</td>
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<td>ICA</td>
<td>internal carotid artery</td>
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<td>LDL</td>
<td>low-density lipoprotein</td>
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<td>MCA</td>
<td>middle cerebral artery</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>PCA</td>
<td>posterior cerebral artery</td>
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<td>PCI</td>
<td>percutaneous coronary interventions</td>
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<td>OPCAB</td>
<td>off-pump coronary artery bypass</td>
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<tr>
<td>TEE</td>
<td>transesophageal echocardiography</td>
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<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
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INTRODUCTION

Since 1953, when John H. Gibbon Jr. performed the first successful clinical operation involving the heart-lung machine,1 the techniques in cardiac surgery have developed extensively. Despite the successful progress, with decreased mortality and morbidity, cerebrovascular accidents (CVA) remain a devastating complication. The result of an otherwise successful cardiac operation can be totally spoiled by this dreadful outcome.2 The incidence of CVA after cardiac surgery is age related,3 and with older patients in today practice the issue is of high relevance. Also in perspectives of the present competition from percutaneous coronary interventions (PCI), it is of outmost importance to improve the surgical outcome in terms of CVA.

Definition of CVA

Clinically, a CVA is defined as an acute neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) onset of symptoms and with signs corresponding to focal cerebral involvement.4 Ischemic CVA includes cerebral infarctions due to thrombosis and/or embolism, whereas hemorrhagic CVA includes subarachnoid and/or intracerebral hemorrhage.5 Transient ischemic attack (TIA) is a related phenomenon, defined as a complete disappearance of symptoms within 24 hours.4

Cerebral circulation and clinical outcome of CVA in different vascular territories

The brain receives about 20% of the cardiac output through the two internal carotid arteries (ICA) and the two vertebral arteries (fig. 1 and 2). The ICAs are the main blood supplier to the brain hemispheres via the anterior and middle cerebral arteries (ACA and MCA, respectively). The vertebral arteries arise from the subclavian arteries and each side is merged to form the basilar artery. The basilar artery divides into the two posterior cerebral arteries (PCAs). Arteries arising from the vertebrobasilar system supply the brainstem, cerebellum and posterior part of the cerebrum. The circle of Willis is formed from the basilar artery and loops around the brainstem, where it merges with the ICAs.5

CVA most commonly involves the MCA and its branches.6 When the MCA is affected it usually causes a contralateral hemiparesis, and central paresis of facial nerve. Other symptoms are contralateral hemianesthesia and homonymous hemianopia. The decline in cortical functions depend on which hemisphere that is affected by the CVA. For right-handed persons, the left hemisphere is dominant. Dysphasia occurs if the dominant hemisphere is involved. Conversely, apraxia and/or sensory neglect occur when the non-dominant hemisphere is affected. If a large area of the cerebral cortex is damaged, unconsciousness may develop secondary to brain edema.7


A CVA affecting the vertebrobasilar territory can give rise to a variation of clinical symptoms, due to the number of structures in this region. A CVA involving the cerebellum may result in a lack of coordination, clumsiness and balance disorders. Brainstem CVA is the most devastating form that may lead to unconsciousness or death.7

**Diagnostic methods of CVA**

Computer tomography (CT) is the most commonly used method for investigating CVA. However, the CT scan does not always detect smaller ischemic lesions and there is a “silent period” before a focal area of hyper-density appears on CT.8 In clinical practice therefore, the use of CT is mainly performed to exclude intra-cerebral hemorrhage. Magnetic resonance imaging (MRI) and in particular diffusion-weighted MRI has been proven to be a more sensitive tool for detection of early and small ischemic lesions.8,9

**Subdivision of neurological complications after cardiac surgery**

Neurological complications after cardiac surgery are usually divided in two groups; type-I and type-II deficit.10 Type-I deficit includes major focal neurological dysfunction, stupor and coma. Type-II deficit encounters deterioration in intellectual function, confusion, agitation, memory deficit and seizure, without evidence of a focal injury. In most studies there is a further subdivision of CVA into immediate type, symptoms observed at extubation and delayed type, with a free interval between surgery and symptom appearance. The incidence of CVA after cardiac surgery varies between 1.6 and 8.4% in different reports.5,11-14 The main focus of the present thesis is on immediate CVA, although both delayed type-I CVA (study I and II) and type-II deficits (study III-IV) are referred to.

**CVA risk factors and mechanisms in cardiac surgery**

Several CVA-related risk factors in cardiac surgery have been recognized. As addressed above, advanced age is strongly associated with CVA,1 and further; female sex, history of previous CVA, diabetes mellitus, history of hypertension, pulmonary disease, and unstable angina.22 Identified intra-operative risk factors are often related to the use of cardiopulmonary bypass (CPB) and are exemplified in terms of embolic events, reduced cerebral blood flow, and local or systemic inflammatory response.15 During the post-operative period low cardiac output and atrial fibrillation has been identified as risk factors for delayed-type CVA.2

**Emboli in cardiac surgery**

Air is possibly the most common form of embolus, entering the cardiac cavities during open procedures and being expelled into the systemic circulation during CPB reperfusion.16 Other types of emboli emerge from blood clots or tissue debris.17 CPB-associated embolism encounters de-foaming silicon oil, plastic debris,18,19 or wound-fat droplets in retrieved pericardial suction blood.20 However, the most alarming form of embolism has its origin in the atherosclerotic aorta.21,22 Atherosclerotic material can be dislodged during aortic manipulation by clamping and cannulation procedures,23 or from aortic cannula stream jets.24

**Aortic histology and pathogeneses of aortic atherosclerosis**

In terms of histology is the aorta defined as an elastic artery, characterized by a thick intima without a distinct internal elastic lamina and a relatively thin and poorly organized adventitia. The intima is outlined by endothelial cells, under which a layer of loose connective tissue follows with longitudinal elastic fibers that merge with the elastic fibers of the media. The intimal matrix contains collagen, proteoglycans and small amounts of elastin. Smooth muscle cells can also be found in the intima and occasionally are lymphocytes, macrophages and other inflammatory cells present. The media consists of smooth muscle cells with elastin fibres in between. The adventitia is made up of connective tissue. The adventitia but also the media is penetrated by vasa vasorum and autonomic nerve fibres.25,26 Aortic atherosclerosis develops in the intima, but also includes proliferation of smooth muscle cells in the media. Atherosclerosis is formed when low-density lipoprotein (LDL) penetrates trough the endothelium and accumulates in the proteoglycan-rich subendothelial space of the intima. The oxidation of LDL and the inflammatory process induce expression of adhesion molecules for leukocytes. Leukocytes
penetrate the intima and scavenger receptors mediate the uptake of lipoproteins, and with a transformation into foam cells that progressively give rise to a lipid core. The smooth muscle cells of the intima divide and secrete extracellular matrix molecules such as collagen to form the fibrous cap. Smooth muscle cells from the media also migrate to the intima and the process continues. The lipid core grows and induces an inflammatory response and activation of macrophages. The macrophages have the ability to secrete enzymes that weaken the fibrous cap, which in turn cause plaque rupture and thrombus formation.\textsuperscript{24,28}

