Ola D. Sæther

PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING

Clinical and experimental studies


NTNU
Norwegian University of Science and Technology
Faculty of Medicine

TAPIR

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Pathophysiology during proximal aortic cross-clamping

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By

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CONTENTS

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Knowledge is proud that he has learn'd so much;
Wisdom is humble that he knows no more.
William Cowper (1731-1800) in The Task (1785).

List of papers

This thesis is based on the following original papers, which will be referred to by Roman numerals:

I. Sæther OD, Juul R, Aadahl P, Strømholm T, Myhre HO. Cerebral haemodynamics during thoracic- and thoracoabdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 1996;12:81-85.

II. Haaverstad R, Aadahl P, Sæther OD, Myhre HO. Proximal subcutaneous interstitial fluid pressure during cross-clamping of the descending thoracic aorta: A study of patients operated on for thoracic- or thoracoabdominal aortic aneurysms. Int J Angiol 1996;5:38-40.

III. Aadahl P, Sæther OD, Aakhus S, Bjørnstad K, Strømholm T, Myhre HO. The importance of transesophageal echocardiography during surgery of the thoracic aorta. Eur J Vasc Endovasc Surg 1996;12:401-406.

IV. Aadahl P, Aakhus S, Sæther OD, Strømholm T, Myhre HO. Cardiac output measurements during cross-clamping of the descending thoracic aorta in pigs. A comparison between transit-time ultrasound, thermodilution and Doppler ultrasound. Accepted for publication. Acta Anaesthesiol Scand

V. Sæther OD, Bäckström T, Aadahl P, Myhre HO, Norgren L, Ungerstedt U. Microdialysis of the spinal cord during thoracic aortic cross-clamping in a porcine model. Preliminary series. Accepted for publication. The Spine.

VI. Sæther OD, Bäckström T, Norgren L, Aadahl P, Myhre HO, Ungerstedt U. Spinal cord metabolism during thoracic aortic cross-clamping in pigs with special reference to the effect of allopurinol. In manuscript.

Introduction

Etheredge[1] introduced surgical treatment of thoracoabdominal aortic aneurysms in 1955, and DeBakey reported the first series of operated patients in 1956[2]. Some years later Crawford had further developed and reported the use of graft inclusion technique for repair of thoracoabdominal aortic aneurysms[3], which still remains the standard procedure. Crawford mainly used the technique of direct cross-clamping of the aorta without application of shunting or extracorporeal circulation. He had developed a unique experience in this field of aortic surgery and his personal series was reported in 1993[4].

At the Department of surgery, University hospital of Trondheim, we started to apply this technique in 1984 and mainly operated on symptomatic patients[5, 6], since these major operations are often connected with complications from various organ systems in the postoperative period[7, 8].

In experimental investigations we have previously demonstrated that cardiac function and cerebral haemodynamics were significantly influenced by proximal aortic cross-clamping[9, 10]. It was therefore the intention to further explore cerebral haemodynamics in patients undergoing surgery for thoracic- and thoracoabdominal aortic aneurysms, using direct cross-clamping of the descending thoracic aorta (I). For this purpose we used transcranial Doppler investigations in a clinical series.

We further noticed that patients undergoing these operations usually developed heavy oedema of the neck and the face in the postoperative period. This oedema may affect the upper airways and represent a problem when changing from a double lumen endotracheal tube to a single lumen tube after the operation. The oedema was investigated in seven patients measuring interstitial tissue fluid pressure by the wick-in needle technique (II).

Cardiac function has previously been investigated in an experimental pig model, showing that immediately following cross-clamping of the thoracic aorta there is an initial decrease in contractility followed by a hyperdynamic cardiac function[11].
We wanted to explore cardiac function in a clinical series. This is a critical issue since many of these elderly patients have concomitant cardiac disease. Therefore investigation of the cardiac function was performed during nine consecutive operations. We used transesophageal echocardiography with the intention of measuring left ventricular dimensions including inner and outer areas in end-systole and inner area in end-diastole. Pulmonary artery catheterisation was performed to measure central venous pressure, mean pulmonary artery pressure and pulmonary artery wedge pressure. Cardiac output was recorded with the thermodilution method (III).

Although most authors have claimed that the cardiac output is increased following direct cross-clamping of the descending thoracic aorta both in the clinical[12] and the experimental situation[11, 13] the topic still remains controversial. Thus, some publications have concluded that the cardiac output may be unchanged or even decreased[14, 15]. In an

experimental pig model we therefore measured cardiac output following cross-clamping of the descending thoracic aorta comparing three different methods (IV).

One of the major problems following operations for descending thoracic- and thoracoabdominal aortic aneurysms is the risk of paraplegia and paraparesis which may occur with an incidence between 0,5 and 38% depending upon the nature of the aortic lesion, the extent of aortic replacement and whether the operation is acute or elective[16].

In animal experiments we have investigated the microcirculation of the spinal cord using the laser Doppler technique[17]. Since the introduction of the technique of microdialysis it became possible to investigate the tissue metabolism reflected by the concentration of metabolites in small volumes of interstitial fluid. We wanted to investigate the various metabolites in the spinal cord before and after thoracic aortic cross-clamping using microdialysis (V, VI). Special attention was given to the concentration of the energy related metabolites glucose, lactate and pyruvate as well as the neurotransmitter glutamate and the fatty acid glycerol.

Since it has been postulated that neurologic sequelae following aortic cross clamping may be caused by oxygen derived free radicals[18], the effect of allopurinol (a xanthine oxidase inhibitor) on the metabolism of the spinal cord was studied with microdialysis technique in a pig model (VI). Xanthine oxidase mediates conversion of hypoxanthine to xanthine and is thereby influencing the formation of oxygen-derived free radicals.

Study objectives

Paper I

To investigate cerebral haemodynamics (blood flow velocity and pulsatility index of the middle cerebral artery) during operations for thoracic- and thoracoabdominal aortic aneurysms.

Paper II

To investigate oedema formation of the head and neck as well as subcutaneous tissue interstitial fluid pressure before and after operations for thoracic- and thoracoabdominal aortic aneurysms.

Paper III

To investigate left ventricular dimensions and cardiac output in patients operated on for thoracic- and thoracoabdominal aortic aneurysms.

Paper IV

To measure cardiac output following cross-clamping of the descending thoracic aorta using three different methods (Thermodilution, Pulsed Doppler ultrasound, Transit-time ultrasound flowmetry) in an experimental animal model.

Paper V

To evaluate microdialysis as a method for the investigation of metabolites in the spinal cord following cross-clamping of the descending thoracic aorta in a porcine model.

Paper VI

To investigate further the metabolic response of the spinal cord on cross-clamping of the descending thoracic aorta in a porcine model and to study whether allopurinol could modify this response.

Methodological considerations

In the present investigations both clinical and experimental studies are included.

More detailed descriptions of concentrations, doses, trade names and manufacturers of pharmacological agents as well as specifications of equipment used, are given in the original papers.

Clinical series

The patients were operated on consecutively for either descending thoracic- or thoracoabdominal aortic aneurysms during the period 1992 to 1994. In this series direct cross-clamping of the aorta was applied without use of shunting or extracorporeal circulation. All patients underwent surgery with a combination of epidural and general anaesthesia. They were monitored with arterial pressure and a pulmonary artery catheter was used for measurements of central venous pressure, mean pulmonary artery pressure and pulmonary artery wedge pressure. The diuresis was measured continuously. As a part of the routine an intrathecal catheter was applied prior to the operation and the spinal fluid pressure was monitored. Prior to cross-clamping of the aorta, cerebrospinal fluid was removed until a spinal fluid pressure below 10 mmHg was reached. During aortic cross-clamping cerebrospinal fluid was then drained using a closed collection

system with a valve mechanism to keep the pressure below 10 mmHg. This catheter was removed on the second postoperative day.

45 g mannitol was given prior to cross-clamping for protection of the kidneys and spinal cord. During cross-clamping a small dose of dopamine was given, mainly for renal protection.

Sodium nitroprusside was infused to reduce the systolic blood pressure to about 80 mmHg prior to aortic clamping, and to control proximal hypertension and pulmonary artery pressure during cross-clamping. Nitroglycerin was administered additionally if necessary. Vasodilators were discontinued prior to removal of the aortic clamp. At declamping, rapid infusion of blood, fresh frozen plasma and platelets was started. If necessary, inotropic agents or vasopressors were given.

Measurements performed in the clinical series.

Transcranial Doppler blood flow velocity measurements

Transcranial Doppler (TCD)[19] has gained wide acceptance for haemodynamic monitoring of the basal cerebral arteries using low frequency pulsed ultrasound which readily penetrates the skull. Several experimental and clinical studies indicate that TCD may be used to monitor relative changes in cerebral blood flow, even during arterial hypertension[20-23].

In paper I, blood flow velocity of the middle cerebral artery was measured through a temporal approach using transcranial Doppler technique. The recordings were made

during induction of anaesthesia and performed continuously before, during and after cross-clamping of the aorta. Peak systolic (V_{syst}), peak diastolic (V_{diast}) and mean blood flow velocity (V_{mean}) were recorded and the pulsatility index (PI) was calculated. Pulsatility indices calculated from TCD data are used as a method to describe the velocity waveform and obtain ratios, which are independent of beam/vessel angle. We used the ratio PI = $(V_{syst}-V_{diast})/V_{mean}$, which also reflects the peripheral vascular resistance.

Subcutaneous tissue interstitial fluid pressure

Subcutaneous tissue interstitial fluid pressure (P_{if}) was measured with the "wick-in-needle" technique (II). P_{if} recordings were performed as baseline measurements during the operation before cross-clamping and when the reconstruction was finished and the aorta declamped. The method is well established in the clinical setting and is reproducible and reliable for experimental and clinical work[24, 25].

Transesophageal echocardiography (TEE)

We used a standard 5 MHz mechanical TEE probe, which allows direct visualisation of the left ventricle and gives a good visualisation of the ventricular lumen as well as the left ventricular wall (III). The wall thickness, abnormalities in contractility and wall motion, ventricular dilatation and valvular function can be evaluated.

The ultrasound scanner was connected to a computer for continuous sampling of the digital signals, and the computer was also used for display and processing of the data. The left ventricular dimensions were measured with manual tracing of the borders

giving inner and outer area in end-systole and inner area in end-diastole. These areas represent ventricular volumes in a symmetrically contracting ventricle when no wall movement changes occur[26].

Pulmonary artery pressures

A pulmonary artery catheter was introduced through the internal jugular vein for measurements of central venous pressure, mean pulmonary artery pressure and pulmonary artery wedge pressure.

Cardiac output measurements by the thermodilution technique(CO_{TD})

The same pulmonary artery catheter, as previously described, was used to measure cardiac output with the thermodilution technique. During major surgery and in the intensive care unit, CO_{TD} has been the gold standard for estimating cardiac output. Saline (whose temperature is lower than the body temperature) is injected into the right atrium and is then carried with the venous blood into the pulmonary artery. A drop in temperature is detected by a thermistor located at the tip of the catheter. CO is calculated by a computer using the Stewart-Hamilton equation[27], incorporating the area under the thermodilution curve obtained by plotting the decline in pulmonary artery temperature against time. There must be a relatively constant pulmonary artery blood flow during the measurements to give reproducible results. During mechanical ventilation blood flow is modulated by variations in intrathoracic pressures affecting both preload and afterload. To minimise the influence of respiration, we averaged 3 measurements, all made at random

with respect to the respiratory cycle[28]. Thermodilution has been compared with other measurements of CO with acceptable results[29-32].

Heart rate

Heart rate was measured by ECG.

Systemic blood pressures

Blood pressures were measured continuously with pressure transducers connected to a catheter placed in the right radial artery.

Experimental series

We have previously used a similar experimental porcine model for the investigation of physiological consequences following cross-clamping of the proximal descending thoracic aorta. For that purpose we have studied the relationship between cerebrospinal fluid pressure and spinal cord perfusion[17, 33,34], as well as cerebral[9, 35] and central haemodynamics[10, 36,37] after cross-clamping of the thoracic aorta. These studies were performed without doing laminectomy, but with this exception the present investigations (V and VI) were performed with the same experimental model.

Land-race pigs were premedicated with azaperone and diazepam. Anaesthesia was induced with pentobarbital, ketamine and atropine, and was then maintained with ketamine, fentanyl and pancuronium. A solution of glucose and NaCl was infused for basal fluid requirements during the experiments.

The pigs were tracheostomized and ventilated by a respirator pump. A catheter was inserted into the right femoral vein for additional volume infusion at declamping of the aorta. A heating blanket was used to maintain normothermia during the procedure.
A left thoracotomy was performed in the fifth interspace. The descending thoracic aorta as well as the azygos vein were dissected, and the aorta was prepared for cross-clamping just distal to the left subclavian artery.
In paper IV the aortic cross-clamp time was 30 minutes. In paper V the cross-clamp time was extended to 60 minutes and in paper VI to 90 minutes in order to obtain a longer ischaemia time for the spinal cord. During cross-clamping, sodium nitroprusside and sodium bicarbonate were infused to control hypertension and to prevent acidosis, respectively. Five minutes before declamping sodium nitroprusside was discontinued and the respiration rate was increased. To counteract declamping hypotension, electrolyte solutions (IV) or colloid (V, VI) were rapidly infused intravenously before clamp release. After declamping no vasoactive medication was given.

In paper IV the fifth rib was also resected and the pericardium was opened in order to gain access for the Doppler ultrasound probe and the ascending aorta was exposed for cardiac output measurements. In addition, a pulmonary artery catheter was inserted through the jugular vein into the pulmonary artery.
In paper V and VI the spinal cord was exposed by laminectomy at the L2- L4 level since it is impossible to apply the probe for microdialysis transcutaneously into the spinal cord. This is different from the model previously used for investigation of the spinal cord circulation[17].

Pigs are excellent research animals, and young pigs have been used in circulatory system research for many years. The anatomy and physiology of the cardiac- and cerebrovascular system in pigs are similar to that of humans[38, 39]. There are, however, limitations using an animal model in surgical research. A young pig is physiologically never comparable to an elderly patient, often with coronary artery disease, undergoing extensive surgery. There are also some differences in the spinal cord vascular anatomy. Whereas the artery of Adamkiewicz in the pig always enters the spinal cord at the level of L_1-S_1, usually L_4[40], in man, it enters the spinal cord at the level of T_5 to L_5, with 60% entering at the level of T_9-T_{12}. Both man and pig has a continuous anterior spinal artery, but in man there are less than five radicular arteries in 45% of the cases, while pigs have multiple radicular arteries[41].

In paper V we used six pigs. In paper VI the pigs were divided into two groups of four animals each. The intervention group was pre-treated with allopurinol for three days whereas the control group did not receive allopurinol.
At the conclusion of each experiment, the animal was sacrificed with an overdose of pentobarbital sodium.

MEASUREMENTS PERFORMED IN THE EXPERIMENTAL SERIES

Arterial pressure.

Proximal arterial pressures were measured via a fibre optic pressure-monitoring catheter introduced through the axillary artery (IV).

Heart rate.

Heart rate was monitored using a single-vector electrocardiogram (IV).

Cardiac output.

In paper IV the cardiac output was measured with three different techniques.

Pulmonary artery thermodilution method (CO_{TD})

To measure cardiac output with the thermodilution technique a catheter was introduced into the pulmonary artery. The thermodilution technique is described under Measurements performed in the clinical series: Cardiac output by the thermodilution technique (Page 14).

Pulsed Doppler ultrasound on the aortic annulus ($CO_{DOPPLER}$)

Two-dimensional ultrasound imaging and Doppler velocity recordings were made directly on the exposed anterior aspect of the heart. Silicon gel was applied between the ultrasound probe and the pericardium to give stand-off and acoustic coupling. A standard 2,5 MHz duplex probe and ultrasound scanner were used.

To calculate flow, the aortic anulus diameter and the mean blood flow velocity integral were measured. The left ventricular outflow diameter was measured with the trailing-to-leading edge method in mid-systole as the distance between the insertion of the aortic valve leaflets on a long axis image, and an average of three consecutive measurements was used. The blood flow velocities through the aortic annulus were recorded by pulsed wave Doppler with the ultrasound beam directed through the centre of the aortic annulus. The average of five consecutive measurements was calculated.

Transit-time ultrasound flowmetry of the ascending aorta (CO_{TT})

A precalibrated ultrasound transit-time flow probe was applied between the orifices of the coronary arteries and the brachiocervical trunk on the exposed ascending aorta. Continuous measurement of aortic blood flow was obtained.

Transit-time flowmetry measures volume blood flow by determining the time difference for an ultrasound signal to be transmitted upstream and downstream via a reflector. The measurements are independent of probe alignment, profile of blood flow and haematocrit.The transit-time technique is also independent upon vessel diameter in estimating flow by reflecting ultrasound, and is thus regarded to be superior to electromagnetic measurement of blood flow[42-44]. The method has been validated in animal experiments and for clinical use with acceptable results[45, 46].

Measurement of aortic blood flow above the origin of the coronary arteries excludes myocardial blood flow and is therefore not identical to pulmonary artery blood flow measured by thermodilution technique. Coronary blood flow represents about 10% of CO. Measurement of ascending aortic blood flow will therefore underestimate CO correspondingly.

Measurements of cardiac output were made before cross-clamping, at 5, 15 and 25 minutes during cross-clamping and at 5, 15 and 30 minutes after declamping of the aorta.

Microdialysis

Microdialysis is a technique for sampling small quantities of interstitial fluid from the individual tissues with a thin dialysis tube perfused with a physiological liquid. Diffusion of substances over the dialysis membrane gives a dialysis perfusate reflecting the composition of the extracellular fluid[47]. While the accurate measurement of absolute concentrations of components in the extracellular space with microdialysis is connected with difficulties, microdialysates have repeatedly been shown to accurately reflect changes in concentrations of neurotransmitters and other metabolites both in brain and spinal cord[48, 49].

One of the key issues in microdialysis is the concept of recovery. Relative recovery is defined as the concentration of a substance in the microdialysate sample expressed as a percentage of the concentration in the surrounding tissue. Absolute recovery is the total amount of a substance recovered during a defined time period. In vitro, relative recovery decreases and absolute recovery increases as the perfusion flow is increased. The recovery of substances from the extracellular fluid is dependent on the area of the dialysis, the flow rate of the perfusion liquid, the speed of diffusion of the substance through the extracellular fluid and the properties of the membrane.
In vivo the relative recovery is constant provided the perfusion conditions remain the same. The absolute recovery of a substance varies with its release/metabolism in the tissue, which is what we wanted to measure in the present investigations (V, VI).

We used a microdialysis probe with a diameter of 0,64 mm, a membrane length of 2 mm and a molecular cut-off of 20.000 Daltons, perfused with Ringer's solution at a rate of 2μl/min using a microinfusion pump.