**Assessment of aortic quality in cardiac surgery**

Digital palpation is the most common method to assess aortic quality. However, the use of epiaortic ultrasound has increased and it is now considered the golden standard. In comparison, palpation has been shown to only detect about one third of the plaques evidenced by epiaortic scanning.\textsuperscript{29} Transesophageal echocardiography (TEE) is an alternative to epiaortic scanning, although limited in visualizing the distal part of the ascending aorta.\textsuperscript{30,32} In a study comparing epiaortic ultrasound, TEE and palpation, Davila-Roman and colleagues concluded that the former is more accurate than TEE, however both are superior to palpation.\textsuperscript{32} CT investigation prior to surgery has been evaluated, but found less specific compared to epiaortic ultrasound.\textsuperscript{33}

**Surgical procedures and new techniques to avoid aortic manipulation**

Off-pump coronary artery bypass (OPCAB) was proposed to reduce the incidence of CVA in cardiac surgery.\textsuperscript{34} However, this technique often requires aortic manipulation by the side-biting clamp. Therefore, the non-touch technique has been developed by which vein grafts are connected to the internal mammary arteries to avoid aortic manipulation.\textsuperscript{35} Hand-sewn proximal anastomoses can also be performed without side-biting clamp, with use of a membrane sealing the punched hole of the ascending aorta.\textsuperscript{36} Anastomotic devices for the aorto-saphenous vein connections have been tested, a method that eliminates the need of side-biting clamp. However, these devices are at present less encouraging due to a decreased graft patency.\textsuperscript{37} In patients with a severely calcified aorta the ascending aorta may be replaced with a graft tube rather than exposing it to manipulation.\textsuperscript{38} For CPB-supported coronary artery bypass grafting (CABG), a single-clamp technique is an alternative to avoid the additional side-biting clamp.\textsuperscript{39} Also less traumatic clamps have been introduced to minimize the aortic trauma and thereby prevent embolic events.\textsuperscript{31,40,41} The aortic cannula is assumed to cause unfavorable stream jets eroding the intima. Stream-jet problems may be reduced by technical modifications of the cannula tip with improved flow characteristics.\textsuperscript{42} Alternative cannulation sites have been proposed to reduce the incidence of CVA.\textsuperscript{43,44} Catheter-based CPB with balloon occlusion of the aorta exemplifies a more extreme technical solution, often discussed in relation to endoscopic or robotic surgery.\textsuperscript{44}

Another approach to the problem is to remove embolic material from the aortic circulation. This idea was recently launched in terms of the intra-aortic filter (IAF), and found successful in capturing embolic material.\textsuperscript{35-46}
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AIMS

The aims of the thesis were:

I. to evaluate the neurological pattern of CVA associated with cardiac surgery.

II. to evaluate the correlation between CT findings and symptom data of CVA in terms of hemispheric side difference and vascular distribution.

III. to evaluate how the number and character of embolic particles varies with repetitive aortic cross-clamping.

IV. to evaluate the risks associated with intraluminal aortic manipulation caused by IAF and cannula, in terms of embolic particles.

V. to evaluate the plaque distribution in the thoracic aorta, and set in relation to manipulation sites by aortic cannula and cross-clamp.
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MATERIAL AND METHODS

Study I and II: Patent cohort
2641 consecutive patients, undergoing cardiac surgery at the University Hospital of Northern Sweden between January 1999 and May 2001 were retrospectively evaluated in study I. Of these patients 104 suffered CVA. In study II, a subgroup of 77 patients from study I were extracted, who had undergone CT scan (fig. 3).

The database registry included all patients referred to the clinic. Preoperative data were entered upon acceptance for surgery and completed at patient’s admission. Data describing clinical details of the procedure and postoperative course were entered on a daily basis by surgeons, anesthesiologists, perfusionists, and nurses. The database enlisted events, defined as deviations from a normal postoperative course. The database contained detailed information about CVA symptoms. Given the design of the study, the observational period was limited to the length of stay at the cardiothoracic unit. One-year mortality was collected from the Swedish National Registry.

Study II: Protocol and CT evaluation
Study II was a sub-analysis of study I, which had focus on CT evaluation. CT reports were systematically reviewed according to a protocol. The observer was blinded to the neurologic pattern of CVA. Acute and old cerebrovascular lesions were recorded according to level (cerebrum, cerebellum, and brain stem), size (lacunar/territorial), side and location (vascular territories). Definitions of vascular territories were according to Osborn’s Diagnostic Neuroradiology.

Study I and II: Surgical techniques
Typically, on-pump coronary artery bypass grafting (CABG) was performed using standard aortic cross-clamping, with distal graft connections, followed by de-clamping and partial clamp for proximal anastomoses. The study cohort contained 111 OPCAB procedures. However, all CVA occurred for procedures using CPB. In the great majority of cases the aortic quality was assessed by palpation only, and in selective cases by aortic scanning. A curved-tip/end-hole aortic cannula was used for all routine cases. Open-heart procedures comprised routine venting via apex, pulmonary vein, or pulmonary artery. Carbon-dioxide wound flushing was not used during the study period. Pericardial suction blood was routinely recycled into the CPB circuit.
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Study III – V: Autopsy subjects
Study III, IV and V had experimental design involving human cadaver aortas (10 and 17 autopsy cases, study III and IV, respectively). In the descriptive study V, subjects from study III and IV were pooled together as described in figure 4.