Microdialysis in the spinal cord may be a method well suited to studying indirect signs of cell injury and measuring changes in the utilisation of energy. In papers V and VI the energy related metabolites glucose, lactate, pyruvate and the excitatory amino acid glutamate were measured. In addition the fatty acid glycerol was determined in paper VI.

Glycerol

Being the endpoint of lipolysis, extracellular glycerol may be an important marker for cell membrane disintegration. Ischaemia and hypoxia are known to cause membrane phospholipid hydrolysis with accumulation of free fatty acids and other breakdown products of phospholipids in tissues [50,51].

Glycerol is an integral component of the double layer of most cellular membranes in the body. Degradation of phospholipids could therefore lead to impairment of membrane functions, for example barrier and channel functions. Calcium influx further activates phospholipases accelerating the membrane break down and liberation of glycerol into the extracellular fluid. Glycerol levels in the brain have previously been investigated in cerebral trauma patients[52] and elevated glycerol levels have been indicated. Experimental studies in rats[53, 54] have confirmed these findings.

Glutamate

Glutamate is believed to be the primary excitatory amino acid transmitters of neuronal tissue, including the spinal cord[55]. Under physiological circumstances most glutamate is located within the cells and released glutamate is rapidly taken up by astrocytes and neurones leaving low extracellular concentrations of the transmitter[56].

Investigations of changes in extracellular levels of glutamate after ischaemia[57] and graded compression trauma to the spinal cord in rats[58], have concluded with a significant increase in glutamate levels, as have studies in pigs[59, 60]. It appears likely that inhibition of the reuptake systems owing to profound ischaemia contributes to the extracellular glutamate accumulation.

Increased levels of excitatory amino acids may be involved in the production of secondary injury to the cord[61].

Glucose, lactate, pyruvate

Glucose is normally the only source of energy for the brain and spinal cord. The deposits of glucose in neuronal tissue are small, and the tissue is therefore dependent of continuous delivery for normal energy production. Glucose is metabolised to pyruvate and in the presence of oxygen, further oxydated in the citric acid cycle to carbondioxide and water. In situations with lack of oxygen (ischaemia and/or hypoxia) the metabolism shifts to the anaerobic pathway producing lactate and resulting in acidosis.

Lactic acidosis is always the result of a disturbance between lactate production and utilisation. The most common reason for a pathological lactate accumulation is an intra-cellular lack of oxygen. Lactate is a well-known marker of ischaemia, especially in

muscle tissue, but also in the spinal cord. Interpretations of the changes in lactate levels could be complicated since the concentrations not only reflect changes as a result of ischaemia but also variation of the inflow and the utilisation of glucose in the tissue[62]. Tissue lactate concentrations and the lactate-pyruvate ratio can therefore fluctuate considerably due to variations in neuroendocrine activation. Hyperlactatemia and elevated lactate-pyruvate ratio are also parts of the metabolic response to stress and trauma and these changes do not necessarily indicate tissue hypoxia[63].

All the extracellular fluid metabolites measured with microdialysis (V, VI) may be derived from cells in the ischaemic spinal cord, but leakage of substances from the blood due to opening of the blood-spinal cord barrier is also possible. This mechanism is probably minimal during the clamping period due to the low perfusion, but may have an influence during the initial reperfusion period.

In paper V the microdialysate samples were frozen, packed in dry ice, and transported to the Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden for analysis. In paper VI the microdialysates were analysed at site using a fully automated multichannel microdialysis analyser.

The spinal cord was in four cases (V, VI) collected after termination of the experiment and examined with standard histopathological techniques to identify the exact placement of the microdialysis probe within the spinal cord.

Laser Doppler flowmetry

In paper VI the microcirculation of the lower thoracic segments of the spinal cord was investigated using laser Doppler flowmetry. A laser Doppler needle probe was inserted in a ventro-lateral direction into the spinal cord as to be preferentially located in the grey matter, and connected to a laser Doppler flowmeter. Regional differences in blood perfusion between grey and white matter in the spinal cord may, however, not have been detected by these experiments.

When laser light is applied in tissue, the light will scatter in a tissue volume of a few mm^3 and some light will be reflected from moving blood cells, mainly erythrocytes. The reflected light will have an altered frequency due to the Doppler shift, representing the flux of red blood cells. Flux is defined as the product of the number of red blood cells and their mean velocity. The Doppler shifted signal is converted into a voltage signal which is linearly related to flux of red blood cells. The recorded output signal gives a continuous estimate of microvascular blood perfusion and will show fluctuations caused by heart beats and respiration. The flux values are always expressed in arbitrary units. Although laser Doppler flowmetry measures microvascular blood perfusion and not organ blood flow, it is a valuable tool in estimating relative changes in organ perfusion and has been widely used both clinically and experimentally[64, 65].

Statistics

Clinical series:

In paper I and III the two-sided Students *t*-test for paired data was used to assess differences between means, and in paper II Wilcoxon`s signed rank test for paired data was used.

Experimental series:

In paper IV, V and VI the two-tailed Wilcoxon`s signed rank exact test was used to assess differences within groups, and in paper VI the two-tailed Mann-Witney U exact test was used to evaluate differences between groups.

Summary of results

Paper I

Following 10 min of aortic cross-clamping blood flow velocity of the middle cerebral artery increased from 44 to 55 cm/s ($p < 0.01$). A further increase to 69 cm/s ($p < 0.01$) was observed 5 min after declamping. The pulsatility index averaged 0.74 before clamping, increasing to 1.21 ($p < 0.05$) at clamping and reaching 0.87 ($p < 0.05$) after declamping.

Paper II

There was a typical oedema formation of the head and neck as evaluated clinically. The oedema was at its maximum immediately following termination of the operation, and lasted for approximately 3 days. The median subcutaneous interstitial tissue fluid pressure at the neck was -0.7 mmHg prior to aortic cross-clamping, increasing to +3.7 mmHg during cross-clamping ($p < 0.02$).

Paper III

Cardiac output increased by 43% from baseline values during cross-clamping of the thoracic aorta ($p < 0.01$) and was still 55% above baseline at declamping ($p < 0.05$). Left ventricular end-systolic inner area was reduced by 32% during cross-clamping ($p < 0.01$). Pulmonary artery pressures and central venous pressure increased during declamping ($p < 0.05$). Heart rate increased by 38% from 66 beats/min to 92 beats/min ($p < 0.01$) during aortic cross clamping and was still 30% elevated at declamping.

Paper IV

Fifteen minutes following cross-clamping of the descending thoracic aorta cardiac output increased by 171% above baseline values using transit-time technique, 119% with thermodilution and 150% using the Doppler technique ($p < 0.05$). There was an increase in mean arterial pressure of 81% and heart rate increased by 76% ($p < 0.05$). Thus, the cardiac output increased as measured with all techniques used in the present series.

Paper V

It was possible to apply the microdialysis technique in the spinal cord in the experimental pig model. A significant increase in the lactate-pyruvate ratio was observed during the last 30 minutes of a one-hour cross-clamping period of the descending thoracic aorta. The maximum increase was 169% from basal levels at the end of the clamping period. In the declamping phase there was no change in this ratio compared to the clamping phase. No significant changes in glutamate levels during the clamping or reperfusion period were found.

Paper VI

There was a significant decrease in concentrations for the energy related metabolites glucose and pyruvate combined with a significant increase in lactate-pyruvate ratio during aortic cross-clamping. Glycerol decreased during the stabilisation period and the first 10 minutes after cross-clamping, followed by a significant increase after 60 minutes of cross-clamping. Glutamate decreased continuously from the start of measurements

until 70 minutes following cross-clamping. Thereafter the glutamate level stabilised and did never increase.

In the allopurinol treated pigs there was a tendency towards less increase of glycerol levels in the spinal cord 60 and 80 minutes following cross-clamping of the descending thoracic aorta. There were no differences in the concentrations of glutamate, glucose, pyruvate, lactate or lactate-pyruvate ratio between animals used as controls and those treated with allopurinol.

The laser Doppler flux stabilised at about 40% of baseline levels at the end of the cross-clamping period. A normalisation was seen after declamping of the aorta.

General discussion

In the clinical part of this investigation we used direct cross-clamping and graft interposition for the treatment of thoracic- and thoracoabdominal aortic aneurysms. This operating technique induces major pathophysiologic changes affecting cardiac function as well as blood circulation to the kidneys, the bowel and several other tissues and organs distal to the aortic clamp. In addition, the circulation of the proximal part of the body is significantly influenced by this technique. Since there is an increased cardiac output one could suspect that the circulation to the central nervous system, mainly the brain, is increased. Again this could lead to cerebral oedema or indirectly contribute to the increase in cerebrospinal fluid pressure observed during some of these operations. Increased cerebrospinal fluid pressure might reduce the perfusion pressure to the spinal cord, increasing the risk of paraplegia and paraparesis. Our findings conclude that there is an increased blood flow velocity of the middle cerebral artery during cross-clamping of the descending thoracic aorta. It is possible that the increased blood flow and a concomitant increase in blood volume of the intracranial structures can explain the acute increase in cerebrospinal fluid pressure observed in these patients during cross-clamping of the aorta. The increased pulsatility index observed after application of the clamp probably reflects a decreased "Wind-kessel" function of the aorta because the volume of the aorta and major vessels available for receiving the cardiac output is significantly decreased during cross-clamping.

We did not investigate further the possibility of cerebral oedema, since this would have required CT-scanning or MRI which is difficult to perform in the postoperative period and also rather cumbersome for the patient.

The increased cardiac output during clamping of the descending thoracic aorta also indicates that extracerebral vessels might have an increased blood flow during this period. It is possible that the normal autoregulatory mechanisms in the skin and subcutaneous tissue may be unable to cope with the hypertension, which is observed during cross-clamping in these patients. Furthermore, these mechanisms could be inhibited by some of the medication given during the operation. Therefore a considerable oedema of the head and neck is observed in the postoperative phase. The interstitial tissue fluid pressure is significantly increased immediately after termination of the operation. The oedema is declining gradually in the postoperative period but might represent a problem, especially when the double lumen endotracheal tube is changed to a regular tube in the postoperative period. The oedema may then affect the upper airways and could also represent a problem when the patient is about to retain normal spontaneous respiration. We do not have any special prophylactic measures to avoid this oedema except that we keep the upper part of the body somewhat elevated in the postoperative phase. It is possible that the oedema can be reduced by using extracorporeal circulation or shunting provided such techniques could modify some of the haemodynamic changes observed during direct cross-clamping.

Several patients operated on for thoracic- and thoracoabdominal aortic aneurysms have concomitant cardiovascular diseases and they are often in the mature age. For monitoring of the cardiac function we decided to explore the possibility of using transesophageal echocardiography, which can be performed in a way that does not interfere with the operation or the anaesthesia of the patient.

Transesophageal echocardiography has been used during operations for thoracoabdominal aneurysms to assess left ventricular function and found to be useful[66]. We confirmed that the method can easily be applied during the operations and that it represents a valuable supplement to pressure measurements for evaluation of cardiac function. Our study confirmed that cardiac output is increased and that the left ventricular end-systolic inner area is decreased during aortic cross-clamping. Heart rate increased during cross-clamping of the aorta and our findings indicate that there is a hyperdynamic state of the circulation mainly due to increased heart rate combined with a more complete emptying of the left ventricle in the systolic phase.

In the literature, haemodynamic data are often presented as average values prior to clamping, during clamping and at the declamping phase. However, a rather dynamic cardiovascular state is present, especially in the immediate post-clamp period, and average values over a period of time do not disclose these rapid changes. Since transesophageal echocardiography gives on-line direct visualisation of the heart, it provides valuable information throughout the whole operation. This is of special importance immediately after clamping and declamping, which are critical periods for the patient. Transesophageal echocardiography can in this manner be used to detect impending myocardial dysfunction, necessitating the use of shunting or bypass. It would

also be of great interest to investigate whether the cardiovascular response seen during direct cross-clamping of the aorta could be modified by such techniques.

Transesophageal echocardiography is advantageous for detecting early pathologic changes in cardiac function and to study the effect of pharmacological intervention. Mitral valve regurgitation has occasionally been observed using this technique during aortic cross-clamping. This may be of ischaemic nature, and nitrate has been given successfully[66]. Furthermore, a fall in systemic blood pressure during cross-clamping is rarely caused by decreased myocardial function, but rather by hypovolemia. Pulmonary artery wedge pressure can however indicate sufficient preload while transesophageal echocardiography readily depicts an insufficient ventricular filling. (Unpublished data). We suggest that transesophageal echocardiography should be used routinely during these operations.

The increased cardiac output during cross-clamping of the thoracic aorta might be regarded as a paradox, both in the experimental setting and the clinical situation. The reason for the observed increase in cardiac output[12, 13] is not completely understood. Some authors, claiming that this increase may be explained by methodological factors, have questioned these findings. Further, some authors find no increased cardiac output while others have observed a decrease[14, 15], particularly when vasodilators were not administrated[67]. There could be several reasons for this discrepancy. First of all there are rapid changes in the cardiovascular parameters in the early clamping period, and methods, which are not continuously following the haemodynamic changes, might give a false impression of the situation. Therefore one is dependent upon continuous

measurements to observe the dynamic changes taking place. In our investigation (IV) we conclude that with all the methods used, a significant increase in cardiac output during cross-clamping of the descending thoracic aorta was observed in pigs. Redistribution of blood from the lower part of the body during cross-clamping[68], or the release of catecholamines taking place during the same period have been proposed as mechanisms for the increased cardiac output[37, 69-71].

It can be discussed whether an increased cardiac output is harmful to patients during aortic surgery. This may be dependent upon the duration of cross-clamping. In patients with concomitant coronary artery disease and aortic valvular insufficiency, the hyperdynamic state of the heart could be deleterious. In such cases shunting or bypass are probably indicated[72].

Because surgical treatment for descending thoracic- and thoracoabdominal aortic aneurysms requires aortic cross-clamping, it carries a risk of distal organ ischaemia as a result of diminished arterial perfusion during the cross-clamp period. Among the organs at risk of ischaemic injury, the spinal cord is the most sensitive to ischaemia and reperfusion injury. Thus, one of the most serious complications is the occurrence of paraplegia and paraparesis. The incidence of this complication depends, among other factors, on the extent of the disease. It is much higher following operations for Crawford type II aneurysms (about 38%) compared to Crawford type IV aneurysm where it is less than 5%. The incidence is further dependent upon whether the operation is acute or elective[16]. Since first reported by Adams and Van Geertruyden in 1956[73], neurologic

complications of aortic surgery have remained a constant challenge to surgeons and researchers for more than 40 years.

The pathophysiology of ischaemic spinal cord injury implies a complicated interaction of multiple overlapping factors. These are factors influencing the severity and duration of the spinal cord ischaemia and neuronal metabolic rate during the ischaemic insult as well as neuronal reperfusion injury after reestablishment of spinal cord blood flow. Failure to re-implant critical intercostal arteries during the operation may also be a part of the aetiology of spinal cord injury.

Reflecting the multifactorial aetiology, an increasing number of approaches to prevent spinal cord injury are used[74-77]. Some of them are technically complex and time-consuming; some may in fact act indirectly on other factors raising the risk of injury and have their own complications, while some are effective in decreasing the risk of injury. An optimal organisation of the operation and expedient surgery to shorten occlusion and operation time is prerequisites to minimise the complication rate. In addition, different shunting and bypass techniques with or without removal of cerebrospinal fluid are used[78-80]. Attempts to reduce the metabolic rate of the neurones with hypothermia including general or spinal cord surface cooling and different pharmacological interventions are also in use[81, 82]. Pharmacological modifications with vasodilators, different neuroprotective drugs and interventions to counteract reperfusion injury are employed. It seems important to avoid drugs that could potentiate spinal cord injury[74, 83]. Finally, monitoring of sensory or motor evoked potentials to detect spinal cord

malfunction during surgery makes it possible to intervene with for instance intercostal and lumbar artery reimplantation in case ischaemia is detected[84, 85]. None of these techniques guarantees protection against ischaemic spinal cord injury and it is thought provoking that some surgeons still advocate simple single-clamp application without any adjuncts for descending thoracic aortic repair[86].

To obtain further information about the metabolic changes taking place in the spinal cord during aortic cross-clamping in an experimental model, we wanted to use a new method, microdialysis. We then had to modify our previous experimental model by performing laminectomy to expose the spinal cord at the L2- L4 level. Our conclusion from paper V was that microdialysis could be used in such a model. In our animal model we found marked changes of extracellular energy-related metabolites (pyruvate and lactate), reflecting the disturbed energy metabolism of the spinal cord following proximal aortic cross clamping. The increased lactate-pyruvate ratio might however also be influenced by the general increase in lactate concentration taking place in the lower part of the body during cross-clamping of the aorta. In a previous investigation we have found an increase in lactate levels, measured in a central artery, of 541% from basal values immediately after release of the cross-clamp, which had been applied on the descending thoracic aorta for 30 minutes (Unpublished data). One can therefore not rule out the possibility that lactate is diffusing from the circulation into the spinal cord.

At the cellular level, neural tissue injury is caused by ischaemia or by a reperfusion injury, and it has been claimed that neurologic sequelae following operations performed

during cross-clamping of the thoracic aorta are not entirely due to the ischaemic period per se. Instead, much of the damage could take place during the reperfusion period[87]. Possible mediators of reperfusion injury are toxic metabolites of molecular oxygen, which represent intermediate states of its electrochemical reduction to water[88]. Free radicals produce damage in the cell membrane through lipoperoxydation, and perioperative pharmacological interventions, either to scavenge or reduce the production of these reactive oxygen metabolites, have been investigated[18, 89].

One possible method of reducing reperfusion injury could be by inhibition of the enzyme xanthine oxidase with allopurinol. Xanthine oxidase mediates conversion of hypoxanthine to xanthine and thereby contributes to the formation of oxygen-derived free radicals. Allopurinol acts as a competitive oxidase inhibitor and could thereby theoretically reduce the amount of oxygen-derived free radicals produced in the spinal cord during aortic surgery[89].

Because allopurinol is readily available and can be used clinically, we wanted to investigate its possible effect on the metabolism of the spinal cord during thoracic aortic cross-clamping in our pig model of spinal cord ischaemia (VI).

To minimise the possibility that the lack of glutamate increase found in paper V was due to a short ischaemia time, we extended the period of aortic occlusion to 90 minutes in paper VI.

Increased glycerol concentration in controls was the only metabolite that almost reached a level of significance in difference compared to the allopurinol group (p=0,056). This

tendency of increased glycerol levels found in the interstitial fluid of the lumbar spinal cord of the control group, could indicate a more pronounced ischaemia-induced breakdown of the cellular membranes. However, more investigations are necessary to confirm this theory.

Despite the extended aortic cross-clamp time we could, however, not confirm any increase in glutamate levels in the lumbar spinal cord after proximal aortic cross-clamping as reported from similar pig models[59, 60]. On the contrary, we found a significant decrease in glutamate levels. It is unlikely that limited ischaemia-time could be an explanation for the absence of increase in glutamate concentration. The absence of increased glutamate concentrations could at least partly be explained by an insufficient grade of ischaemia in the lumbar spinal cord in our experimental model. The reduction of the lumbar spinal cord microcirculation to 40% of the basal value during cross-clamping indicates a reasonably good collateral circulation. The significant decrease in concentrations of the energy related metabolites glucose (20% of baseline) and pyruvate (50%) together with the significant increase in lactate (384% of baseline) and lactate-pyruvate ratio (761%) reflect on the other hand a considerable ischaemia in the spinal cord tissue. Insufficient equilibrium following the microtrauma induced by insertion of the microdialysis probe could also be of importance.

The missing effect of allopurinol on the metabolism of the spinal cord could theoretically be due to insufficient dosage. However, the adequacy of the allopurinol dosage used is well documented in the literature[90, 91]. It is possible that laminectomy can induce hypothermia with vasoconstriction[92], which may initiate a reduction of the

metabolism of the spinal cord compared to our previous model without laminectomy. Laser Doppler flowmetry indicated however, that the microcirculation in the spinal cord of the laminectomized animals decreased only to the same level as in the pigs without laminectomy[17]. This indicates that laminectomy in itself does not reduce the spinal cord microcirculation.

Conclusions

During thoracic- and thoracoabdominal aortic aneurysm repair performed with simple proximal aortic cross-clamping, left ventricular systolic dimensions are reduced, whereas heart rate and cardiac output are increased during aortic cross- clamping. The increased cardiac output is confirmed in an experimental study. Transesophageal echocardiography could be a valuable aid in cardiac monitoring during thoracic- and thoracoabdominal aortic surgery.

The hyperdynamic state of the circulation during proximal aortic cross-clamping gives rise to an increased blood flow velocity of the middle cerebral artery and an oedema of the head and neck with increased subcutaneous tissue interstitial fluid pressure.

Microdialysis performed in the lumbar spinal cord during proximal aortic cross-clamping, reflects the ischaemic state of the spinal cord in pigs and is well suited to the study of such phenomena. During cross-clamping there was a decrease in concentrations of the energy related metabolites glucose and pyruvate, reflecting a considerable ischaemia in the spinal cord tissue. The increase in lactate concentrations and the lactate-pyruvate ratio confirm the ischaemic situation. Allopurinol had no significant effect on the metabolism of the spinal cord in this experimental model.

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Paper I

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Cerebral Haemodynamics During Thoracic- and Thoracoabdominal Aortic Aneurysm Repair

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Objective: *To investigate cerebral haemodynamics during operations for thoracic and thoracoabdominal aortic aneurysms.*
Design: *Prospective clinical study.*
Material: *10 patients operated on consecutively with resection for thoracic (5) or thoracoabdominal aortic (5) aneurysms.*
Methods: *Blood flow velocity of the middle cerebral artery was measured through a temporal approach using a TC Doppler with a 2 MHz probe. Recordings were made during induction of anaesthesia and performed continuously before, during and after cross-clamping of the aorta.*
Results: *Following 10 min. of aortic cross-clamping blood flow velocity of the middle cerebral artery increased from 44 to 55 cm/s ($p < 0.01$). A further increase to 69 cm/s ($p < 0.01$) was observed 5 min after declamping. The pulsatility index averaged 0.74 increasing to 1.21 ($p < 0.05$) at clamping and 0.87 ($p < 0.05$) after declamping.*
Conclusion: *There was an increased blood flow velocity of the middle cerebral artery during cross-clamping of the descending thoracic aorta in patients operated on for thoracic and thoracoabdominal aortic aneurysms. This increase in cerebral blood flow and blood volume could explain the acute increase in cerebrospinal fluid pressure observed during cross-clamping of the thoracic aorta.*

Key Words: Cerebral blood flow velocity; Middle cerebral artery; Transcranial Doppler; Aortic cross-clamping; Thoracoabdominal aneurysm repair.

Introduction

The technique for thoracic- and thoracoabdominal aortic aneurysm repair using direct cross-clamping of the aorta without shunting or bypass was introduced by Crawford and colleagues.[1,2] Cross-clamping of the descending thoracic aorta induces dramatic pathophysiological changes including decreased perfusion pressure to the distal part of the body, whereas cardiac output is generally increased.[3,4] In experimental investigations we have found that cerebral blood flow is increased during aortic cross-clamping.[5,6] Increased blood flow and blood volume of the brain could be responsible for the acute increase in cerebrospinal fluid pressure observed during cross-clamping of the descending thoracic aorta.[7,8] An increased cerebrospinal fluid pressure may, in addition to the decreased distal perfusion pressure, be a contributing factor for the development of ischaemic sequelae of the spinal cord, which in turn could lead to paraplegia or paraparesis postoperatively.[9]

During surgery for thoracic and thoracoabdominal aortic aneurysms we have found indications of increased blood flow to the upper part of the body causing oedema of the head and neck.[10] To our knowledge, investigations of cerebral haemodynamics during these operations have not been presented. The aim of this investigation was to study cerebral haemodynamics when thoracic- and thoracoabdominal aortic aneurysm repair was performed during direct cross-clamping of the aorta.

Material and Methods

Ten patients operated on for descending thoracic (5) and thoracoabdominal (5) aortic aneurysms were consecutively selected for the study. Of the thoracoabdominal aneurysms, one belonged to type I

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according to Crawford, one to type II, two to type III and one to type IV. Two patients were operated on for rupture, three for impending rupture, including pain, whereas five were asymptomatic. The series consisted of eight men and two women. The mean age was 65 years (range 50–78).

A double lumen tube was applied in patients with high aneurysms to minimise manipulation of the left lung. Central venous pressure, pulmonary artery pressure and cardiac output was measured by a Swan-Ganz catheter inserted via the internal jugular vein. All patients were operated on with a combination of general and epidural anaesthesia. General anaesthesia was induced by fentanyl 0.3–0.4 mg, barbiturate 3–4 mg/kg and pancuronium 6–8 mg for muscle relaxation. Anaesthesia was maintained by fentanyl 0.05–0.1 mg/h and pancuronium 1 mg/h in addition to N_2O and isofluorane. Thoracic epidural anaesthesia was administered through a catheter in the TH5-TH6 interspace. A total dose of bupivacain (Marcain®, 5 mg/ml) from 6–8 ml was given prior to surgery. Provided the systemic arterial blood pressure was kept within normal limits, 2 ml of bupivacain was administered every second hour, but was discontinued prior to declamping to avoid drop in blood pressure.

Prior to cross-clamping of the aorta 200 ml of mannitol was administered mainly for protection of the kidneys. Sodium-nitroprusside was administered to a maximum of 5–10 μg/kg/min to maintain the proximal systolic blood pressure at about 120–140 mmHg during cross-clamping of the thoracic aorta. This dose was reduced to a minimum prior to removal of the aortic clamp. During cross-clamping nitroglycerine 0.2 μg/kg/min was administered in addition to a small dose of dopamine; 2 μg/kg/min mainly for renal protection.

The thoracic aneurysms were operated through a left thoracotomy in the 4th interspace. For the thoracoabdominal procedures, a thoracolaparotomy was preferred and the thoracic part of the incision selected according to the proximal extent of the aneurysm. A low porosity woven tube graft was applied for all procedures. During the thoracoabdominal reconstructions the orifices of the visceral arteries were anastomosed to a side-hole in the graft in three patients. In two patients with a type I and type IV aneurysm respectively, the anastomosis including these orifices were performed by the creation of a tongue of the graft. In this way the orifices of the visceral arteries with the adjacent part of the aorta was kept intact. No shunting or bypass were used in this series. During thoracoabdominal aortic resection the kidneys were cooled with about 400 cc of Ringer's acetated solution with a temperature of +4°C containing 1000 IU of heparin/litre. Cerebrospinal fluid was drained using a 16 gauge catheter introduced through the L3-L4 interspace. A closed collecting system was used with a valve mechanism allowing cerebrospinal fluid drainage if the pressure was increasing above 10 mmHg. This catheter was removed on the second postoperative day.

Blood flow velocity of the middle cerebral artery was measured through a temporal approach using a transcranial TC-Doppler 62 B, EME, Germany, with a 2 MHz probe. The recordings were made during induction of anaesthesia and performed continuously before, during and after cross-clamping of the descending thoracic aorta. Systolic, diastolic and mean flow velocity were recorded and pulsatility index was calculated.

Statistics

The data are reported as mean values and range. The statistical calculations were based on Students *t*-test for paired data. $p < 0.05$ was accepted as the level of statistical significance. Comparison was made against the previous phase of the operation.

Results

Following 10 min. of cross-clamping of the descending thoracic aorta blood flow velocity of the middle cerebral artery increased from 44–54 cm/s ($p < 0.05$, Fig. 1). A further increase to 69 cm/s. was observed 5 min after declamping ($p < 0.01$). Flow velocity recordings from the middle cerebral artery before and after cross-clamping of the aorta are shown in Fig. 2. Prior to cross-clamping, the pulsatility index averaged 0.74 increasing to 1.21 at clamping ($p < 0.05$), and 0.87 ($p < 0.05$) after declamping.

Before cross-clamping, mean arterial blood pressure averaged 88 mmHg compared to 96 mmHg during cross-clamping of the aorta ($p > 0.05$). At 15 min following declamping a slight hypotension with a mean pressure of 72 mmHg was observed ($p < 0.05$). CVP averaged 10, 12 and 12 mmHg before, during and after clamping, respectively. Cardiac output increased from 5 l/min to 7.3 l/min during clamping ($p < 0.05$) and 9.8 l/min as the maximum value 5 min after declamping of the aorta ($p < 0.05$).

The time of aortic cross-clamping averaged 56 min

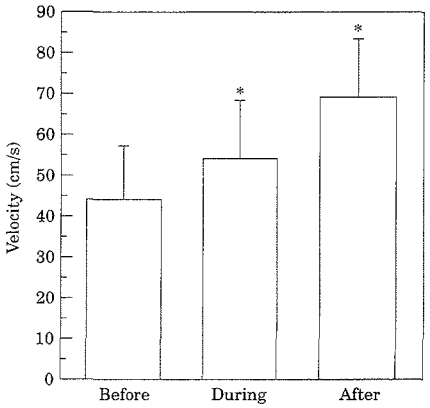

Fig. 1. Mean blood flow velocity of the middle cerebral artery before and during aortic cross-clamping and 5 min after declamping of the aorta during thoracic- and thoracoabdominal aortic aneurysm repair (mean, S.D.). * = Statistically significant difference compared to the previous phase of the operation.

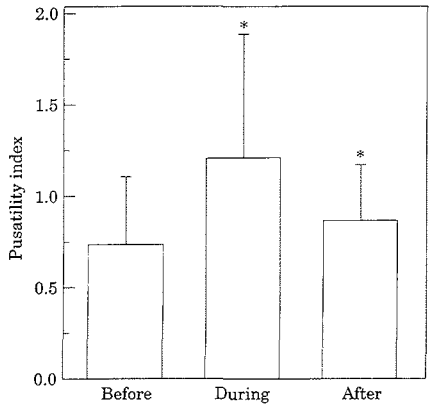

Fig. 3. Pulsatility index (Vsyst-Vdiast)/Vmean of the middle cerebral artery before, during and after cross-clamping of the thoracic aorta during thoracic and thoracoabdominal aortic aneurysm repair.* = Statistically significant difference compared to the previous phase of the operation.

(range 15–90) and the total operating time averaged 218 min (range 140–295). An average of 1750 ml of colloids and 8470 ml of crystalloid fluids were given. A mean of 11 units of blood (SAG, 250 ml) was given and at termination of the operation the mean rectal temperature was 34.2°C. 66.8 ml of cerebrospinal fluid was drained before and during cross-clamping of the aorta. The average volume drained in the postoperative period was 498 ml. This volume was removed during an average period of 66 h following termination of the operation.

One patient succumbed on the first postoperative day due to haemorrhage. This patient was operated on for impending rupture. Another patient, operated for a contained rupture, died from pancreatitis 18 days following operation. The patient with the longest time of cross-clamping developed a paraparesis necessitating the use of a wheel-chair. In the rest of the patients, the operation was uneventful without major complications.

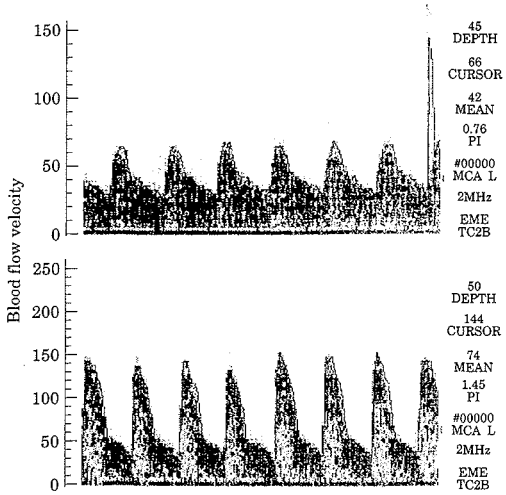

Fig. 2. Flow velocity recordings using transcranial Doppler technique before (above) and during (below) aortic cross-clamping in a patient during thoraco-abdominal aneurysm repair. Note that the scale of flow velocity is different in the two recordings. Mean systolic flow velocity prior to cross-clamping was 42 cm/s and 74 cm/s during cross-clamping.

Table 1. Clinical data and fluid administration during operations for thoracic and thoracoabdominal aortic aneurysms. The data are presented as mean and range

Age (years)	65 (50–78)
Aortic clamp-time (min)	56 (15–90)
Total operating time (min)	218 (140–295)
Units of SAG blood (250 ml)	11 (2–36*)
Colloids (ml)	1750 (0–4000*)
Crystalloid solutions (ml)	8470 (3800–25400*)
Rectal temperature at termination of the operation (°C)	34.2 (32.3–35.7)

*One patient succumbed because of haemorrhage and large volumes of blood, colloid and crystalloid solution was given during and immediately after operation in this patient.

Table 2. Haemodynamic values in patients operated on for thoracic- and thoracoabdominal aortic aneurysm using direct cross-clamping of the descending thoracic aorta. The data are presented as mean and range

	Baseline values	During cross-clamping	After declamping
Systemic arterial blood pressure (mmHg)	84 (70–117)	96 (71–123)	72 (61–94)
Central venous pressure (mmHg)	10 (3–15)	12 (6–18)	12 (7–20)
Cardiac output (l/min)	5.0 (4.2–6.5)	7.3 (4.3–10.0)	9.8 (8.6–10.4)

Discussion

Measurement of blood flow velocity with transcranial Doppler technique has been compared with other methods,[11–13] and has been documented as a reliable indicator of cerebral blood flow. A significant increase in middle cerebral artery blood flow velocity was observed during cross-clamping of the thoracic aorta during thoracic- and thoracoabdominal aortic aneurysm repair. During cross-clamping this could partly have been caused by an increase in arterial blood pressure. However, in the declamping phase there are indications that the vascular resistance of the brain was decreased. Furthermore, cerebral vasodilatation could have been induced by anti-hypertensive drugs like Sodium-nitroprusside, but increased cerebral blood flow has also been observed in animal experiments independent on the use of vasoactive agents.[6] In these experiments, however, the control cases had a proximal systemic blood pressure which was significantly higher than those who were treated by Sodium-nitroprusside. During surgery normotension, or a slight hypertension, is allowed whereas severe hypertension should be avoided since it may represent an intolerable stress to the heart. With our regimen of treatment, hyperdynamic cardiac function is seen and cardiac output was increased during aortic cross-clamping mainly by tachycardia, whereas the stroke volume was relatively unchanged.[14] The same pattern as seen in elderly atherosclerotic patients has also been observed in an experimental model using young animals.[4]

The increased pulsatility index observed after application of the aortic clamp probably reflects a decreased wind-kessel function of the aorta, since the volume of the aorta and the major vessels receiving the cardiac output is significantly decreased during cross-clamping. Increased blood flow and blood volume of the brain may at least partly be responsible for the acute increase in cerebrospinal fluid pressure observed during these operations. In addition to the decreased arterial pressure of the spinal cord, the increased cerebrospinal fluid pressure could contribute to the decreased perfusion pressure of the cord, thereby increasing the risk of ischaemic damage.[9] Although still a controversial topic, we tried to keep the cerebrospinal fluid pressure at normal levels during and after surgery in an attempt to minimise the risk of postoperative neurologic sequelae. Since we controlled the cerebrospinal pressure, we could not study the influence of this pressure on the occurrence of paraplegia or paraparesis. In theory both the production and the absorbtion of cerebrospinal fluid could have been changed in this period and the present series is too small for statistical evaluation of this particular problem.

Our findings are in accordance with previous observations from animal experiments, where an increase of internal carotid blood flow, and the middle cerebral artery blood flow velocity was observed. Also an increase in the microcirculation of the cerebral parenchyma has been demonstrated.[5] In the animal studies there was a rapid decrease of cerebral blood flow at declamping, whereas in the present investigation a further increase in the middle cerebral artery flow velocity was observed when the aortic clamp was released. The increase in cardiac output in the early declamping phase is also in contrast to findings from animal experiments. However, in an experimental model using MRI of the brain, the ventricular volume further decreased in the declamping period indicating that the cerebral vascular volume further increased during this period.[7] It is possible that a decrease of the sagittal sinus pressure and cerebral tissue pressure at aortic declamping may increase the perfusion pressure during this phase of the procedure. In the clinical situation it is also possible that a certain time interval is needed to normalise the mechanisms responsible for reestablishment of a normal intracranial vascular tone after removal of the aortic clamp.[13,15,16]

In conclusion, a significant increase in blood flow velocity of the middle cerebral artery during and immediately after cross-clamping of the descending thoracic aorta was demonstrated in patients operated on for thoracic and thoracoabdominal aortic aneurysms. This is in accordance with previous experimental investigations and supports the accumulating evidence that the cerebral blood flow and blood volume is increased during cross-clamping of the descending thoracic aorta. In turn, these phenomena could be responsible for the acute increase in cerebrospinal fluid pressure observed during operations where direct cross-clamping of the thoracic aorta is applied.