![Figure 4](image)

Study III and IV: Aortic perfusion model
A cadaver-aorta perfusion model was developed in order to evaluate effects of surgical manipulation on the release of embolic material. The heart and lungs were removed en block according to standard autopsy procedures. The aorta was freed from surrounding connective tissue and side-branches were sealed. Retrograde perfusion was implemented via the descending aorta. The cannula tip was positioned at the subclavian-artery level. The cannula was connected to a constant hydrostatic pressure of 60 mmHg derived from an elevated 10-L infusion bag. The perfusion medium consisted of 9 g/L NaCl. The aorta was flushed with about 400-mL perfusion medium to remove debris, followed by a 50-mL perfusate sample that represented the baseline prior to manipulation. A standard 70-mm aortic cross-clamp (ACC) was applied to the ascending aorta as during routine surgery (Pilling Co, Fort Washington, PA, USA). The study protocol required repeated clamp maneuvers, and the yaws were therefore fixated to the aortic adventitia with stitches in order to precisely repeat the clamp positioning (fig. 5). To gain the same occluding force during repeated maneuvers, the clamp was closed to half of its full range in all experiments.

During constant pressure load, the ACC was momentarily released and a washout sample was collected in a test tube, aimed to be 50-mL. Upon closure, the pressurized aorta filled up with new medium from the infusion bag. This procedure was repeated 10 times (sample ACC 1-10). The entire washout volume of perfusate was collected, thus including all dislodged particulate matter from the manipulated aorta.

![Figure 5](image)

In study IV intraluminal aortic manipulations were added, referring to aortic cannulation and the IAF procedure (fig. 6). This study design required the ACC to control perfusate washout. The clamp position was washed free from embolic material by initiating the experiment with 10 ACC maneuvers. Similar to routine cardiac surgery purse-string sutures were applied to the pressurized aorta, being followed by cannulation and a repeated ACC maneuver to collect a washout sample. The IAF was inserted according to the manufacturer’s recommendations. With the IAF in position an additional ACC procedure and sample collection was performed. The IAF was then removed followed by a final ACC washout collection. The removed filter was everted and stirred in a test-tube with 50-mL saline and trapped particles were collected for analysis.
Study III and IV: Sample processing
Each washout was centrifuged at 1500g for 10 minutes at 22°C. The supernatant was carefully aspirated, leaving the deposit in the test tube. De-ionized/filtered water (50-mL) was added to lyse remaining erythrocytes and for washing purpose to remove NaCl. The sample was re-centrifuged and the supernatant was again aspirated. The collected material was fixed for 10 minutes at 22°C, by adding 5 mL of 10% formalin in phosphate buffer. The fixation was stopped by adding de-ionized/filtered water, followed by washing and re-centrifugation. The material was stained for 10 minutes at 22°C using 20-μL cresyl violet (study III) or Giemsa (study IV) and terminated by 2 washing and centrifugation cycles. The sample was aspirated in a Pasteur pipette and deposited on an uncoated microscopic slide. The droplet was spread out and left to dry at room temperature. In case of extensive particle load additional slides were used to avoid severely condensed material that would hamper image analysis. With multiple slides, the particulate matter from all microscopic slides was summarized during image analysis.

Study III: Image analysis of particles
The microscopic slides were assessed using an image analyzer (Zeiss KS 300, version 3.0, Carl Zeiss Vision GmbH, Hallbergmoos, Germany). Each deposit was analyzed both macroscopically and under the microscope. For macroscopic evaluation the slide was positioned on a lighted stage and recorded via a video camera (Sony DVC-10MP, Tokyo, Japan). With this method the entire deposit from each ACC maneuver was scanned in one image, or with duplicate slides, the summation of two recordings. For microscopic evaluation the sample was viewed using an inverted microscope (x10 magnification, Olympus CK40-F200, Olympus Optical Company Ltd, Tokyo, Japan) and recorded by camera (C5405-01 Hamamatsu Photonics, Hamamatsu City, Japan). In this configuration, two microscopic views were sampled at random from each slide. The amount of particles was expressed versus sample volume, and for microscopic evaluation, also per microscopic view.

After appropriate geometric calibration, the images were processed by computerized technique to measure particle count, area, and shape factor. The image handling included: (1) contrast enhancement to full gray scale, (2) manual editing for technical artifacts, (3) 1-step pixel dilation followed by pixel erosion, and (4) geometric measurement from preset gray threshold levels. On the macroscopic level the particulate matter was dense in contrast and evaluated by a single threshold setting for calcified particles. On the microscopic level, at which both calcified dense and cellular semitransparent particulate matter were detected, the image analysis was performed using two windows of gray scale attenuation. All threshold settings were constant throughout the study.

Study IV: Image analysis of particles
The methods were essentially as previously described for study III, and to which reference is made for further details. However, study IV had several methodological improvements in image analysis as compared with study III. The cellular spectrum did not overlap the dense calcified spectrum in threshold settings, a routine that allows easier comparison between groups. Further, the subdivision into cellular and calcified particles was used on both macroscopic and microscopic level. The programming of the image analyzer included a background subtraction to compensate for
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skewed illumination, but was in other terms identical that described for study III. The microscopic evaluation in study IV merged triplicate random views per slide rather than two. Moreover, the observer was blinded to the identity of the sample. Raw data were logarithmically transformed, due to a right-skewed distribution of particle counts and the logarithmic raw data were used without correction for sample volume.

Study V: Aortic mapping technique
Study V used a macro-anatomic mapping technique to record plaque distribution in cadaver aorta. This analysis followed to the perfusion experiments performed in study III and IV. The aorta was cut open along its major curvature, dividing the cervical branches in half. The specimen was unfolded and spread out on a polystyrene bed to which it was fixated with its intimal side facing upwards. A transparent plastic sheet was positioned in between the aorta and the bed. By use of a needle tip the aortic outline and the location of side-branches were traced by penetrating into the plastic sheet. Plaque geometry and location were traced in a similar fashion, but using needles of another tip and print-off character. Plaques were defined by their visual appearance and by palpation, including hard-calcified material (ulcerative and non-ulcerative) and wall thickness of well-defined outline. The plastic sheet resulted in a 1:1-scale aortic map of plaque distribution. The above procedure followed a protocol, which in addition to aortic geometry and clinical data also included information about any damage caused by the ACC, cannula, and/or IAF manipulation. However, no damage was seen that would interfere with the analysis of plaque distribution.