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Paper II

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Proximal Subcutaneous Interstitial Fluid Pressure during Cross-Clamping of the Descending Thoracic Aorta: A Study of Patients Operated on for Thoracic- or Thoracoabdominal Aortic Aneurysms

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Abstract. Seven patients were operated on for thoracic (n = 2) or thoracoabdominal (n = 5) aortic aneurysms during cross-clamping of the aorta. Interstitial tissue fluid pressure was measured at the neck during cross-clamping of the descending thoracic aorta by the wick-in-needle technique, whereas control measurements were obtained prior to cross-clamping. The subcutaneous interstitial fluid pressure was significantly higher on the neck during cross-clamping of the thoracic aorta compared with control measurements (median 3.7 mmHg vs −0.6 mmHg, $p < 0.05$). Increased subcutaneous interstitial tissue pressure of the upper part of the body is probably caused by increased capillary filtration rate induced by inhibited autoregulatory functions during aortic cross-clamping. The pressure measurements objectively confirm the problem of edema formation of the head and neck during these operations. The edema may occasionally affect the upper airways and represent a problem for intubation of the patient in the postoperative phase.

Introduction

Repair of thoracic- and thoracoabdominal aortic aneurysms is often performed during direct cross-clamping of the descending thoracic aorta with pharmacological control of proximal blood pressure and cardiac function [1,2]. Despite the fact that the lower part of the body is, to a great extent, deprived of its blood circulation during these procedures, cardiac output is significantly increased. In experimental investigations, a significant increase of blood flow of the carotid arterial system has been observed [3]. In the clinical situation, blood flow velocity of the middle cerebral artery is increased during cross-clamping and immediately after declamping (Juul et al, unpublished data). During and after these operations, a significant edema of the head and neck is a common occurrence. The edema lasts for 1–2 days postoperatively. It may affect the larynx and interfere with respiration. The edema may represent a problem should reintubation be necessary in the postoperative phase [4].

The aim of this investigation was to study whether this subcutaneous edema could be evaluated quantitatively by the measurement of subcutaneous interstitial tissue pressure. Measurements were performed prior to cross-clamping of the aorta for control and following termination of the reconstruction when the aortic clamps had been released.

Materials and Methods

Seven patients (six males and one female) with a median age of 64 years (range 39–71 years), were operated on for thoracic- (n = 2) or thoracoabdominal (n = 5) aortic aneurysms. In the latter group, one patient had a type II aneurysm and four had a type IV aneurysm according to the classification of Crawford [5]. Four patients were operated on as emergencies due to rupture, contained rupture, or pain. Proximal arterial blood pressure was monitored via a catheter placed in the right radial artery. Central venous pressure, pulmonary artery pressures, and cardiac output was measured by a Swan-Ganz catheter, inserted via the internal jugular vein. All patients underwent surgery with a combination of general and epidural anesthesia [6]. General anesthesia was induced by a combination of Fentanyl and Pancuronium. Anesthesia was maintained by a combination of oxygen and nitrous oxide together with Isoflurane. A moderate thoracic epidural anesthesia was induced by Marcaine for postoperative pain relief.

Prior to cross-clamping of the descending thoracic aorta, Sodium Nitroprusside was given to keep the systolic blood pressure slightly above 100 mmHg. During cross-clamping, a combination of Sodium Nitroprusside and Nitroglycerine was given in addition to a small dose of Dopamine. Immediately prior to declamping, the infusion of

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Sodium Nitroprusside and Nitroglycerine was discontinued. The administration of pressor was performed as needed to keep the systolic blood pressure above 100 mmHg during the declamping phase.

The thoracic aneurysms were operated on through a left thoracotomy in the fourth interspace. For the thoracoabdominal procedures, a thoracolaparotomy was prefered and the thoracic part of the incision was selected according to the proximal extent of the aneurysm. A tube graft was inserted for the thoracoabdominal procedures, and the visceral arteries were anastomosed to a side hole in the graft in one case. In the other cases, the proximal anastomosis was performed by the creation of a posterior tongue of the graft. In this way the orifices of the visceral arteries with the adjacent part of the native aorta were kept intact. No shunts or bypasses were used in this series. Each kidney was cooled to +4°C with about 200 cc of Ringer's acetated solution that contained 1000 I.U. of Heparin per liter. Spinal fluid drainage, using a 16 gauge catheter introduced through the L_3–L_4 interspace, was performed to keep the cerebrospinal fluid pressure below 10 mmHg.

Subcutaneous tissue interstitial fluid pressure (P_{if}) was measured in all patients with the "wick-in-needle" technique, which has been described previously [7,8]. Hypodermic needles (0.8 mm diameter, 40 mm length) with a 4 mm side hole approximately 7 mm from the tip were loosely filled with cotton thread and sterilized. The needle was connected to a pressure transducer (Statham P23 D6) with a polyethylene tube (Portex manometer line, 60 cm, 200/490/060). The whole system was connected to an amplifier unit and the actual mean pressure was shown directly on a display in front of the pressure monitor and recorded on a printer.

Control measurements of P_{if} were taken at the neck before clamping in three patients, in the left arm in three, and on the thigh in one patient. After termination of aortic cross-clamping when the reconstruction was finished, P_{if} was measured on the neck in all patients.

Statistics

The statistical calculations were based on Wilcoxon's signed rank test for paired data. $p < 0.05$ was accepted as the level of statistical significance.

Results

The total time of aortic cross-clamping varied from 44 to 82 minutes with a median of 56 minutes. The mean operating time was 3.9 hours. An average of 3.8 l (median 3.1) of colloids including plasma, albumen, and a gelatine solution (Heamaccel®) were given. The volume of blood transfusion averaged 4.1 l of packed cells (median 3.0 l). The lowest body temperature during the operation averaged 33.3°C. The maximum central venous pressure during the operation was a median of 12 mmHg (range 9–18).

The mean arterial blood pressure averaged 80.9 mmHg before cross-clamping, 83.7 mmHg during cross-clamping, and 76.7 mmHg during the first 15 minutes of the declamping phase. Before cross-clamping, the average cardiac output was 5.3 l/minute, increasing to 7.3 l/minute 15 minutes after application of the aortic clamp. Cardiac output normalized later in the declamping period.

All patients developed significant clinical edema of the head and neck during cross-clamping of the thoracic aorta. The edema was at its maximum immediately following termination of the operation, but lasted for approximately 3 days. Clinical edema of the upper extremities was not observed during cross clamping of the aorta, but seemed to develop to some extent later in the postoperative period.

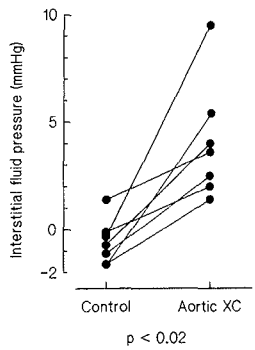

Fig. 1. Interstitial fluid pressure (P_{if}) during operations for thoracic and thoracoabdominal aneurysms. The control measurements are shown to the left and the measurements to the right were performed immediately following declamping of the thoracic aorta. The lines connect the control values with the postreconstructive levels of the neck in the same patients, respectively.

Following aortic cross-clamping, P_{if} of the neck varied from 1.4 to 9.5 mmHg with a median of 3.7 mmHg (mean 4.1). This value was significantly higher than control measurements, having a median value of −0.7 mmHg (range −1.6 to +1.4 mmHg, mean −0.6, $p < 0.02$) (Fig. 1). There was a tendency for a higher median P_{if} when the cross-clamping was done just distal to the left subclavian artery (N:3) compared to the cases where cross-clamping had been performed more distal on the descending thoracic aorta (n = 4), 5.4 mean (6.8) mmHg vs 2.3 (mean 2.5) mmHg. The numbers were, however, too small for statistical calculations.

One patient died 14 days after operation due to necrotizing pancreatitis whereas a second patient operated on for a ruptured thoracic aneurysm, having severe pre- and intraoperative hemorrhage, succumbed later on the day of operation. Five patients recovered without complications. The double lumen tube was routinely changed with a regular endotracheal tube immediately following the operation. No reintubations became necessary later in the postoperative phase. There were no cases of paraplegia or paraparesis in this series.

Discussion

This study confirms that the subcutaneous tissue interstitial fluid pressure of the neck is significantly increased during operations performed during cross-clamping of the descending thoracic aorta. The present control values for P_{if} are in agreement with control values from the chest and leg measured with the subject in the supine position [8,9].

The edema subsides in the postoperative period, but may be quite severe during the first postoperative day. Despite few observations, our measurements indi-

cated a higher P_{if} in the edematous neck, the more proximally on the thoracic aorta where the cross-clamping had been performed. Due to a limited number of recordings we were unable to explore further whether P_{if} was dependent upon the time of cross-clamping and the extent of arterial repair, although some correlation seems likely. Further, it would be of interest to follow the development of the subcutaneous interstitial tissue pressure in the postoperative period. This was not performed for practical reasons as an invasive method had to be used for measurement of P_{if}.

The described edema has been reported to affect the larynx and impair the respiration when the patient is otherwise ready to be extubated. Laryngeal edema may represent a problem when reintubation is indicated in the postoperative period. This could be the case when the double lumen tube is to be replaced by a regular tube after termination of the operation [4]. However, no problems with edema of the airways were observed in this series.

Cardiac output is increased during cross-clamping although mainly the upper part of the body is perfused with blood. Simultaneously, a considerable increase in blood flow through the carotid system has been observed in animal experiments [3]. An impaired function of the arterioles supplying the edematous tissue inducing increased blood flow and capillary filtration is probably one mechanism for edema formation following thoracic aortic cross-clamping. The use of anesthetic pharmacological agents could also interfere with transcapillary fluid balance in these patients [10]. Further, the edema preventing mechanisms of subcutaneous tissue may be less effective than in the brain [12] as no signs of brain edema have been observed on magnetic resonance imaging (MRI) following cross-clamping of the descending thoracic aorta in an experimental model [13]. Venous congestion is unlikely to be the cause of the edema as central venous pressure was kept within normal limits during these operations. This is in agreement with observations from experimental investigations [10].

Although previous investigations have shown a considerable increase of blood flow through the carotid arteries during cross-clamping of the descending thoracic aorta [4], blood flow through the arteries of the upper extremities, the vertebral arteries, and the external carotid arteries has to our knowledge, not been studied. It is likely that there is considerable increase in blood flow through tissue supplied by the external carotid artery during cross-clamping of the descending thoracic aorta. This has been supported by angiographic investigations during cross-clamping of the descending thoracic aorta in pigs (Strømholm, unpublished data). In the present investigation the edema as well as the region selected for pressure measurements were supplied with blood mainly from branches of the external carotid artery.

Edema-preventing measures may be considered, for instance, by elevating the upper part of the body in the postoperative period. Intense diuretic therapy should probably be avoided because it could cause an unstable hemodynamic situation giving rise to decrease of blood pressure. This situation may further decrease spinal cord circulation and has been suggested as one of the mechanisms responsible for late paraplegia [11].

No shunts or bypass techniques were applied in this series. We have used a heparinized shunt occasionally in other patients with decreased cardiac function, but no systematic evaluation of edema formation was made. Although a more stable hemodynamic situation may be obtained by either bypass or shunting, to our knowledge no investigation regarding its effect on subcutaneous interstitial tissue fluid pressure or proximal edema formation has been performed.

In conclusion, this investigation confirms increased subcutaneous tissue interstitial fluid pressure on the neck during thoracic- and thoracoabdominal aneurysm repair performed during simple aortic cross-clamping. Although the edema formation on the neck and head usually subsides within the first postoperative days, the edema may also affect the larynx and could represent a problem for intubation in the postoperative period.

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Paper III

Eur J Vasc Endovasc Surg 12, 401–406 (1996)

The Importance of Transesophageal Echocardiography during Surgery of the Thoracic Aorta*

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Objectives: *To assess left ventricular dimensions and cardiac output during thoracic and thoracoabdominal aortic aneurysm repair.*

Material and methods: *Nine patients undergoing thoracic and thoracoabdominal aneurysm repair using direct cross-clamping without shunt or by-pass were studied prospectively. Prior to, during cross-clamping (XC) and after declamping left ventricular cross-sectional areas were monitored with transesophageal echocardiography. A pulmonary artery catheter was used for measurements of cardiac output with the thermodilution technique.*

Results: *Cardiac output increased 43% from baseline during XC ($p < 0.01$) and was still 55% above baseline at declamping ($p < 0.05$). Left ventricular end-systolic inner area was reduced 32% during XC ($p < 0.01$). Pulmonary artery pressures and central venous pressure increased during declamping ($p < 0.05$). Heart rate increased 38% from 66 beats/min to 92 beats/min ($p < 0.01$) and was still 30% elevated at declamping ($p < 0.01$).*

Conclusion: *During thoracic aortic XC, cardiac output is increased and left ventricular end-systolic dimension is reduced. TEE is a valuable supplement to pressure measurements for the evaluation of cardiac function during surgery of the thoracic aorta.*

Key Words: Transesophageal echocardiography; Aortic cross-clamping; Thoracic aneurysm; Thoracoabdominal aneurysm; Cardiac output; Left ventricular dimension.

Introduction

Direct cross-clamping (XC) of the descending thoracic aorta without shunting or by-pass is widely used during thoracic and thoracoabdominal aortic aneurysm repair. During these procedures peripheral resistance is elevated and proximal arterial pressures are increased. In some patients this technique can impair cardiac function.[1,2] With extensive use of vasodilation, descending thoracic aortic cross-clamping is remarkably well tolerated, although there are still controversies regarding the haemodynamic response to this procedure. Different responses regarding the performance of the left ventricle have been observed in experimental studies; whereas cardiac output increased in some studies[3–5] it decreased in others.[6,7] In clinical studies too, there are varying observations regarding cardiac output during descending thoracic cross-clamping.[1,2,8] In previous experimental animal studies left ventricular dimensions increased when segmental length measurements were made during cross-clamping,[7,9,10] Similar observations have been made in patients using transesophageal echocardiography (TEE).[11] However, based on echocardiography in pigs, we recently found reduced ventricular dimensions and increased contractility during XC.[12] In patients undergoing thoracic and thoracoabdominal aneurysm repair, TEE has been reported to be more sensitive than the measurement of pulmonary artery pressure for the detection of left ventricular failure during XC.[13]

The aim of this study was to investigate the application of TEE for assessment of left ventricular dimensions during surgical treatment for thoracic and thoracoabdominal aortic aneurysms using direct aortic cross-clamping without shunting or by-pass techniques. Further, it was the intention to compare these findings with measurement of cardiac output and pulmonary artery pressures.

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Materials and Methods

Ten patients were consecutively included in the investigation. Three patients were operated on for thoracic aneurysms, whereas seven had thoracoabdominal aortic aneurysm repair. In the latter group, three patients belonged to type I, one to type II, one to type III and two to type IV. In addition one patient had a type B aortic dissection. The mean age was 66 years (range 50–70 years) and two were female. Altogether six patients were operated on acutely, three of these had a ruptured aneurysm, but were haemodynamically stable at the induction of anaesthesia. Three patients were operated on for severe pain, most likely caused by expansion of the aneurysm.

One patient received 500 mg of barbiturate immediately prior to XC in an attempt to minimise ischaemic damage to the spinal cord.[14] This patient was preoperatively found to have normal coronary angiography, but developed ventricular dilation with profound increase in pulmonary artery pressures during XC. As barbiturates are well known cardiodepressive agents, this patient was excluded from further statistical analysis.

Anaesthesia

All patients were premedicated with Morphine-Scopolamine. A thoracic epidural catheter was placed in the T5–T6 interspace and a 16 gauge catheter was introduced at the L3–L4 level for cerebrospinal fluid drainage. Cerebrospinal fluid pressure was maintained below 10 mmHg during XC. Following induction of anaesthesia with fentanyl (0.3–0.4 mg), pancuronium (6–8 mg) and barbiturate (3–4 mg/kg), a double lumen endotracheal tube was placed in patients with high aneurysms to avoid manipulation of the left lung during surgery. A pulmonary artery catheter (Oximetric, Abbott, U.S.A.) was introduced through the internal jugular vein for measurements of central venous pressure (CVP), mean pulmonary artery pressure (PAP) and pulmonary artery wedge pressure (PCWP). Maintenance of anaesthesia was obtained by a combination of regional and general anaesthesia. Fentanyl and pancuronium were repeated in doses of 0.05–0.1 mg/h and 1 mg/h, respectively in addition to N_2O and isoflurane. Thoracic epidural anaesthesia (TEA) was achieved by the administration of 6–8 ml of bupivacain (5 mg/ml) prior to surgery. Provided the systemic arterial blood pressure was within normal limits, 2 ml of bupivacain was administered every hour. However, TEA was discontinued prior to declamping thereby avoiding an additive hypotensive effect.

Surgery

The thoracic aortic aneurysms were operated through a left thoracotomy in the 4th interspace. For the thoracoabdominal procedures a thoracolaparotomy was preferred, and the thoracic part of the incision selected according to the proximal extent of the aneurysm. A low porosity woven tube graft was applied for all procedures. During the thoracoabdominal reconstructions, the orifices of the visceral arteries were anastomosed to a side-hole in the graft in four cases, whereas in one case a separate graft to the left renal artery became necessary. In two patients with a type I and one with a type IV aneurysm respectively, the anastomoses, including these orifices, were performed by the creation of a tongue of the graft. In this way the orifices of the visceral arteries with the adjacent part of the aorta was kept intact. No shunting or bypass was used in this series. During thoracoabdominal aortic resection the kidneys were cooled with approximately 400 cc of Ringer's solution at a temperature of + 4°C containing 1000 IU of heparin/1.

Prior to XC, 300 ml of mannitol was infused i.v. for renal protection. Sodium nitroprusside (SNP) was infused to reduce systolic blood pressure to about 80 mmHg before cross-clamping. During XC a small dose of dopamine was routinely administered. In order to avoid serious metabolic acidosis, sodium bicarbonate was given to maintain normal blood gases. With increasing blood pressure and pulmonary artery pressure following XC, SNP was administered to a maximum of 5–10 μg/kg/min together with nitroglycerin 2 μg/kg/min. Both infusions were terminated when the aortic clamp was about to be removed. At declamping, rapid infusions of blood, fresh frozen plasma and platelets were started. If necessary, inotropic agents or vasopressors were given.

Methods of measurements

Left ventricular dimensions: Using two-dimensional ultrasound imaging of the left ventricle (LV), midcavitary cross-sectional images were obtained using a standard 5 MHz TEE probe. The probe was connected to a scanner (CFM 750, Vingmed Sound, Horten,

Norway) which was interfaced to a computer (Macintosh II-series, Apple Computers, Cupertino, CA, U.S.A.) for display and processing of digital images by use of dedicated software for handling of digital ultrasound and cardiovascular data (EchoDisp 3.0 Vingmed Sound). The images were transferred as digital scanline ('raw') data without loss of information. The borders of the left ventricle were manually traced giving inner and outer areas in end-systole (ESi, ESo) and inner area in end-diastole (EDi). These areas will represent ventricular volumes in a symmetric contracting ventricle when no wall movements changes occur.[15]

Pulmonary artery catheterisation: In one patient we were unable to insert the pulmonary catheter due to technical reasons. Cardiac output was measured with the thermodilution method, injecting 10 ml saline at room temperature for each measurement. Three measurements were made randomly with respect to the respiratory cycle and averaged. The calculations were made in a cardiac output computer (Oximetrix 3, Abbott, U.S.A.).

Baseline recordings were made 5–10 min prior to XC to avoid effects of anaesthesia induction and surgical preparation. During XC, measurements were recorded continuously, but the data obtained at 20–30 min following clamping were chosen to give the patient time to stabilise from the immediate effect of XC.[12] In one patient, LV areas were only available at 15 min, and in another patient CO data were only available at 15 min. Finally, a complete series of measurements was obtained within 5–15 min after clamp removal.

Statistical analysis

All values are given as means and standard error of measurements (S.E.M.). The statistical significance of differences between means was assessed with two-side paired *t*-test and $p < 0.05$ accepted as the level of statistical significance.

Results

Left ventricular cross-sectional area in ESi decreased 32% from a baseline value of 7.3 cm^2 to 5.0 cm^2 ($p < 0.01$) during aortic XC. There were no significant changes in ESo or EDi during the procedure. Cardiac output increased 43% from an average of 5.3 l/min prior to XC of the thoracic aorta to 7.6 l/min ($p < 0.01$). After declamping cardiac output was 8.2 l/min and still 55% elevated from baseline ($p < 0.05$) (Fig. 1).

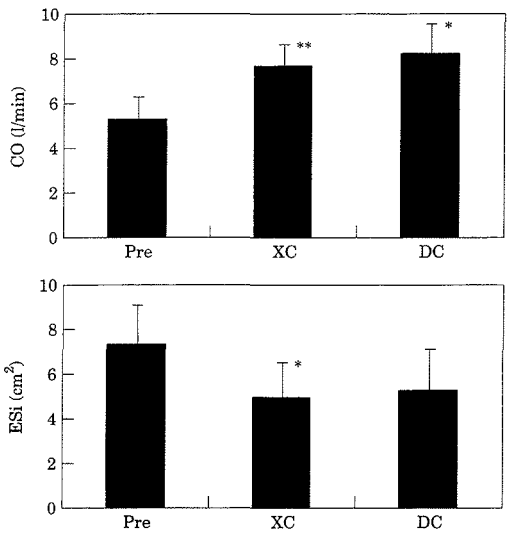

Figure 1 Cardiac output (CO) and left ventricular end-systolic inner area (ESi) during thoracic and thoracoabdominal aortic anerysm repair. Values are presented as mean and S.E.M. at baseline (Pre), during cross-clamping (XC) and after declamping (DC).

Heart rate increased 38% from 66 beats/min prior to XC to 92 beats/min ($p < 0.01$) during XC, and was still 30% elevated from baseline in the declamping phase ($p < 0.01$). Systolic arterial blood pressure averaged 111, 128 and 92 mmHg during the three phases of operation, respectively. There were no changes in CVP, PCWP or PAP during XC. However, following declamping there was an increase in CVP from 8 to 12 mmHg ($p < 0.01$) and in PAP from 18 to 23 mmHg ($p < 0.02$) (Table 1).

One of the patients died shortly after the operation, two succumbed from multiorgan failure and one of pancreatitis within 30 days. Of these patients, two were operated on for rupture and two had pain probably caused by expansion of the aneurysm. The patients were haemodynamically stable at induction of anaesthesia. One patient had an extensive dissection of the entire descending thoracic and abdominal aorta in addition to his ruptured aneurysm and suffered a permanent paraparesis. Clamp-time and volume replacement during surgery is summarised in Table 2.

Discussion

The present investigation shows that cardiac output is

Table 1. Haemodynamic data in patients operated on for thoracic and thoracoabdominal aortic anerysms.

	Pre	XC	DC
Heart rate (beats/min)	66 (2.9)	92 (8.1)*	86 (6)*
Systolic arterial blood pressure (mmHg)	111 (6.5)	128 (9.1)*	92 (5)*
Mean pulmonary artery pressure (mmHg)	18 (0.8)	21 (2.4)	23 (1.7)*
Central venous pressure (mmHg)	9 (1.3)	10 (2)	12 (1.7)*
Pulmonary artery wedge pressure (mmHg)	11 (1)	13 (2.3)	15 (2.1)
End-diastolic inner area (cm^2)	18.9 (2)	17.7 (2.4)	16.3 (1.9)
End-systolic outer area (cm^2)	32 (3.8)	31.2 (3.9)	24.4 (3.5)

Values are presented as mean and SEM at baseline (Pre), during cross-clamping (XC) and after declamping (DC).
*$p<0.05$ *vs.* baseline.

significantly increased when thoracic and thoracoabdominal aortic repair is performed during direct XC of the aorta. End-systolic dimensions of the left ventricle is decreased and proximal arterial blood pressure and heart rate are increased. Thus, a hyperdynamic circulatory state proximal to the aortic clamp is the result in spite of the fact that only approximately one-third of the body is perfused with blood. This haemodynamic paradox is known from previous experimental work although not all authors have been able to confirm it.[3–5,11] Clinically, only Godet *et al.* has reported increased CO in patients undergoing thoracoabdominal aneurysm repair.[8] Some authors believe that the reason for the increased CO is volume displacement from the splanchnic circulation to the non-compliant upper part of the body increasing preload and thus activating the Frank-Starling mechanisms. Provided this mechanism had been responsible for the increased CO one would have expected an increase LV diastolic diameter. In the present study, however, no changes in LV diastolic diameter were observed.[3,9] Others believe that sympathetic discharge due to ischaemia distal to the aortic clamp is responsible for the haemodynamic response to XC.[16–18]

Cardiac output may increase as a result of increased stroke volume, increased heart rate or both. In our study, heart rate increased 38% and explains part of the increased CO. However, a reduced ESi and unchanged EDi also implicate that stroke volume is increased. This is in contrast to Roizen *et al.* who found increased end-systolic and end-diastolic dimensions during supraceliac aortic XC in patients.[11] However, in his study measurements were made 2–5 min after application of the aortic clamp. In animal experiments we have recently observed that thoracic aortic XC initially produced an instant left ventricular dilation which was gradually normalised for the first 5 min and was thereafter followed by decreased LV dimensions due to an increased myocardial contractility.[12]

Table 2. Clinical data and fluid administration during operations for thoracic and thoracoabdominal aortic aneurysms.

Age (years)	66 (2.2)
Aortic clamp time (min)	70 (7)
Total operating time (min)	251 (22)
SAG blood (ml)	3970 (1031)
Plasma (ml)	1766 (417)
Colloids (ml)	1755 (276)
Crystalloid solutions (ml)	9900 (2045)
Rectal temperature at termination of the operation (°C)	33.9 (0.4)

Values are presented as mean and S.E.M.

The changes in left ventricular dimensions observed in the present study, indicate that the wall thickness increases during XC. This is the only way the normal LV can maintain wall stress within normal limits when the afterload is abruptly elevated.[12,19] The physiological basis for this phenomenon is an increase in myocardial contractility due to an increased sympathetic tone. This explanation is supported by increased levels of catecholamines found during and after XC in patients[16–18] and in experimental studies.[6] Thus, oxygen consumption has to be increased. Accordingly, Bjørnstad *et al.* has found increased coronary blood flow proportional to increased afterload during graded proximal XC.[20]

The increase in PAP and CVP following declamping was not reflected in LV diastolic dimensions, thus no change in preload occurred. The increase in PAP may be explained by changes in pulmonary vascular resistance seen in reperfusion states.[13,21] Since alterations in the ventricular pressure-volume relationship occur in dynamic situations as aortic clamping and declamping, neither CVP nor PCWP can be regarded as reliable indicators of right or left ventricular preload.[22,23] Therefore, accurate evaluation of cardiac performance should not be based on pressure alone. In our study, there was no left ventricular dilation after declamping, even if there was a trend towards an increase in PCWP simultaneously with an increase in PAP.

On the contrary, end-systolic area was still reduced and when hypotension was observed, additional

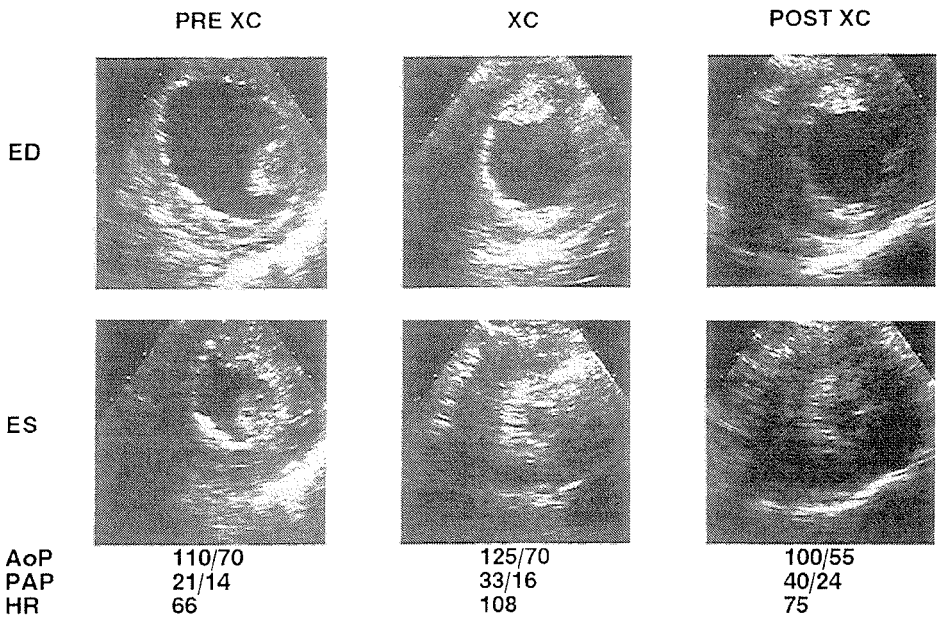

Figure 2 Transesophageal ultrasound short axis images of left ventricle (LV) in end-diastole (ED) and end-systole (ES) in a patient undergoing surgery for thoracoabdominal aortic aneurysm. Images were recorded before cross-clamping (PRE XC), during cross-clamping (XC) and after declamping (POST XC). AOP: proximal aortic pressure; PAP: pulmonary artery pressure; HR: heart rate.

volume was given, regardless of the levels of PCWP or PAP. Thus, a hyperdynamic state was present although the pulmonary artery pressure and the central venous pressure were increased. Had only the pressures been recorded the situation might have been misinterpreted as cardiac insufficiency. Therefore TEE is a valuable supplement to pressure measurements and could significantly influence the anaesthetic management and fluid therapy during these operations.

The high mortality in this series can be explained by a high number of patients operated on acutely. Three patients were operated on for rupture and an additional three had pain caused by aneurysm expansion. It is well known that patients who are operated on for symptomatic acutely-expanding aneurysms have a higher mortality than those who are operated on electively. We do not think that these results influence our conclusion since all patients were haemodynamically stable when the measurements were performed. Furthermore, we have been able to confirm our data from more recent clinical experience with a significantly lower complication rate.

In conclusion, during thoracic aortic XC left ventricular systolic dimension is reduced, whereas heart rate and cardiac output are increased. TEE could be a valuable aid in cardiac monitoring and fluid therapy during thoracic aortic surgery.

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Paper IV

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ORIGINAL, ACCEPTED

Cardiac output measurements during cross-clamping of the descending thoracic aorta in pigs.

A comparison between transit-time ultrasound, thermodilution and pulsed Doppler ultrasound

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ABSTRACT

Background: Cross-clamping of the descending thoracic aorta (XC) induces an increase in cardiac output (CO). The intention of this study was to evaluate the high CO during XC by the use of clinically available methods (thermodilution and pulsed Doppler ultrasound) compared to transit-time ultrasound flowmetry of the ascending aorta as the gold standard.

Method: Ten pigs were anaesthetised with ketamine and fentanyl. The descending thoracic aorta was cross-clamped for 30 minutes, and cardiac output was measured with pulmonary artery thermodilution technique, pulsed Doppler ultrasound on the aortic annulus and transit-time ultrasound flowmetry of the ascending aorta.

Results: Fifteen minutes following XC, CO increased from 1.7 L/min to 4.6 L/min measured with transit-time ultrasound ($P<0.05$). With thermodilution technique, CO increased from 2.6 L/min to 5.7 L/min ($P<0.05$), and from 2.4 L/min to 6.0 L/min measured with Doppler ultrasound ($P<0.05$). There was an increase in mean arterial pressure of 81% and heart rate increased 76% ($P<0.05$).

Conclusion: XC of the descending thoracic aorta induces an increase in CO 171%. Thermodilution and pulsed Doppler ultrasound are reliable methods for detecting high cardiac output during thoracic aortic surgery.

key words: cardiac output; cross-clamping; Doppler ultrasound; ketamine; thermodilution; thoracic aorta; transit-time ultrasound

Cross-clamping of the descending thoracic aorta (XC) during thoracic aortic surgery is associated with a complex haemodynamic response, which includes elevation of systemic vascular resistance and arterial blood pressure proximal to the aortic clamp. This may impair the performance of the left ventricle (1). Cardiac output (CO) during XC has varied among different studies and was found to increase in several reports during graft replacement surgery (2,3,4) and in most experimental studies (5,6). However, in other reports CO remained unchanged or in fact decreased (1,7) particularly when vasodilators were not administered (8). The reason for the increase in CO observed in some of the studies is not completely understood. Redistribution of blood from the lower part of the body during XC (9) or an increased sympathetic stimulation due to ischemia have been proposed to be the cause of the haemodynamic response to descending thoracic XC (10,11,12,13). In addition, volume substitution and the use of vasodilating therapy may strongly influence the CO response (3). Regardless the mechanism of the increased flow through the heart during aortic clamping, the methodology of CO measurements during thoracic aortic occlusion has not been studied. Whereas both thermodilution catheters and aortic electromagnetic flowmetry have been used in experimental studies, thermodilution is still the preferred technique in routine clinical use, although recirculation of the injected saline may cause inaccurate measurement (14). Numerous comparisons between different cardiac output measurement techniques have been performed in pump-circuits (15) and in haemodynamic stable patients (16). More recently, CO measurements obtained by Doppler ultrasound and thermodilution technique have been compared during different interventions (17,18,19). Choosing a reference method for flow measurements in experimental studies is not easy. Transit-time ultrasound (TT) probes applied on the aorta measures stroke volume on a beat-by-beat basis. Contrary to electromagnetic flowmetry, the TT measurements are independent of vessel

diameter, sonation angle and movements (20). A comparison between TT ultrasound, Doppler ultrasound and thermodilution in a pig model has been performed by Wong (21). However, an evaluation of cardiac output measurements during the complex haemodynamic response of thoracic aortic cross-clamping has not been performed. Using the TT ultrasound as a gold standard, the aim of the present study was to evaluate the reliability of clinical available techniques like thermodilution and Doppler ultrasound to detect cardiac output changes during thoracic aortic cross-clamping in an open-chest pig model.

METHODS

Surgical preparation:

This study was approved by the National Experimental Animal Board. Ten fasting domestic pigs (median weight 24 kg, range 20-30 kg) of either sex were premedicated with azaperonium 15 mg/kg and diazepam 1 mg/kg im. Anaesthesia was induced with ketamine 20 mg/kg, thiopentone 100 mg and atropine 0.5 mg iv. To maintain anaesthesia, ketamine 20 mg/kg/h, fentanyl 0.05 mg/kg/h and pancuronium 0.2 mg/kg/h were infused. The animals were tracheostomised and ventilated (Harvard Apparatus series 680, So. Natick, MA, USA) with a mixture of oxygen and air. Normoventilation was achieved with a tidal volume of 10 ml/kg, and a frequency of 12/min. Glucose (35 mg/ml) in saline (50 mmol/l) was infused (10 ml/kg/h) for basal fluid requirements. A heating blanket was used to maintain normothermia during the procedure. Proximal arterial pressures were measured via a fibre optic pressure monitoring catheter (Camino Laboratories, USA) introduced through the axillary artery. A thermodilution catheter (5.5 F Opticath, Abbott, USA) was inserted via the right internal jugular vein, into the pulmonary artery for measurement of central venous (CVP) and pulmonary artery pressures.

A single-vector electrocardiogram was used for monitoring of heart rate, and pressure catheters were connected to disposable transducers (Sorensen Transpac II, USA) for continuous recording of arterial pressures (Grass 7D polygraph, Grass Instrument, USA). Arterial blood gases were analysed on a blood gas analyser (IL 1302, Instrumentation Laboratories, Milan, Italy).

After positioning of all pressure-monitoring catheters, the animals were turned to the right lateral position. A left thoracotomy was performed with resection of the 5th rib and the pericardium was split. The descending aorta was prepared for cross-clamping just distal to the origin of the subclavian artery.

After baseline measurements, the aorta was cross-clamped for 30 minutes, and haemodynamic recordings were made 5, 15 and 25 minutes during clamping. Sodium bicarbonate (50 mmol) was given over 25 minutes to prevent acidosis.

To counteract unclamping hypotension due to hypovolemia, 500 ml of Ringers acetate was rapidly infused five minutes before clamp release. Ventilation was then increased to a frequency of 20/min and the aorta was gradually unclamped in 3 steps, each of 1 minute's duration. Haemodynamic measurements were obtained 5, 15 and 30 minutes after release of the aortic clamp. At the end of each experiment, the animal was sacrificed with sodium pentobarbital.

Cardiac output measurements:

I. Transit-time (CO_{TT}):

The aortic root was dissected free and separated from the pulmonary artery. A precalibrated 20 mm ultrasonic transit-time flow probe (Transonic Systems Inc., Ithaca, New York), was positioned without constriction on the aortic root for recording of instantaneous volume flow. Analogue flow signals were digitised at 200 Hz with a 12 bits converter (NB MIO 16, National Instruments, Austin, Texas), and sampled by customised data logging software (Lab VIEW 2, National Instruments) operating on a personal computer (Macintosh II series, Apple Computers Inc., Cupertino, California) for on-line display and later storage of data. Continuous data sampling was performed over a 10 second period simultaneously with the other measurements in the protocol.

II. Thermodilution (CO_{TD}).

Pulmonary artery blood flow was determined with thermodilution technique by injecting 5 ml saline of room temperature into the right atrium. To ensure correct injection into the right atrium, continuous monitoring of the right atrial pressure wave was obtained from the proximal lumen of the pulmonary catheter. When the thermodilution trace curve was accepted, CO was calculated in a

cardiac output computer (Abbott, USA). Three measurements were obtained randomly with respect to the respiratory cycle and the mean value was determined.