Study V: Digital image analysis of plaque distribution
The aortic map was developed by tracing the needle punctures by a marker pen. The map was positioned on a lighted stage and the image was transferred to two individual sheets, separating the aortic outline and plaque distribution, respectively. The image analysis was applied to hard-contrast tracing without need for elaborate techniques. The geometric scale was calibrated. Measurements encountered; area, long-axis diameter, and shape factor (0-1 of which 1 equals a perfect circle). The plaque area was recalculated into its corresponding circular diameter for easier interpretation.

Study V: Plaque interference by ACC and cannula
Risks associated with cross-clamping and cannulation in relation to plaque location was evaluated in a blinded fashion. The interaction surface of a standard 70-mm aortic cross-clamp (Pilling Co, Fort Washington, Pa) and cannulation tip (24F, Baxter, Irvine, Ca) was superimposed onto the aortic map outline. Its positioning was guided by the brachiocephalic trunk to mimic the locations of clamp and cannula under surgical conditions. An experienced cardiac surgeon, blinded to the location of plaques, conducted this step. The plaque distribution, being stored on a separate map, was then superimposed onto the marked clamp and cannulation sites, and their interference was recorded.

Evaluation of post-mortem aortic changes
A pig model was designed to study post-mortem alterations in aortic histology. The heart and lungs were removed en bloc from pigs (n=10) within 60 minutes after death. The aorta was dissected free from surrounding tissues, still remaining attached to the lungs. A 120-mm long section of the descending aorta was prepared. From this section a 30-mm segment, representing baseline, was cut out and fixed in 10% formalin in phosphate buffer. The remaining aorta was stored at 4°C to simulate the situation of body storage prior to autopsy. During storage the lungs were folded around the aorta to prevent drying. After 72 hours another 30-mm specimen was collected and processed in an identical way. The two samples were stained by Haematoxylin & Eosine, Elastine-Van Gieson, and by immunohistochemical endothelial staining CD31. The samples were evaluated in a random and blinded fashion using a standard light microscopy at x 200 magnification. All aortic wall layers were considered in the evaluation. However, a protocol was designed that focused on the vessel intima. The endothelial circumference was overviewed. Endothelial disruption was defined positive when 10 or more consecutive endothelial cells had disappeared or lost contact with the vessel.
wall. Intimal edema was evaluated by measuring the maximum distance between the endothelial layer and the internal elastic lamina, based on triplicate recordings.

**Ethics**
All studies were approved by Umeå University ethical committee (study I – II: Dnr 01-145, study III – V: Dnr 01-142).

**Statistics**
The recorded variables contained all forms of data from nominal to numerical continuous parameters to which appropriate statistical methods were applied. In general were mean values reported. Variance was described by standard deviation in clinical studies (I and II) or by standard error in experimental analyses (III-V). Statistica (StatSoft Tulsa, OK, USA) version 6.1 was used in all studies. A P-value above 0.05 was considered non-significant throughout.

**Study I: Statistics**
Typically, the statistical model compared three groups: control, immediate CVA, and delayed CVA. For parametric data was ANOVA used with Duncan post hoc analysis. Nonparametric and nominal data were analyzed by 3-column contingency tables to which a log-linear model and maximum likelihood \( \chi^2 \) output was applied. Post hoc analysis was conducted by excluding one group to restrain the statistical model. For analyses containing few observations was Fisher exact test used.

**Study II: Statistics**
In general terms were data analyzed using contingency tables, by Fisher’s exact, McNemar, Cohen’s Kappa, and Sign tests, as well as by exact probability calculation. Factorial analysis was performed by logistic regression.

**Study III: Statistics**
Particle counts showed skewed distribution to which non-parametric statistics were applied. For analysis of within-group differences was Wilcoxon signed ranks test used. Between-groups differences were evaluated by Kruskal-Wallis test and with post hoc comparison by Mann-Whitney U test. Correlation matrices were tested using Spearman’s rank coefficient.

Slope values were calculated by linear regression versus consecutive clamp opening.

**Study IV: Statistics**
Raw data were logarithmically transformed to which paired two-tailed Student’s t-test was applied throughout. A few samples (macroscopic calcified only) contained no visible particles. In the logarithmic transformation these were replaced by the near-zero value of 0.1 that logarithmically becomes -1. The routine generated a close to normal distribution after logarithmic correction.

**Study V: Statistics**
Non-parametric statistics were used for group comparison, including Wilcoxon signed ranks test, Mann-Whitney U-test, and Spearman’s rank correlation. For continuous variables was linear regression of least-square method used to calculate slope values and statistical dependence. ANCOVA was used to investigate confounding relationships.
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RESULTS

Incidence of CVA
The overall incidence of immediate and delayed CVA in the selected patient cohort (n=2641) was roughly 3% and 1%, respectively (table 1). Immediate CVA varied with type of surgical procedure, a phenomenon not seen for delayed CVA. For immediate CVA was the lowest rate observed for isolated CABG, and the incidence increased with more complex types of surgery, to a maximum of 7.5% for the combination of CABG and AVR (table 1, study I).

Aortic disease in relation to CVA
Aortic quality was a strong predictor of CVA. In the three-group comparison (control, immediate, delayed), immediate CVA showed a high and significant correlation to aortic wall calcification (P<0.001) whereas no such relationship was found for delayed-type CVA (study I). This is exemplified for CABG patients with immediate CVA among whom a diseased aorta had been recorded in 56.7% but only in 21% for control subjects. With an alternative approach (study II) using multiple regression analysis, the finding of a severely calcified aorta in CABG patients related to a near 12-times higher risk of developing immediate CVA (P<0.001, univariate comparison).

Additional factors correlating with CVA
Immediate but not delayed-type CVA was age dependent (group level P=0.001, CABG, study I). For delayed CVA, female sex appeared over-represented (P=0.048). Furthermore, history of previous cerebral events correlated with immediate CVA and with a corresponding group-difference versus delayed CVA (P=0.025). Higgs risk score was sensitive to immediate but not delayed CVA (P=0.027). Additional relationships versus CVA were observed in the all-type surgery cohort.

Post-operative effects of CVA
Immediate CVA resulted in prolonged ventilation period, ICU time, and length of stay by approximately two days in relation to control CABG subjects (P<0.001-0.016, study I). Delayed CVA showed a deviant pattern. However, hospitalization was biased by increased mortality, in particular and statistically, observed for delayed CVA being 18.8% (P<0.001). Hospital mortality was surprisingly low for CABG patients suffering immediate CVA (3.3%, non-significant versus control) but the rate increased dramatically during the first post-operative year (16.7%, P=0.001 versus control).