III. Doppler ultrasound ($CO_{DOPPLER}$).

Doppler velocity recordings were performed from the anterior aspect of the heart with a standard 2.5 MHz duplex probe connected to an ultrasound scanner (CFM 750, Vingmed Sound; Horten, Norway). A highly flexible silicone gel ultrasound standoff with thickness 3 cm (3M Sweden AB, Sollentuna, Sweden) was used at body temperature between probe and epicardium in order to facilitate acoustic coupling without interfering with cardiac performance. The aortic annulus diameter was measured with the trailing-to-leading edge method in mid-systole as the distance between the insertion of the aortic valve leaflets on a long axis image. The average of 3 consecutive diameter measurements was used to calculate the aortic area, assuming a constant and circular orifice. The blood flow velocities through the aortic annulus were recorded by pulsed wave Doppler with the ultrasound beam directed through the centre of the aortic annulus. The angle between assumed blood velocity and ultrasound beam varied between 35 and 40 degrees between animals, but was almost constant during the protocol in each individual. Compensatory angle correction was not carried out. Doppler recordings of blood flow velocities from at least 5 consecutive cardiac cycles were transferred (Echolink 3.0, Vingmed Sound) to the computer for analysis.

Data processing:

The digitised TT flow signals were processed in specially designed software that operates under a general program for handling of digital ultrasound and cardiovascular data (EchoDisp 3.0, Vingmed Sound). At least 10 cardiac cycles were selected for analysis, low pass filtered at 50 Hz, and averaged. The outer envelope (peak velocities) of at least 3 cardiac cycles on the Doppler velocity

recording was traced manually on the computer, averaged, and volume flow obtained by multiplication with the aortic annular cross-sectional area. Stroke volume was determined as the integral of the aortic root volume flow over cycle length, and cardiac output obtained as the product of stroke volume and heart rate.

Measurements were made before cross-clamping, 5, 15 and 25 minutes during XC and 5 15 and 30 minutes after release of the aortic clamp.

Statistical analysis

Data are summarised as median values with the interquartile range (25-75 percentile). Wilcoxons signed rank test was performed to determine if there were differences from baseline values and $P<0.05$ was considered to be significant. Bonferroni`s correction for multiple comparisons was applied when comparisons were made involving the same medians. A correlation coefficient was estimated between the cardiac output measurements.

RESULTS

All animals completed the experiments and the results are summarised in Table I. Cardiac output measured by the ultrasound transit-time method (CO_{TT}) increased 171% from a median of 1.7 L/min to a maximum value of 4.6 L/min above baseline at 15 minutes following XC ($P<0.05$). Simultaneously the heart rate increased 81% from 93 b/min to 168 b/min ($P<0.05$). Mean arterial pressure reached a maximum of 154 mmHg ten minutes following cross-clamping which was an increase of 86% from the baseline value of 83 mmHg ($P<0.05$). The baseline values of cardiac output measured by thermodilution (CO_{TD}) and pulsed Doppler ($CO_{DOPPLER}$) were 53% and 41% above CO_{TT} respectively. CO_{TD} increased 119% at 15 minutes of XC from 2.6 L/min to 5.7 L/min ($P<0.05$). $CO_{DOPPLER}$ increased 150% from a baseline value of 2.4 L/min to 6.0 L/min ($P<0.05$).

The correlation coefficient between CO_{TT} and CO_{TD} was 0.904 ($P<0.001$), between CO_{TT} and $CO_{DOPPLER}$ was 0.726 ($P<0.001$) and finally between CO_{TD} and $CO_{DOPPLER}$ it was 0.728 ($P<0.001$).

DISCUSSION

In this open-chest pig model, the most important finding was that during occlusion of the descending thoracic aorta cardiac output (CO) increased more than 100% measured with all three methods. CO_{TD} and $CO_{DOPPLER}$ overestimated the real-time values of CO compared to the gold standard CO_{TT} throughout the experiment. The relative changes in CO were, however, underestimated by both CO_{TD} and $CO_{DOPPLER}$ (119% and 150%, respectively). Although we have found variations between the different methods, these estimates of cardiac output by CO_{TD} and $CO_{DOPPLER}$ are adequate for clinical use and for evaluation of CO during XC.

CO_{TD} overestimates cardiac output in high output states with 15-20% (23). Injection technique as well as the volume, temperature and localisation of injectate may influence the measurements. The impact of respiration on thermodilution is well known (14) and it has been proposed to perform 3-4 injections ignoring the respiration and then to average the results. According to Fanconi, all these effects will be exaggerated in children (24) and most likely in piglets as well since their bodyweight was 20-30 kg. Compared to ascending aortic blood flow as measured by CO_{TT}, both CO_{TD} in the pulmonary artery and $CO_{DOPPLER}$ measurements at the aortic annulus includes coronary artery blood flow in CO measurements, and coronary artery blood flow is known to be increased during XC of the thoracic aorta (25). This may represent some of the overestimation when CO_{TD} and $CO_{DOPPLER}$ were used. Any presence of intracardiac left-to-right shunts will result in recirculation of the injected bolus and a falsely high measurement when pulmonary artery CO_{TD} is used (26). Although such shunts are more common in piglets than in humans, this effect is unlikely to be of particular significance in our study since both CO_{TT} and $CO_{DOPPLER}$ measurements also increased

during XC. Clinically significant shunts would also have been easily detected with cardiac ultrasound.

There are several obvious advantages using a pulmonary artery catheter: measurements of CO can be made continuously although the time response of the continuous cardiac output pulmonary catheter is delayed compared to other continuous measurements (27). In addition the pulmonary artery catheter facilitates a continuous registration of pulmonary artery pressures and mixed venous oxygen saturation (SvO_2). Some catheters also have a paceport in case of bradycardia. However, both the interpretation of the data obtained from and the insertion of these catheters requires experience and insertion is not without technical complications. For long-time use infection is the most common disadvantage.

Although the application of ultrasound is increasing, the majority of anaesthesiologists or surgeons are not experienced in cardiac ultrasound-techniques, mainly due to a long «learning curve» and a general lack of ultrasound equipment in operation theatres. In our experimental setting the heart was surgically exposed providing optimal conditions for imaging and Doppler flow recordings. However, the variability of $CO_{DOPPLER}$ measurements was still more pronounced than the CO_{TD} results. This is in accordance both with Donovan (17) who found reduced accuracy of $CO_{DOPPLER}$ compared to CO_{TD} in ICU-patients, and with Gregorietti (18) who compared $CO_{DOPPLER}$ with electromagnetic flowmetry and CO_{TD} in an animal model (17,18). Both authors used the transthoracic approach in the jugular notch. Transesophageal echocardiography (TEE) was applied by Keyl during coronary by-pass surgery and by Estagnasie in critically ill patients (19,28). They both concluded that $CO_{DOPPLER}$ was unable to replace the pulmonary catheter in cardiac output estimations. In an animal study, Wong found that $CO_{DOPPLER}$ overestimated CO when afterload as

represented by the aortic diameter was varying, and when contractility was increased (21). On the other hand, besides CO estimation, there are advantages using ultrasound when evaluating contractility and preload (6), none of which is readily obtained by the pulmonary artery catheter. Although the transit-time ultrasound measurement is a reliable method of CO measurement (20,27), aortic flow probes are not easily placed in patients and are therefore uncommon in clinical practice.

All three methods consistently demonstrated a significant major increase in CO during XC. Already in 1912, Krogh`s in vitro circulatory model predicted that CO would increase during XC of the thoracic aorta due to volume displacement from the large hepatosplanchnic reservoir to the less compliant vascular compartment proximal to the vascular clamp (29). In animal experiments, Barcroft confirmed this theory and even estimated the magnitude of the translocated volume necessary to induce an increase in CO (30). Later, many experimental studies have confirmed that CO in fact increases and that this phenomenon is also present in patients (3,4). One physiological mechanism for this theory could be an increase in preload, which in turn activates the Frank-Starling mechanism. However, indirect measures of preload as central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), or left atrial pressure (LAP) were not found to correlate with increases in cardiac output (31). Since alterations in the ventricular pressure-volume relationship occur in dynamic situations like aortic clamping or unclamping, neither CVP nor PCWP nor LAP can be regarded as reliable indicators of cardiac preload (32). Stokland used segmental length measurements on the left ventricle (LV) in an animal model and found increased end-diastolic dimensions three minutes after XC indicating an increased preload (33). This is in accordance with a clinical echocardiographic study in which Roizen found increased LV volumes 2-5 minutes after supraceliac aortic occlusion (34). We have previously demonstrated in both an experimental (6) and a clinical study (4) that this is the normal response to an acute increase in afterload. However,

following ten to fifteen minutes of aortic XC, left ventricular dimensions subsequently decrease due to a significant increase in myocardial contractility independent of preload and afterload alterations (6).

These results may be supported by the another possible explanation for the increased cardiac output during thoracic aortic XC presented by Katz in 1927 (35). According to his theory, the left ventricle can only pump a greater volume due to an increased contractility. In general, contractility may increase as an acute response to increases in systolic arterial blood pressure, a phenomenon known as the Anrep effect. This effect is instantaneous and accentuated by tachycardia (36). In addition, recent experimental and clinical studies have revealed an increase in catecholamines and renin during XC (7, 10-13) that may contribute to the haemodynamic changes observed during thoracic aortic XC. Potentially the sympathetic discharge may be caused by ischemia of splanchnic organs distal to the aortic clamp.

In conclusion, we have confirmed the clinical and experimental experience of a high cardiac output state during cross-clamping of the descending thoracic aorta. For clinical purposes, both thermodilution and pulsed Doppler ultrasound are reliable methods for detecting increased cardiac output during thoracic aortic surgery.

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Legend

Table I

Changes in cardiac output during cross-clamping of the descending thoracic aorta measured by three different techniques: thermodilution (CO_{TD}), transit-time ultrasound (CO_{TT}) and Doppler ultrasound ($CO_{DOPPLER}$) measured in L/min.
HR= heart rate (b/min) and MAP= mean arterial pressure (mmHg). Data are presented as median values, the interquartile range and minimum and maximum values.
XC5min, XC15min, XC25min: Five, fifteen and twenty-five minutes after cross-clamping.

UnXC5min, UnXC15min, UnXC30min: Five, fifteen and thirty minutes after unclamping of the aorta.

*Indicates a significant level of $P<0.05$ compared to baseline.

Table I

Variable	Baseline	XC5min	XC15min	XC25min	UnXC5min	UnXC15min	UnXC30min
CO_{TT} (L/min)							
median	1.7	3.2*	4.6*	4.0*	2.9*	2.3	2.2
range	1.4-2.3	2.9-3.3	3.6-4.8	3.2-4.2	1.9-3.4	1.7-2.4	1.5-2.5
(n)	10	10	10	9	10	10	10
min-max	1.3-2.5	2.1-4.3	3.2-5.2	2.9-4.8	1.3-4.6	1.3-2.7	1.3-2.9
CO_{TD} (L/min)							
median	2.6	4.8*	5.7*	5.4*	4.6*	3.3	3.1
range	2.4-3.3	3.8-5.0	4.4-6.7	4.8-6.3	3.1-5.1	2.7-3.7	2.6-3.7
(n)	9	9	9	9	9	9	9
min-max	2.1-3.8	3.3-6.0	3.3-7.7	3.6-7.3	2.3-6.5	2.4-3.9	2.3-4.4
CO_{DOPPER} (L/min)							
median	2.4	6.2	6.0*	4.8*	5.1*	4.1	4.0
range	2.1-3.3	3.9-7.1	5.1-6.6	4.2-6.1	3.7-6.6	3.8-4.7	3.8-4.7
(n)	8	6	9	7	8	7	7
min-max	1.9-4.7	3.9-8.8	4.4-10.0	4.0-8.4	3.1-7.3	3.2-4.9	3.3-4.9
HR (b/min)							
median	93	126*	168*	169*	140*	117*	112*
range	78-99	107-137	132-185	130-186	126-150	111-132	108-138
(n)	10	9	9	10	10	10	10
MAP (mmHg)							
median	83	154*	145*	137*	53*	46*	47*
range	74-93	145-178	142-160	126-143	44-64	43-55	37-49
(n)	10	10	10	10	10	10	10

Paper V

MICRODIALYSIS OF THE SPINAL CORD DURING THORACIC AORTIC CROSS-CLAMPING IN A PORCINE MODEL

Preliminary series

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Key words: aortic cross-clamping, spinal cord ischaemia, microdialysis, pig

Running title: Microdialysis of the spinal cord

ABSTRACT

Objective: Utilising microdialysis to measure the concentrations of glucose, lactate, pyruvate and glutamate in the spinal cord during cross-clamping of the thoracic aorta in a porcine model.

Design: Experimental study with a porcine model

Setting: University hospital

Subjects: Six pigs

Main outcome measure: Glucose, lactate, pyruvate and glutamate concentrations in the microdialysis perfusate from the spinal cord

Results: A significant increase of the lactate-pyruvate ratio during the last 30 minutes of a one hour period of aortic cross-clamping. The maximum increase of 169% from the basal value occurred during the last ten minutes before declamping. There were no significant changes in this ratio comparing the clamping and the reperfusion period. No significant changes in glutamate levels were observed during clamping or reperfusion period.

Conclusion: Microdialysis reflects the metabolic changes in the spinal cord during cross-clamping of the thoracic aorta in pigs.

Introduction

During thoracoabdominal aortic aneurysm surgery paraplegia occurs in 0,5-38%[1]. The aetiology of spinal cord injury is multifactorial, and the main reasons are decreased perfusion pressure during surgery, failure to re-establish blood flow to the spinal cord after the repair and a biochemically mediated reperfusion injury. Reduction of cerebrospinal fluid pressure (CSFP), hypothermia and pharmacological protection of the spinal cord as well as various shunting and perfusion procedures have been tried in an attempt to reduce the incidence of neurologic sequelae[2]. The metabolic changes taking place in the spinal cord during proximal aortic cross-clamping are not entirely clear, and it is therefore of interest to study the spinal cord metabolism under such circumstances.

In a porcine experimental model described previously, thoracic aortic cross-clamping caused a significant decrease of laser-Doppler flux (LDF), measured in the spinal cord at the L2-L4 level, to about 40% of baseline values. Additional occlusion of the azygos vein decreased the perfusion even more (to 17% of baseline LDF values)[3].
Microdialysis is a technique for sampling small quantities of fluid from the individual tissues with a thin dialysis tube perfused with a physiological liquid. Diffusion of substances back and forth over the dialysis membrane gives a dialysis perfusate reflecting the composition of the extracellular fluid[4]. Microdialysis has frequently been used to study brain ischaemia and brain injuries[4, 5, 6]. In animal studies a certain increase of the excitatory amino acid glutamate level is recorded [7,8,9,10]. During brain and spinal cord ischaemia a glutamate increase has been proposed as a possible risk factor for

irreversible neuronal damage[11, 12]. Microdialysis of the spinal cord in larger animals has to our knowledge only been described by one research group[12, 13].

The purpose was to investigate the effect of thoracic aortic cross-clamping and azygos vein occlusion on the concentrations of metabolites (glucose, lactate, pyruvate and glutamate) in the spinal cord.

Material and Methods

Anaesthesia and Experimental conditions

Six Norwegian land-race pigs with a median weight of 23 kg were premedicated with azaperone (15 mg/kg i.m.) and diazepam (1 mg/kg i.m.). Anaesthesia was induced with injections of pentobarbital sodium (25 mg/kg), ketamine (20 mg/kg) and atropine (1 mg) through an ear vein, and was then maintained with ketamine (20 mg/kg/hour i.v.), fentanyl (0.05 mg/kg/hour i.v.) and pancuronium bromide (0.14 mg/kg/h i.v.).

The pigs were tracheostomized and ventilated with 40% O_2 in room air by a dual phase respirator pump (Harvard Apparatus, U.S.A) with a respiration rate of 12 strokes per minute and tidal volume of 350. A solution of glucose (35 mg/ml) and NaCl (3mg/ml) was infused (10 ml/kg/h i.v.) for basal fluid requirements. A catheter was inserted into the right femoral vein for additional volume infusion at declamping of the aorta. A heating blanket was used to maintain normothermia during the procedure.

A left thoracotomy was performed in the fifth interspace. The descending aorta as well as the azygos vein were dissected, and the aorta was prepared for cross-clamping just distal to the left subclavian artery.

A two-segment laminectomy was performed at the L2-L3 level. After skin incision, the muscles attached to the spinous processes and laminae of the L2 and L3 vertebrae were separated from bone by blunt dissection. The spinous processes of L2 and L3 were removed with a bone-cutting forceps, and the laminae excised with a rongeur. After laminectomy, the epidural fat was gently dissected away to expose the dura mater. The dura and the arachnoid membrane were opened with a longitudinal incision in the midline over the entire length of the laminectomy.

A microdialysis probe (CMA-12, CMA Microdialysis AB; Stockholm, Sweden) with a diameter of 0,64 mm, membrane length of 2 mm and a molecular cut-off of 20.000 Daltons was then inserted into the spinal cord in a ventro-lateral direction to preferably be located in the grey matter.

After a stabilisation period of 60 minutes, collection of microdialysis samples was started. Basal microdialysate levels were obtained as one sample during 30 minutes, after which the thoracic aorta was cross-clamped and the azygos vein occluded for one hour. The clamps were then removed and further samples were collected for 30 minutes. Both during clamping and in the reperfusion period dialysis sampling was done in ten-minute fractions.

During cross-clamping 16 μg/kg/min sodium nitroprusside and 50 mMol of sodium bicarbonate were infused to control hypertension and to prevent acidosis, respectively. Five minutes before declamping sodium nitroprusside was stopped, the respiration rate was increased to 20 strokes per minute and 500 ml of a 3,5% gelatine solution (Haemaccel®, Hoechst Marion Roussel) were infused i.v. After declamping no vasoactive medication was given.

At the conclusion of each experiment, the animals were sacrificed with an overdose of pentobarbital sodium i.v. The spinal cord was in two cases collected and examined with standard histopathological techniques with the purpose to indentify the placement of the microdialysis probe within the spinal cord.

Microdialysis

The perfusion fluid was a Ringer's solution containing 147 mMol Na^+, 4 mMol K^+, 2.3 mMol Ca^{2+}, and 155.6 mMol C1 per litre. The probes were connected to a microinfusion pump (CMA 102; CMA Microdialysis AB; Stockholm, Sweden) and perfused at a rate of 2μl/min.

Chemical Analysis

The samples were frozen to -20°C overnight, packed in dry ice, and transported to the analysis laboratory.

For the lactate and pyruvate analysis, 5-10 μl of the samples were injected with a CMA 200 autoinjector into an HPLC system equipped with a polymeric-resin-based column (polypore H, 10 μm, 220 mm x 4.6 mm; Brownlee Applied Biosystem, CA, U.S.A.) as previously described by Hallström et al [14]. The mobile phase consisted of 2 mMol H_2SO_4 and the flow rate was 0.3 ml/min. An UV detector at 214 nm was used for the peak detection.

Glutamate was analysed by HPLC with fluorescence detection after precolumn o-phthaldialdehyde (OPA) derivatization [15]. The method was modified to suit the microdialysis samples, with a Nucleosil C_{18} reverse phase column (5 μm; 60 mm x 4

mm; Knauer, Germany) eluted with a buffer consisting of 0.1 M sodium acetate (pH 6.95), 5% (v/v) methanol and 2.5% (v/v) tetrahydrofuran. The flow rate was 1.2 ml/min. Ten microliters of the sample was mixed with 10 µl of OPA reagent by a CMA 200 autoinjector. The amino acid-OPA complex was detected by a Hitachi F 1000 fluorescence detector with an excitation wavelength of 330 nm and an emission wavelength of 440 nm, or by a CMA 280 fluorescence detector with a fixed wavelength (a tungsten lamp, excitation 340-360 nm) and a filter (emission maximum 495 nm). Glucose was analysed on a CMA-600 (CMA Microdialysis AB; Stockholm, Sweden) analyser. The method used was an oxidation of glucose by glucose oxidase (GOD), which forms gluconic acid and H_2O_2. Peroxidase (POD) then catalysed the reaction between the hydrogen peroxide formed and phenol and 4-aminoantipyrine to form the coloured substance quinonemine. The rate of formation of the coloured substance was then measured photometrically at 546 nm[16].

Statistical analysis

Data are given as median after calculation of the mean value of the measurements during the last 30 minutes before clamping, and then transformation of this value into 100%. Changes were then calculated and presented in percentage of this basal value. Differences between samplings were assessed by 2-tailed Wilcoxon signed ranks test with a probability less than 0,05 considered as significant.

Ethics

The experiments were performed from September 1995 to January 1997 and the protocol was approved by the local responsible laboratory animal science specialist under the surveillance of the Norwegian Animal Research Authority (NARA) and registered by the Authority.

Results

Table 1 shows the median values and range of glutamate, lactate, pyruvate and the lactate-pyruvate ratio prior to cross-clamping. Initially, lactate levels increased and pyruvate levels decreased slightly, followed by an insignificant increase during the clamping period. The lactate-pyruvate ratio increased correspondingly, and the three last measurements before declamping reached the level of statistical significance (p=0,031) compared with pre-clamping values. Fig. 1.B-D depict the course of the metabolite concentrations before, during and after aortic cross-clamping. At 30 minutes of ischaemia, the median lactate-pyruvate ratio had increased by 128%, and at 60 minutes by 169% compared to baseline values. There was no evident change in this ratio between the ischaemic and the reperfusion period, but lactate levels increased slightly more during reperfusion.

It was only possible to analyse glutamate concentrations in five out of six pigs, due to technical problems. There was a tendency that glutamate levels decreased from baseline levels during the cross-clamp period, but this decrease did not reach the level of statistical significance (p=0,063). During the last ten minutes sampling of the 30

minutes reperfusion period, there was a tendency to increase in glutamate levels, in contrast to the observation during the cross-clamp period.

Glucose levels were incompletely analysed due to small amounts of microdialysate, but decreased by 40% or more during cross-clamping.

Discussion

In this series, aortic cross-clamping induced a significant increase in the lactate-pyruvate ratio, corresponding to findings expected in muscle ischaemia. However, no significant increase in glutamate levels were observed, contrary to the results from Rokkas and coworkers[12, 13]. They also showed that pre-treatment with dextrorphane[12] and hypothermia[13] prevented increase in glutamate levels. Without knowledge of all details to compare the experimental settings used in Rokkas' studies and the present experiments, it is difficult to explain these differences. Both studies have utilised laminectomy to facilitate the insertion of the microdialysis probes. It has previously been shown that laminectomy may cause a decline of the spinal cord blood flow (SCBF). In a feline model with one segment laminectomy and intact dura mater, Anderson and coworkers[17], utilising radio-labelled microspheres, reported a significantly (22% to 45 %) reduced SCBF along the entire length of the spinal cord 15 min after the laminectomy. With the laminectomy site closed, SCBF approached pre-laminectomy levels one hour after closure, but there were still areas of reduced flow along the spinal cord. The authors suggested that a temperature-induced vasoconstriction could explain these findings.

It is less probable that a lowered blood flow to the spinal cord, locally or generally, could be the explanation for the lack of increased glutamate levels, due to the fact that the increase in glutamate levels per se should depend on the reduced blood flow during the aortic cross-clamp period. On the other hand, it cannot be excluded that a reduced temperature of the spinal cord, caused by the laminectomy, could induce hypothermic conditions sufficient to prevent glutamate release. Another explanation might be that 60 min of aortic cross-clamping was insufficient for glutamate to be released, or that the ischaemia did not reach a certain critical level. From our previous experiments, measuring microcirculation with laser-Doppler technique, it was evident that the cross-clamping procedure including occlusion of the azygos vein produced a significant decrease of spinal cord tissue perfusion, even if there was some collateral circulation left. In those studies the laser Doppler probe was inserted percutaneously making only a small puncture of the dura, and therefore spinal fluid pressure could be maintained and contribute to a reduced perfusion of the spinal cord.

Another possible explanation for the lack of glutamate increase could be that the microdialysis probe was incorrectly inserted into the spinal cord. In two cases histologic studies were performed, showing convincingly however, that the probe was located in the grey matter (Fig. 2).

No samples were taken during the initial 60 min stabilisation period, and the first samples taken just before clamping showed higher glutamate levels than what was achieved during the aortic cross-clamp period. The most probable explanation for this initial increase in glutamate levels is that glutamate is released by the trauma

represented by insertion of the microdialysis probe. This finding also indicates that the probe was located in an anatomical area where glutamate could be found, if released. The tendency to increased glutamate levels during the last part of the reperfusion period, points in the same direction.

Our main findings are thus changes of lactate and pyruvate levels, corresponding to what is observed in muscle ischaemia. This result raises the question whether substances like allopurinol, known to reduce reperfusion injury of muscle[18], could be of value in reducing ischaemic damage of the spinal cord as well.

Our experimental setting does not enable correlation to any clinical findings of paraplegia. Other experimental studies in pigs, in which neurologic status was examined after the animals had returned to consciousness after 30 min of aortic cross-clamping[19], revealed that control animals were all paraplegic. In contrast, the animals treated with a combination of allopurinol and deferoxamine all had complete recovery. This effect was not explained by any improved spinal cord blood flow during the cross-clamping period in the pre-treated animals.

Since paraplegia following thoracic and thoracoabdominal aortic surgery is still a major problem, we think it is important to study further the metabolic response of the spinal cord during proximal aortic cross-clamping. Microdialysis seems to give good opportunities to study this response. However, further questions have to be addressed, such as factors that could inhibit glutamate increase during ischaemia. Also the perfusion of the spinal cord in our experimental setting should be investigated more

thoroughly, using laser Doppler flux measurements or colour-labelled microspheres. These kinds of experiments are at present going on.

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Table 1

Basal concentration of metabolites in the spinal cord measured by microdialysis during a 30 minutes stabilisation period prior to aortic cross-clamping. Data are expressed as median and range.

Substance	Median (range)	
Glutamate	3.2 (0.8-13.5)	μMol/l
Lactate	230.3 (129.0-996.0)	mMol/l
Pyruvate	38,1 (15.4-70.9)	μMol/l
Lactate-pyruvate ratio	6,54 (3,87-18.3)	

Legends to the illustrations:

Figure 1

Fig. 1.A: glutamate levels as per cent change from basal values. It was only possible to analyse glutamate in five out of six pigs, due to technical problems.

Fig. 1.B: lactate levels as per cent change from basal values.

Fig. 1.C: pyruvate levels as per cent change from basal values.

Fig. 1.D: lactate-pyruvate ratio values as per cent change from basal levels.

The figures 1.A - D all have the same format and depict the time-course of the measurements. Per cent change from basal values is shown on the ordinate, with the individual basal values all recalculated to 100. PreXC: basal value before cross-clamping: XC1-XC6 and DC1-DC3: samples drawn every ten minutes during one hour of aortic cross-clamping (XC) and 30 minutes after declamping (DC) respectively. The thin, continuous line connects the individual measurements for each animal and the thicker, broken line represents the median value.

There are missing values in the reperfusion period for one animal in all measurements, due to technical reasons.

Figure 2

Histopathology of the spinal cord. The quadrant in the right corner represents the area depicted. The darker blue area is white matter, and the brighter area grey matter.

The arrow is pointing at traces of bleeding along the microdialysis probe channel in grey and white matter.

Figure 1A

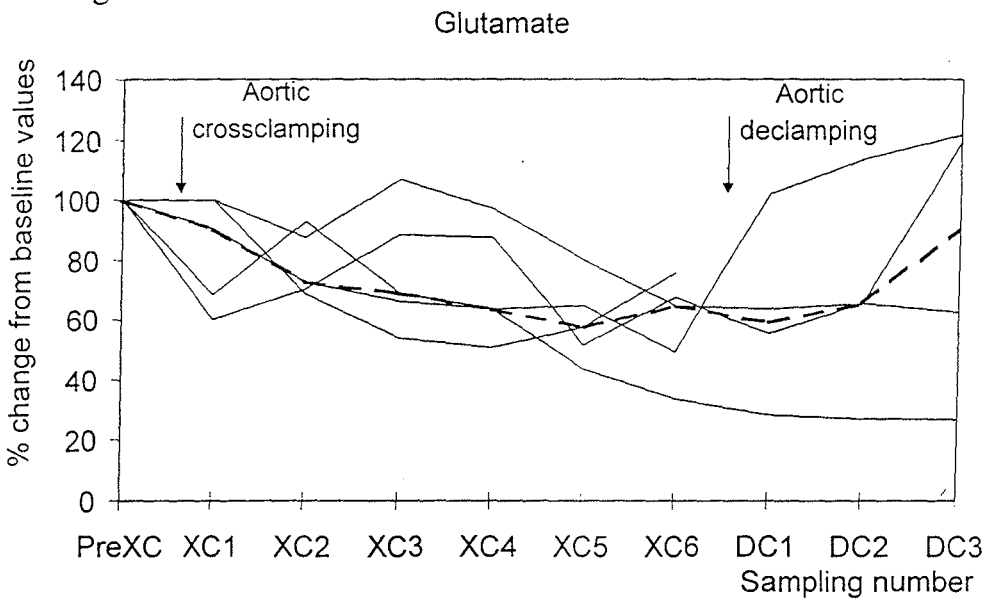


Figure 1B

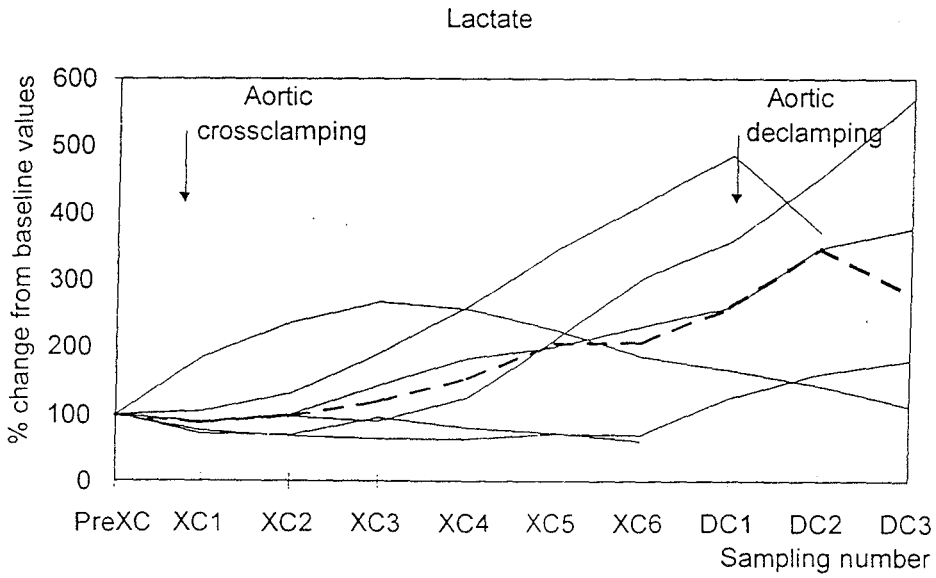


Figure 1C

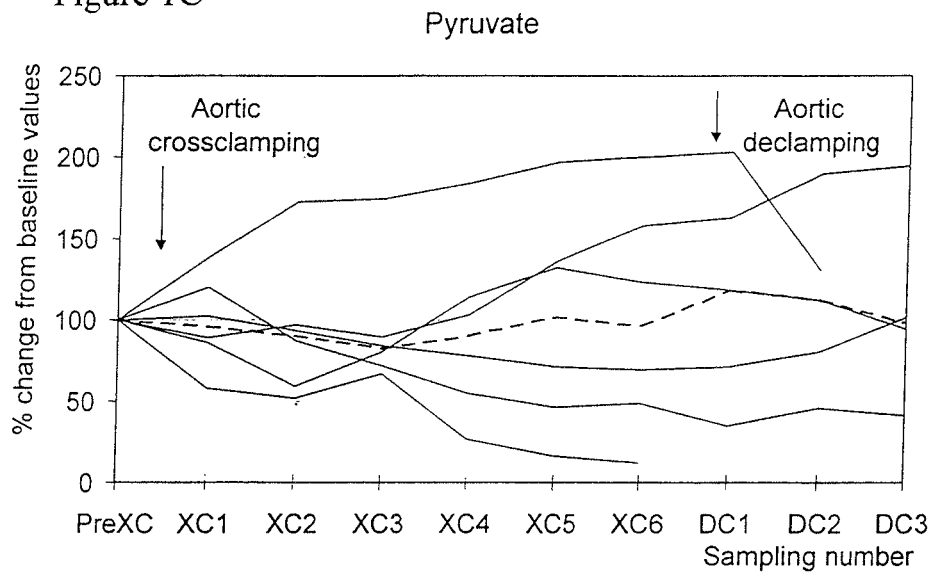
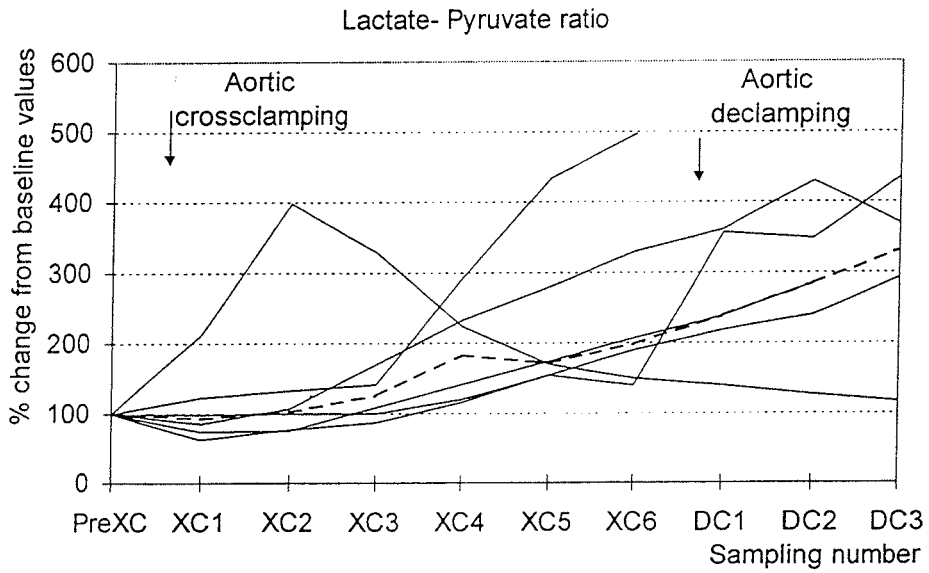
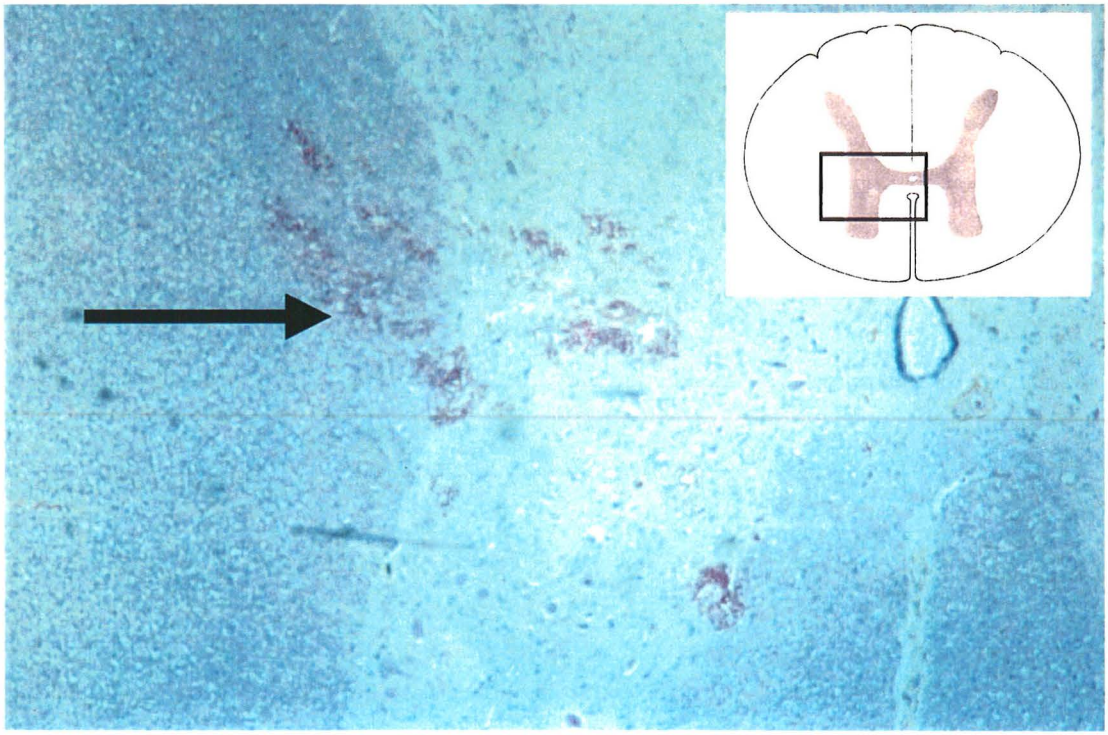


Figure 1D



Figur 2



Paper VI

Spinal cord metabolism during thoracic aortic cross-clamping in pigs with special reference to the effect of allopurinol.

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Key words: aortic cross-clamping, spinal cord ischaemia, allopurinol, pig.