Hemispheric side differences of CVA
Lateral distribution of immediate CVA showed a strong dominance for left-sided symptoms (arm and leg), being almost twice as frequent as contra-lateral symptoms (CABG P=0.037, and pooled patients P=0.036, respectively, study I). A similar numeric pattern was seen for delayed CVA, although non-significant (study I). The left-sided dominance was confirmed in study II encountering those patients with performed CT (‘cardiac-type’ group, immediate CVA, P=0.006, table 2). Patients operated for aortic dissections did not show this side difference, although this assumption was based on few observations.

Table 1. CVA rates versus groups of surgery

<table>
<thead>
<tr>
<th>All patients</th>
<th>CABG isolated</th>
<th>P value</th>
<th>AVR isolated</th>
<th>P value</th>
<th>CABG/AVR isolated</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=2641)</td>
<td>(n=1882)</td>
<td></td>
<td>(n=196)</td>
<td></td>
<td>(n=200)</td>
<td></td>
</tr>
<tr>
<td>Immediate CVA (%)</td>
<td>2.99</td>
<td>1.59</td>
<td>0.003*</td>
<td>3.57</td>
<td>0.046*</td>
<td>7.50</td>
</tr>
<tr>
<td>Immediate CVA (n)</td>
<td>79</td>
<td>30</td>
<td>7</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed CVA (%)</td>
<td>0.95</td>
<td>0.85</td>
<td>0.736*</td>
<td>1.53</td>
<td>0.341*</td>
<td>1.00</td>
</tr>
<tr>
<td>Delayed CVA (n)</td>
<td>25</td>
<td>16</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* denotes difference versus all patients pooled
* denotes difference versus corresponding data of isolated CABG procedures
AVR=aortic valve replacement

*P values calculated by Sign test.
In study II, 66% of patients with clinical symptoms had signs of acute cerebrovascular lesions evidenced by CT scan. For immediate CVA the left-sided symptom pattern was confirmed, corresponding to a right-hemispheric dominance on CT (P=0.005, ‘cardiac-type’ group). There was a good agreement between symptom data and CT findings, confirmed by a Cohen’s Kappa value of 0.824 and a non-significant difference by McNemar test (P=0.480).

Vascular distribution of CVA
Most cerebrovascular lesions appeared within the MCA territory for both immediate and delayed CVA (study II). For immediate CVA there was a significant dominance for right-sided involvement in the MCA territory, compared with its contralateral side (P=0.022). For the other vascular territories there was a more uniform hemispheric distribution, as presented in figure 7.

![Vascular distribution, immediate CVA.](image)

<table>
<thead>
<tr>
<th>TABLE 2. Symptom pattern and CT-findings for immediate CVA</th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Number of cases (n)</td>
</tr>
<tr>
<td>Right-sided symptoms</td>
</tr>
<tr>
<td>Arm (%)</td>
</tr>
<tr>
<td>Leg (%)</td>
</tr>
<tr>
<td>Total (%)</td>
</tr>
<tr>
<td>Left-sided symptoms</td>
</tr>
<tr>
<td>Arm (%)</td>
</tr>
<tr>
<td>Leg (%)</td>
</tr>
<tr>
<td>Total (%)</td>
</tr>
<tr>
<td>Acute cerebral CT-findings</td>
</tr>
<tr>
<td>Left hemisphere only (%)</td>
</tr>
<tr>
<td>Right hemisphere only (%)</td>
</tr>
<tr>
<td>Both hemispheres (%)</td>
</tr>
</tbody>
</table>

*P values denote within-group difference between bilateral and unilateral distribution.

**P values denote within-group right-to-left difference.

***P values denote difference in bilateral involvement between aortic-dissection group and ‘cardiac-type’ operation.
in study IV. Particle size and range must be set in relation to technical details and optical resolution in macroscopic and microscopic mode, as discussed in study III and IV and as exemplified in figure 8.

Figure 8. Typical example of deposit. Upper panel) macroscopic view. Lower panel) microscopic view.

**ACC manipulation and particle output**

The initial ACC maneuver produced a significant peak in particle output. This phenomenon was apparent for all spectral analyses of particles (P=0.013-0.023) except macroscopic calcified material (P=0.060, study IV). With repeated ACC the number of particles significantly decreased, as demonstrated by a negative slope value versus steps of ACC, significant for all tested particle spectra (study III and IV, table 3). In study III an alternative evaluation compared the means of ACC 1 to 5 versus ACC 6 to 10 which produced a corresponding and significant reduction in particle output (P=0.012-0.028).

**Effects of cannulation and IAF manipulation on particle output**

In study IV additional steps of manipulation were introduced. The ACC was required to control the sequence of washout cycles when cannulation and IAF were applied. The ACC background noise of particles was known from its slope value of ACC 1 to 10 and was extrapolated and subtracted from the following cannulation and IAF maneuvers. Cannulation caused a significant increase in particles above the ACC background (P=0.001-0.038). Intraluminal manipulation from IAF insertion resulted in a significant output of particles (P=0.006-0.043) except for microscopic calcified debris. A similar pattern was observed at IAF removal (significant for macro- and microscopic cellular particles). Particles were also collected by the IAF, although the experiment was not designed to answer the IAF effectiveness. For comparison however, the IAF collected significantly more macroscopic cellular particles than the amount washed out when the filter was in position (P=0.004).

<table>
<thead>
<tr>
<th>TABLE 3. Particle output at aortic cross clamp opening (log)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>Particles (n)</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Macro calcified</td>
</tr>
<tr>
<td>Macro cellular</td>
</tr>
<tr>
<td>Micro calcified</td>
</tr>
<tr>
<td>Micro cellular</td>
</tr>
</tbody>
</table>

Diameter values refer to maximum-size recordings in individual subjects during ACC manipulation.

Data are expressed on the logarithmic scale as mean values ± sem.

ACC = aortic cross clamp (numerals refer to ACC release sequence).

P values for ACC 1 refer to differences versus baseline.

Slope denotes a linear regression of particle output versus consecutive release of ACC (1-10) and difference to zero.
Particle geometry in relation to ACC
The area of particles was considered to calculate the parameter “embolic load” produced by ACC (area x number of particles, study III). This evaluation amplified the above findings in relation to ACC maneuvers, and was significant for all tested spectra. This method took into account a significant reduction in particle size with repeated ACC, seen significant for the microscopic cellular spectrum (P=0.005, study III). Particles also became more circular as a function of repeated ACC, with an increase in shape factor (P=0.007, study III).

Microscopic cellular material was more numerous than its calcified counterpart, as indicated in study III. This phenomenon was more obvious in study IV showing a multiple of 10 differences in particle density between the two microscopic spectra.

Variability in particle output between subjects
Autopsy subjects showed variable sensitivity to ACC manipulation. Study III indicated that 9 of 10 subjects had visible atherosclerotic changes of the aortic inside but only 5 produced major bursts of dislodged particle output (fig. 9). There was a significant correlation between the number of particles and the magnitude of aortic wall calcification (P=0.014, study III).

![Figure 9](image)
Figure 9. Variability between subjects in ACC-induced particle output.

Aortic plaque distribution
Plaque formations were common and observed at various degrees in all of the included 24 autopsy cases. When plaque density was measured by image analysis (plaque area versus segment outline) three subjects had a plaque density above 50%, while the majority of patients had less than 20%. A plaque density of less than 2.5% was recorded in three subjects only. The anterior wall of the ascending/arch aorta had a more pronounced plaque density compared with its posterior wall (P=0.039). However, plaque density correlated significantly between these walls suggesting a strong coexistence in distribution (P=0.001).

Factors related to high aortic plaque density
Plaque density correlated positively with age (P=0.001-0.006) as exemplified in figure 10. Plaque density increased about 8% per each 10-year increment in age. Presence of coronary, valvular disease, or increase in aortic diameter, were all associated with higher plaque density in various aortic segments. However, when confounding patterns were explored by ANCOVA, age explained the increase in plaque density associated with these variables.

![Figure 10](image)
Figure 10. Plaque density in relation to age.

Interference with plaque during ACC and/or cannulation
Maneuvers of ACC and/or cannulation interfered with one or more plaques in 45.8% of the aortas, when blindly performed. There was an equal risk of 16.7% to hit a plaque by applying the cross-clamp or introducing the cannula. A duplicate hit by both the clamp and the cannula was seen in 12.5% of the cases (table 4). In five of seven cross-clamp hits, interference was seen within more than one plaque.

| Table 4. Risk of plaque interference by clamp and/or cannula |
|----------------|----------------|
|                | Clamp Hit      | No Clamp Hit |
| Cannula Hit    | n (%)          | 3 (12.5)     | 4 (16.7)     |
| No Cannula Hit | n (%)          | 4 (16.7)     | 13 (54.2)    |
| n = 24.        |                |              |


Post-mortem alterations in pig aorta
When the descending pig aorta was stored for 72 hours at 4°C, histological alterations were detected in the intima compared to the baseline sample. After storage, the intima showed higher frequency of endothelial disruption (P=0.031, table 5, fig. 11). Presence of intimal edema was evaluated by measuring the distance separating the endothelium and the internal elastic lamina. The distance increased after storage (P=0.014). No obvious histological differences could be detected in the adventitia or media layers.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=10)</th>
<th>72 hours (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial disruption (µm)</td>
<td>2.60±0.62</td>
<td>6.00±0.99</td>
<td>0.031</td>
</tr>
<tr>
<td>E-EL distance (µm)</td>
<td>18.44±2.10</td>
<td>28.05±2.23</td>
<td>0.014</td>
</tr>
</tbody>
</table>

E-EL=endothelium-internal elastic lamina.
P values were calculated by paired t-test.
Data are mean ± SEM.

Figure 11. Typical example of pig aorta, stained with endothelial marker CD31. Upper panel: baseline. Lower panel: after 72-hours storage at 4°C.
Cerebrovascular accidents associated with aortic manipulation during cardiac surgery
GENERAL DISCUSSION

At present, there is no optimal method to forecast the risk of developing CVA during cardiac surgery. This problem was addressed in this report. It was obvious that CVA showed variable rates and mechanistic relationships in different types of surgery (study I and II). Of particular interest was the challenge of aortic atherosclerosis with known links to CVA. This relationship is a major concern for the operating surgeon, as described in an Editorial referring to study III (see enclosed Hammon JW Aortic nightmares: Can we sleep better?).

Assessment of aortic quality prior to surgery is a technical challenge. The surgeon must therefore rely on intra-operative evaluation when dealing with aortic atherosclerosis and how to avoid CVA. In a recent study by van der Linden and colleagues, the aortic quality was measured by TEE, palpation and epiaortic ultrasound in 921 patients undergoing cardiac surgery. Atherosclerosis of the ascending aorta was observed in 26.2% of these patients. With detailed post-mortem analysis an even higher rate of aortic degeneration was observed (study V). Plaque density was significantly related to increased age. The theoretical risk of interfering with a plaque during a blindly applied cross-clamping and cannulation procedure was near 50%. In consonance with the results by van der Linden et. al., we found a significantly higher plaque density in the anterior wall of ascending aorta/artery compared with its posterior counterpart. These aortic segments are exposed to surgical manipulation and the finding increases the impact of the atherosclerotic problem.

Aortic atherosclerosis and CVA

Several previous studies have suggested atherosclerosis of the ascending aorta to be the major risk factor for CVA following cardiac surgery. Our results confirmed that aortic atherosclerosis was significantly associated with immediate CVA, but no relationship was seen versus delayed CVA (study I and II).

Differences between immediate and delayed CVA

Immediate and delayed CVA showed different statistical patterns (study I). In addition to the issue of aortic atherosclerosis, as described above, immediate CVA correlated to increased age, history of previous CVA, and higher Higgins score (referring to CAGB patients only). Female sex was overrepresented in the group of delayed CVA. Immediate CVA rates varied between different surgical procedures, whereas the incidence of delayed CVA was constant in these subgroups of surgery. The distinction between immediate and delayed CVA seemed to indicate different mechanisms. Immediate CVA, in particular with its association to aortic quality, appears related to the surgical trauma whereas delayed CVA mirrors the postoperative situation. This study had its main focus on immediate CVA. However, an interesting observation referring to delayed CVA was the magnitude of post-operative bleeding. In this group a significantly lower drain output was seen that predicted future CVA. This finding may, in speculative terms, suggest a hyper-coagulation disorder and possibly explain a blood clot mechanism of CVA.

Hemispherical side differences and mechanisms behind CVA after cardiac surgery

In a study from 2001, Weinstein reported that lesions in the left hemisphere dominated in patients with CVA after cardiac surgery. It was suggested that unfavorable stream jets from the aortic cannula was the major cause of CVA. A modified aortic cannula, as proposed by Weinstein, was suggested superior to conventional designs in preventing CVA. In contradiction, we found a right-hemispheric dominance (left-sided symptoms) for immediate CVA after cardiac surgery (study I). The finding was confirmed by CT scans (study II). CT scans showed that MCA was the most commonly involved artery. From these observations, and in perspectives of a strong correlation between aortic atherosclerosis and immediate CVA, it is here postulated that particles are released during manipulation of the ascending aorta and are tangentially expelled via the brachiocephalic trunk to the right hemisphere. The issue of CVA side difference after cardiac surgery is not well investigated and with somewhat conflicting results. This partly true also for CVA in the general population. However, Eriksson and
colleagues found that right hemiparesis dominated (left hemisphere) in a population-based cohort, although no statistics were applied to confirm the difference. The results support this finding (study II), as the majority of old cerebrovascular lesions seemed clustered in the left hemisphere. Of interest, therefore, is the apparent and opposite hemispheric predominance between CVA in the general population and that occurring after cardiac surgery.

**Aortic cross-clamp manipulation**
From the results by Barbut and colleagues, using transcranial Doppler, it was concluded that most embolic particles are released at aortic declamping. In study III, aortic manipulation was evaluated in terms of embolic particles produced by repetitive ACC. It was evident that ACC produced a substantial output of both macro- and microscopic particles. With repeated ACC, the number of embolic particles reduced, however, reaching baseline first after five clamp maneuvers. These findings emphasize the danger of clamp manipulation during cardiac surgery.

**Intraluminal aortic manipulation by cannula and IAF**
Several studies have proved the effectiveness of the IAF in capturing and removing embolic particles from the aortic circulation. In a prospectively controlled study by Schmitz and colleagues, the IAF decreased the incidence of overall neurological adverse events, but CVA was not significantly reduced, probably due to a limited statistical power. In a randomized study, the IAF was shown to prevent renal failure in a subgroup of high-risk patients. In that study, the filter was found to collect particles and was concluded to be clinically safe. However, when the ascending aorta was evaluated by epiaortic scanning, intimal abrasions were seen in 6.5% of the IAF-patients compared to 1.4% in the control group (P<0.001). The IAF introduces a new type of intraluminal aortic manipulation that may explain the observed intimal lesions. In study IV, the effects of intraluminal aortic manipulation by IAF were studied. The experimental model also gave information about the cannulation maneuver, the cannula being integrated in the IAF device. Cannulation resulted in a significant amount of embolic debris. Although the IAF successfully collected particles, a significant amount of embolic material was produced during its insertion and removal. These particles escaped capture by the IAF device, and are likely the result of intimal shedding. It is noteworthy that the pools of embolic material associated with IAF insertion and removal should be added together in order to evaluate the true cost-benefit with the device.

**Limitations**
The two clinical studies (I and II) were limited from their retrospective design. The studies included all types of major operations during a defined period of time, which resulted in a heterogeneous patient cohort. When subdivided into subgroups of procedures, CABG dominated (n=1882). Further, it should be noted that the statistical model was designed for a three-group comparison (control, immediate, and delayed CVA). Confounding patterns and mechanistic relationships are better explored in a restrained model comparing two groups and using multiple regression analysis.

Clinical manifestations of CVA are complex. The present studies generalized the neurology versus hemispheric distribution, assuming strictly crossed pathway of neurons. However, CT evaluations confirmed the right-hemispheric dominance, which is not biased by neurological interpretations.

In study II, CT scans were ordered in relation to the clinical circumstances rather than from a scientific protocol. Patients with discrete CVA symptoms may have passed without CT being performed. Further, the timing of CT scan was not taken into consideration.

The experimental perfusion model described in study III and IV was limited from its use of cadaver aortas, where post-mortem changes may have affected the results. However, the histology of blood vessels is known to be durable in the early post-mortem period. Further, calcified material as addressed herein is inorganic. On the negative side was the evaluation of pig aortas after post-mortem storage for 72 hours. Endothelial disruptions and intimal edema appeared in the stored aorta. Post-mortem alterations must therefore be considered to have affected the results, but possibly limited to microscopic
cellular debris of endothelial nature. Our perfusion model was further limited by the use of retrograde perfusion. However, during aortic de-clamping the flow over the clamp site changes direction that resembles the model used.

The evaluation of plaque distribution in cadaver aortas (study V) was affected by a geometric error from the unfolding of the torus-shaped aortic arch into a two-dimensional map. Nevertheless, the error equally affected the anterior and posterior walls of the aorta.

Clinical implications of the thesis
The overall incidence of immediate CVA in conjunction with cardiac surgery was about 3%. However, for isolated CABG procedures, containing the majority of patients, the incidence was approximately half of this rate. These numerals illustrate the skewed variability in CVA rate between subgroups of surgery. For instance was the CVA rate 7.5% for the combination procedure of CABG and aortic valve. In perspectives of elective surgery, such extreme rates highlight the need for preventive strategies. Delayed CVA was less frequent than immediate CVA, representing about one third of the events. On the other hand, the clinical importance of delayed CVA was profound due to its numerically high hospital mortality. Patients with immediate CVA appeared to sustain the insult better during the hospitalization period but showed a near equally bad one-year mortality outcome as for patients with delayed CVA.

The risk of plaque interference during surgical manipulation of the aorta was high when blindly conducted, a finding that strongly supports the use of epiaortic scanning in cardiac surgery. The dominance of right-hemispheric cerebrovascular lesions for immediate CVA draws the attention to embolic material produced by aortic manipulation. In a perfusion model aortic manipulation caused both macro- and microscopic debris. The macroscopic material can easily be interpreted as causing CVA. The embolic potential of microscopic debris is more speculative but may in theory contribute to type-II neurological deficits. The perfusion model necessitated repeated ACC that may have implications in relation to fibrillating-heart technique during CABG procedures. The fibrillating-heart method is still in clinical use, but must be questioned due to the significant amount of embolic material that is added from repeated ACC. The IAF is a potentially useful method to capture particles cause by aortic manipulation. However, the present thesis demonstrates how the IAF generated particles on its own by intraluminal manipulation. The clinical importance of this finding remains to be elucidated. The risks associated with intraluminal aortic manipulation may have implications not only for cardiac surgery, but also for catheter-based methods in cardiology (e.g., PCI).
Aortic nightmares: Can we sleep better?

John W. Hammon, MD

One of the recurring nightmares facing surgeons who operate on the thoracic aorta involves incising the aorta and visualizing severe degenerative atherosclerosis with toothpaste-like material in the wall of the aorta and the interior of the aorta lined with ulcerations containing platelet, fibrin strands, and, in some cases, actual blood clots. If a clamp is applied to this aorta, it is not difficult to imagine this material breaking away and embolizing to vital organs, causing severe complications. As the authors of “Embolic material generated by multiple aortic crossclamping: A perfusion model with human cadaveric aorta” point out, repeated clamping of atherosclerotic aortas releases not only calcified atherosclerotic debris, but smaller emboli consistent with cellular debris as well. On the basis of their data, it is hard to believe that any patient with aortic atherosclerosis, who undergoes surgery involving aortic clamping, does not end up with some permanent, severe organ damage related to intraoperative embolization.

Fortunately, a quick review of the cardiac surgery literature would suggest that the incidence of permanent stroke, renal failure, and other severe organ damage and death are quite low in clinical cardiac surgery today, although it has been pointed out by a number of authors that risk factors for organ damage during cardiopulmonary bypass are greatly amplified by the presence of severe atherosclerosis of the thoracic aorta and its branches. What then can be done to minimize the risk of potential embolization and what is the future for cardiopulmonary bypass in patients with severe aortic atherosclerosis?

As we have shown from data collected in patients from our own institution, and others have likewise pointed out, patients with palpable aortic atherosclerosis have a higher incidence of ultrasound-detected emboli during cardiac surgery. There is no question that surgeons strive to avoid placing crossclamps and perform other aortic manipulations across areas of palpable atherosclerosis. As Davila-Roman and his group have pointed out, however, all aortic atherosclerosis is not palpable. They have popularized a technique of epiaortic ultrasound scanning to map the aorta in areas of potential manipulation to determine whether atherosclerotic material is present. These techniques have become more widespread throughout the cardiac surgical community and, when combined with transesophageal echocardiography, give the surgeon a concrete idea of the presence of atherosclerosis in areas where clamps or incisions may be applied. Thus, it is possible to manipulate the aorta in areas where atherosclerosis is not present in the vast majority of cases. It appears from the data given to us by Boivie and colleagues that the one patient without calcified atherosclerosis had many fewer potential emboli, even on repeated clamping. Thus, we must focus our attention on patients with detectable, severe atherosclerosis.

What is the surgeon to do if the aorta is extensively diseased? Fortunately, there are many solutions for patients, particularly undergoing CABG operation. A popular option to avoid clamping and pump flow–induced aortic trauma is to perform off-pump operations. Even in these operations, aortic manipulation, especially with partial occlusion clamps, must be avoided as emphasized by Calafiore and associates. Grafts may be based off the internal mammary artery and the only chance for aortic manipulation is when the heart is distracted to provide access to vessels on the obtuse margin and posterior and inferior walls of the heart. If the surgeon chooses to use cardiopulmonary bypass, a no-touch technique may be utilized by allowing the heart to remain beating or fibrillating and the same intraoperative stabilization
maintained for anastomoses, as is used in off-pump surgery. If a clump of atherothrombotic material is encountered, newer anastomotic devices are available to avoid clamping the aorta during the aorto-saphenous vein anastomosis. If the ascending aorta is somewhat diseased but a free area can be mapped by ultrasonad, a single-clamp technique can be utilized to perform all distal and proximal anastomoses. This technique has been shown to reduce the incidence of postoperative neuropsychological deficits following CABG surgery.

Rarely, the ascending aorta can be resected and replaced with a graft, which then can be used to base aorto-coronary grafts, as suggested by Kouchoukos and coworkers.

During aortic valve operations, the aorta must be clamped and incised; thus patients with significant ascending aortic atherosclerosis present a difficult problem. A technique utilizing a short period of circulatory arrest combined with resection and graft replacement of this portion of the aorta has been successfully combined with aortic valve replacement and avoids the difficult problem of suturing and manipulating the calcified, atherosclerotic ascending aorta during aortic valve replacement.

The article by Boivie and colleagues is simple in its methodology but the potential impact of the research is blunted because only a small number of aortas tested and the marked variability of numbers and size of potential emboli released. Despite these limitations the results remind the surgeon that repeated aortic crossclamping in patients with atherosclerotic aortas is potentially dangerous. If one absolutely has to clamp the atherosclerotic aorta, can technology come to the rescue? Devices are now under development that may offer some relief from atherosclerotic embolism. Cumulus with improved flow characteristics and/or balloons to isolate the ascending aorta from the remainder of the circulation, such that clamps do not have to be applied, are now becoming commercially available but have not been rigorously tested. Devices that partition the aorta into a cranio-cervical division and a corporeal division are under development, which offer the possibility of directing potential emboli away from the head and also allowing a protocol in which the head is selectively cooled to minimize embolic injury. Filter devices are being tested, which may offer the ability to trap emboli from the ascending aorta to avoid damage to critical organs.

Although it could be said that the data presented by Boivie and colleagues remind us of something we already know and would rather forget, it is also true that this type of research with simple design and obvious conclusions allows surgeons to modify techniques such that they sleep better and enjoy improved outcomes in very sick patients.

References
Cerebrovascular accidents associated with aortic manipulation during cardiac surgery

CONCLUSIONS

The thesis concludes that:

I. immediate CVA after cardiac surgery was strongly associated with aortic atherosclerosis, and with a dominance of left-sided symptoms.

II. CT findings confirmed the right hemispheric dominance (e.g. left-sided symptoms) of CVA, and most commonly involved the middle cerebral artery.

III. repetitive aortic cross-clamping gave rise to both macro- and microscopic particles, with a maximum output at the first clamp opening, after which particle output decreased towards baseline.

IV. intraluminal manipulation due to intra-aortic filter and cannula produced an output of embolic particles.

V. atherosclerosis of the ascending aorta was common, and the risk of plaque interference at cross-clamping and cannulation was near 50%.
Cerebrovascular accidents associated with aortic manipulation during cardiac surgery
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Cerebrovascular accidents associated with aortic manipulation during cardiac surgery

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REFERENCES


19. Orenstein JM, Sato N, Aaron B, Buchholz B, Bloom S. Microemboli observed in deaths following cardiopulmonary bypass surgery: Silicone antifoam agents and