Running title: Spinal cord metabolism in aortic surgery

Abstract

Objective: To investigate the metabolic response of the spinal cord and the effect of allopurinol following cross-clamping of the descending thoracic aorta in a porcine model

Design: Experimental animal study

Setting: University Hospital of Trondheim

Subjects: Four pigs were pre-treated with allopurinol, while four pigs served as controls

Main outcome measure: Concentrations of glucose, pyruvate, lactate, glycerol and glutamate measured with microdialysis in the lumbar spinal cord. Lumbar spinal laser Doppler Perfusion units

Results: For all animals there was a significant decrease in concentrations of glucose and pyruvate together with a significant increase in the lactate-pyruvate ratio during aortic cross-clamping. There was also a significant increase in glycerol concentrations 60 minutes after cross-clamping, and a significant decrease in glutamate concentrations after 50 minutes.

There was a tendency towards lower levels of glycerol measured 60 and 80 minutes after cross-clamping in the animals pre-treated with allopurinol. No differences in concentrations of glucose, pyruvate, lactate and glutamate or the glutamate-pyruvate ratio were observed between animals used as controls and those treated with allopurinol. The laser Doppler flux decreased to 40% of pre cross-clamp level, returning to normal values at declamping.

Conclusion: The changes in energy-related metabolites reflect a considerable ischaemia in the spinal cord tissue but there was no convincing effect of allopurinol on the lumbar spinal cord metabolism during thoracic aortic cross-clamping in this model.

Introduction

During thoracoabdominal aortic aneurysm surgery paraplegia occurs in 0,5-38%[1]. The aetiology of spinal cord injury is multifactorial, and the main reasons are thought to be decreased perfusion pressure during surgery, failure to re-establish blood flow to the spinal cord after the aortic repair and a biochemically mediated reperfusion injury. Reduction of cerebrospinal fluid pressure, hypothermia and various shunting and perfusion procedures as well as pharmacological protection of the spinal cord have been tried to reduce the incidence of neurologic sequelae[2, 3].

It has been claimed that neurologic sequelae following operations performed during cross-clamping of the aorta are not only developing during the ischaemic period. Instead, much of the damage could take place during the reperfusion period[4, 5]. Toxic metabolites of molecular oxygen, which represent intermediate states of the electrochemical reduction to water, have been suggested as mediators of reperfusion injury after ischaemia in various organ systems, including the spinal cord[4, 6]. Oxygen derived free radicals produce damage to the cell membrane through lipoperoxydation and perioperative pharmacological intervention to scavenge reactive oxygen metabolites has been tried[5, 7-9].

The xanthine oxidase system, which mediates conversion of hypoxanthine to xanthine, is a primary source of oxygen-derived free radicals in tissue ischaemia followed by reperfusion. Allopurinol is a competitive xanthine oxidase inhibitor and may therefore be able to reduce the amount of oxygen-derived free radicals produced during aortic

surgery[10]. Allopurinol has previously been investigated for protection against spinal cord ischaemic injury during cross-clamping of the thoracic aorta in baboons[11] and pigs[9,12], assessed with neurologic outcome and changes in blood flow of the spinal cord using radiolabelled microspheres, but with inconclusive results.

The purpose of the present study was to further characterise the metabolism of the spinal cord during proximal aortic cross-clamping. We applied a porcine experimental model, previously used by us[13]. In this model thoracic aortic cross-clamping caused a significant decrease in the microcirculation of the spinal cord. Measurements were performed by microdialysis[14] (measuring glucose, pyruvate, lactate, glycerol and glutamate concentrations) and laser Doppler flowmetry. The technique of microdialysis has been used in a preliminary series of experiments and was found suitable[15]. Further, we wanted to investigate whether the administration of allopurinol could modify the metabolic response observed during cross-clamping and the reperfusion period.

Material and methods

Anaesthesia and Experimental conditions

Eight Norwegian land-race pigs of either sex with a median weight of 23 kg were divided into two groups of four animals each. In the control group, no allopurinol was given. In the other group the animals were pre-treated with allopurinol using a dose of 50 mg per kg daily for three days[16].

The animals were premedicated with azaperone (15 mg/kg i.m.) and diazepam (1 mg/kg i.m.). Anaesthesia was induced with i.v. injections of pentobarbital sodium (25 mg/kg), ketamine (20 mg/kg) and atropine (1 mg) through an ear vein, and was then maintained with ketamine (20 mg/kg/hour i.v.), fentanyl (0.05 mg/kg/hour i.v.) and pancuronium bromide (0.14 mg/kg/h i.v.).

The pigs were tracheostomized and ventilated with 40% O_2 in room air by a dual phase respirator pump (Harvard Apparatus, U.S.A) with a respiration rate of 12 strokes per minute and a tidal volume of 350 ml. A solution of glucose (35 mg/ml) and NaCl (3mg/ml) was infused (10 ml/kg/h i.v.) for basal fluid requirements. A catheter was inserted into the right femoral vein for additional volume infusion at declamping of the aorta. A heating blanket was used to maintain normothermia during the procedure.

A left thoracotomy was performed in the fifth interspace. The descending thoracic aorta as well as the azygos vein were dissected, and the aorta was prepared for cross-clamping just distal to the left subclavian artery.

A two-segment laminectomy was performed at the L2-L3 level. After skin incision, the muscles attached to the spinous processes and laminae of the L2 and L3 vertebrae were separated from the bone by blunt dissection. The spinous processes of L2 and L3 were removed with a bone cutting forceps, and the laminae excised with a rongeur. After laminectomy, the epidural fat was gently dissected to expose the dura mater. The dura and the arachnoid membrane were opened with a longitudinal incision in the midline corresponding to the entire length of the laminectomy.

After a stabilisation period of 60 minutes, data sampling was started and basal values were obtained for 30 minutes, after which the thoracic aorta was cross-clamped and the azygos vein occluded for 90 minutes. For practical reasons this period will be described as the period of aortic cross-clamping. The clamps were then removed and further samples were collected for 30 minutes.

During aortic cross-clamping 16 μg/kg/min sodium nitroprusside and 50 mMol of sodium bicarbonate were infused to control hypertension and to prevent acidosis, respectively. Five minutes before declamping, the infusion of sodium nitroprusside was discontinued, the respiration rate was increased to 20 strokes pr minute to counteract acidosis and 500 ml of 3,5% gelatine solution (Haemaccel®, Hoechst Marion Roussel) were infused i.v. After declamping no vasoactive medication was given.

Microdialysis

A microdialysis probe (CMA-12, CMA Microdialysis AB; Stockholm, Sweden) with a diameter of 0,64 mm, membrane length of 2 mm and a molecular cut-off of 20.000 Daltons was inserted into the lumbar spinal cord.

The perfusion fluid was a Ringer`s solution containing 147 mMol Na^+, 4 mMol K^+, 2.3 mMol Ca^{2+}, and 155.6 mMol C1 per litre. The probes were connected to a microinfusion pump (CMA 102, CMA Microdialysis AB, Stockholm, Sweden) and perfused at a rate of 2μl/min. Microdialysis sampling was done in ten-minute fractions with an automated

collector (CMA/142 Microfraction collector, CMA Microdialysis AB, Stockholm, Sweden).

The microdialysis samples were analysed on site for glucose, lactate, pyruvate, glycerol and glutamate concentrations by enzymatic fluorometric assays on an automated analyser (CMA/600 Microdialysis analyser, CMA Microdialysis AB, Stockholm, Sweden) using peroxidase methodology[17, 18]. The data were sampled on line using a dedicated data acquisition program (Microscope, CMA Microdialysis, Stockholm Sweden).

Laser Doppler flux measurements

A laser Doppler needle probe with a diameter of 0,45 mm (PF 302 needle probe, Perimed; Stockholm, Sweden) was inserted into the exposed spinal cord and connected to a laser Doppler system (PeriFlux 4001 Master, Perimed, Sweden).

The laser Doppler signals were continuously sampled with a frequency of 4 Hz to a personal computer during the whole experiment, using a dedicated data acquisition software (PeriSoft, Perimed, Stockholm, Sweden), which was also used for recording and analysis. Results are given as mean Perfusion Units (PU) for periods of ten minutes.

The measuring probes for microdialysis and laser Doppler flux were inserted into the spinal cord approximately 1 cm apart from each other in a ventro-lateral direction as to be preferentially located in the grey matter, and stabilised to the operating table to secure the obtained position.

At the conclusion of each experiment, the animal was sacrificed with an overdose of pentobarbital sodium i.v.

Statistical analysis

Data from the first ten minutes of the basal period were recalculated to 100 as baseline values and changes were calculated and presented in percentage of this basal value. Differences within groups were assessed by two-tailed Wilcoxon signed ranks exact test and between groups with two-tailed Mann-Witney U exact test. A probability of less than 0,05 was regarded as significant.

Ethics

The experiments were performed from March to September 1998 and the protocol was approved by the local responsible laboratory animal science specialist under the surveillance of the Norwegian Animal Research Authority (NARA) and registered by the Authority.

Results

In the following we are comparing median values before, during and after aortic cross-clamping in all animals. Furthermore, we compare median values for the control group with the median values for animals treated with allopurinol.

Table 1 shows the median and the 25 and 75 percentiles of microdialysis values for glucose, pyruvate, lactate, glycerol and glutamate as well as the lactate-pyruvate ratio

for the first ten minutes of the basal period. Table 2 presents the per cent change from the basal value at 10, 60 and 90 minutes of aortic cross-clamping and 30 minutes after release of the clamp.

Microdialysis

Energy-related metabolites

Both allopurinol-treated and control animals followed the same pattern concerning the extracellular energy-related metabolites glucose, pyruvate, lactate and the lactate-pyruvate ratio. There were no significant differences between the two groups. The changes in glucose levels and lactate-pyruvate ratios for the two groups are shown in figure 1.A and 1.B.

Glucose

Glucose concentration decreased significantly with the lowest level observed following 20 minutes of aortic cross-clamping when the values were 20% compared to baseline ($p = 0,008$) (Table 2, Figure 1.A). Twenty minutes after declamping there was an increase to 139% of base line value ($p = 0,016$).

Pyruvate

In the sample taken during the first ten minutes after cross-clamping, there was an increase in pyruvate levels to 115% of baseline levels ($p = 0,008$) (Table 2). During the clamping period a decrease of pyruvate levels was observed from 20 minutes of cross-clamping, with levels from 50 to 60% of baseline ($p < 0,05$). In the declamping phase

the pyruvate concentration increased to levels similar to those observed prior to cross-clamping.

Lactate

Lactate levels increased significantly after aortic cross-clamping. During the cross-clamp period, values from 120 to 384% of base line levels were observed ($p < 0,05$) (Table 2). In the declamping phase there was a further increase in lactate levels, and no significant decrease was observed during the 30 minutes that followed after removal of the aortic cross-clamp.

Lactate – pyruvate ratio

Also the lactate-pyruvate ratio increased significantly during aortic cross-clamping, with a maximum 90 minutes after application of the clamp when the ratio was 761% of baseline ($p = 0,008$). Although the values showed a tendency to decrease after release of the clamp, they were still significantly elevated compared to baseline values. (Table 2, Figure 1.B)

Glycerol

In all animals, the glycerol concentration of the spinal cord decreased significantly ($p = 0,016$) following ten minutes of aortic cross-clamping. Then there was a significant increase following 60 minutes of cross-clamping ($p = 0,031$). The increase continued with a maximum in the late declamping phase.

There was a tendency of lower glycerol levels in the allopurinol group compared to controls, 60 and 80 minutes following aortic cross-clamping respectively (p = 0,056), but the difference did not reach statistical significance (Figure 1.C).

Glutamate

Increased glutamate levels were recorded during the stabilisation period and the glutamate levels decreased continuously from the start of measurements with levels significantly lower than baseline at 50, 60 and 70 minutes following aortic cross-clamping (p=0,031). Thereafter the glutamate level stabilised and there was no subsequent increase neither during late cross-clamping nor during the reperfusion period.

There were no statistically significant differences between controls and allopurinol-treated animals (Figure 1.D).

Laser Doppler measurements

The microcirculation of the spinal cord, expressed as perfusion units, was recorded with laser Doppler technique. The flux expressed in PU decreased during the period of aortic cross-clamping for the group as a whole with values varying from 84 to 38% of baseline (Table 2). During the first ten minutes of cross-clamping and after 50 minutes, the values were significantly lower than the values obtained prior to cross-clamping. A return to baseline levels was observed in the declamping phase.

There were no statistically significant differences between controls and allopurinol-treated animals.

Discussion

In our first series of microdialysis during spinal cord ischaemia[15] we found changes of the energy-related metabolites, with decrease of glucose and increase of lactate, but glutamate levels, which should be related to nerve cell damage, did not increase.
The present study was undertaken to investigate further the experience from the preliminary series and furthermore, to evaluate a possible preventative effect of allopurinol, as indicated by less pronounced decrease of the energy-related metabolites during and after ischaemia.

Glucose, pyruvate and lactate

The significant decrease in concentrations of the energy related metabolites glucose and pyruvate together with the significant increase in the lactate-pyruvate ratio reflects a considerable ischaemia in the spinal cord tissue during aortic cross-clamping.
During ischaemia more glucose is utilised than the amount available, giving a shift to anaerobic metabolism producing lactic acidosis. The most common reason for lactate accumulation is the intra-cellular lack of oxygen. Tissue lactate can however fluctuate considerably due to variations in neuroendocrine activation that affects lactate production and utilisation. Hyperlactatemia is also a part of the metabolic response to stress and trauma and these changes do not necessarily indicate tissue hypoxia[19]. The lactate-pyruvate ratio can however distinguish hypermetabolism from hypoxia and ischaemia. Lack of intracellular O_2 slows down or stops the oxidative phosphorylation leading to an inability to handle the H^+ being generated in the citric and glycolytic

cycles. This in turns forces pyruvate to become the primary H^+ acceptor and mass action causes formation of lactate as an end product. Therefore, the increased lactate levels in hypoxia and ischaemia will be associated with an increase in the lactate/pyruvate ratio compared to hypermetabolism, where the lactate and pyruvate concentrations will increase to the same extent keeping the lactate-pyruvate ratio at an unchanged level[20].

Most of the extracellular fluid metabolites measured with microdialysis may be derived from cells within the ischaemic cord, but leakage of substances from the blood due to opening of the blood-spinal cord barrier is also possible. Although this mechanism might be of minimal importance during the clamping period due to the low perfusion, it may become significant during the reperfusion period.

Glycerol

Increased concentration of the fatty acid glycerol in the extracellular fluid is regarded as an important marker for cell membrane disintegration since glycerol is an integral component of the double layer of most cellular membranes in the body. Cell damage and calcium influx activates phospholipases which start the membrane break down and liberation of glycerol into the extracellular fluid. Extracellular glycerol levels in the brain of trauma patients have been investigated previously[21] and elevated glycerol levels have been reported. Experimental studies in rats[22] have confirmed these findings.
Thus, the tendency of lower levels of extracellular glycerol in the allopurinol treated animals could indicate a less pronounced ischaemia-induced breakdown of the cellular membranes in this group. In addition, the general rise in glycerol may partly be induced

by increased sympathetic activity since extremely high serum catecholamine levels have previously been found during aortic cross-clamping in a similar experimental model[23].

Glutamate

In this series with 90 minutes of cross-clamping, we found a significant decrease in glutamate levels, confirming our previous observations with 60 minutes of aortic cross-clamping using the same model[15]. Microdialysis of the spinal cord during aortic cross-clamping in pigs has been performed by Rokkas[24, 25], who found an increase in extracellular glutamate levels during ischaemia. Increased concentrations of glutamate, an excitatory amino acid, have been regarded as a major risk factor of irreversible ischaemic neuronal damage[26-30].

The decrease of glutamate concentrations during the first part of the ischaemic period might be explained by an initial release of glutamate from the trauma induced by insertion of the microdialysis catheter into the spinal cord. The increased glutamate levels recorded during the stabilisation period are probably not normalised until 60 minutes after cross-clamping of the aorta.

On the other hand, one would expect an increase of the glutamate concentration as a response to the ischaemic injury of the spinal cord during aortic cross-clamping. This was not the case in the present experiments, and one explanation could be that the degree of ischaemia in the spinal cord was insufficient. Thus, the laser Doppler flux values of approximately 40 % of basal levels before declamping might imply a reasonably good collateral circulation to the cord. On the other hand, the lactate and pyruvate levels followed a pattern consistent with a considerable degree of ischaemia.

Another explanation might be that the time of ischaemia was still limited. However, 90 minutes of aortic cross-clamping makes this latter explanation unlikely.

Laser Doppler flowmetry

The spinal cord flux decreased to the same extent as previously reported with 30 minutes of aortic cross-clamping in a similar model, but without using laminectomy[13]. This indicates a significant decrease in the spinal cord microcirculation. Although a one-segment laminectomy and an intact dura mater in a feline model reduced spinal cord blood flow significantly (22% to 45 %)[31], laminectomy did not in itself reduce the spinal cord microcirculation in the present model compared to our previous experiments[15].

Conclusion

The study verifies our preliminary findings that only energy related metabolites are affected during aortic cross-clamping. Furthermore, the increased glycerol levels indicate a breakdown of cellular membranes. Whether a more extensive period of ischaemia is necessary to induce increased glutamate concentrations remains a controversial issue. Perhaps the collateral blood flow to the spinal cord in the present experimental model is sufficient to prevent further neuron damage, although the glucose and lactate levels were affected.

Only minor and statistically insignificant effects of allopurinol could be demonstrated, although an effect on the breakdown of cellular membranes cannot be ruled out. The minimal effect of allopurinol could be due to insufficient dosage, but the pre-treatment

dose of allopurinol in pigs of 50 mg/kg for three or four days[16, 32] has been found effective when evaluated with red cell antioxidant state.

In conclusion, the ischaemic condition in the spinal cord, shown by a decreased laser Doppler flux and changes of energy related metabolites, is not affected by pre-treatment of the animals with allopurinol in the present experimental model. Further experiments are necessary to explore whether the slightly lower increase of glycerol in the allopurinol treated pigs is an indication of cellular membrane protection.

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Table 1

Basal concentration of metabolites in the spinal cord measured by microdialysis during the first ten minutes of the stabilisation period prior to aortic clamping. Data are expressed as median(25-75 percentile).

Substance	Median (25-75 percentile)	
Glucose	0,10 (0,07-0,12)	mMol/l
Pyruvate	8,60 (7,12-9,05)	μMol/l
Lactate	0,13 (0,09-0,14)	mMol/l
Lactate-Pyruvate ratio	13,4 (12,3-17,1)	
Glycerol	18,8 (10,7-19,8)	μMol/l
Glutamate	1,68 (1,14-2,32)	μMol/l

Table 2

Per cent change in glucose, pyruvate, lactate, glycerol and glutamate concentrations, lactate-pyruvate ratio and spinal cord flux prior to aortic cross-clamping (Pre1), during cross-clamping (XC1=10, XC6=60 and XC9=90 minutes) and 30 minutes (DC3) after release of the clamp. For each variable values are given for the control group and for the group pre-treated with allopurinol. There are missing values for some animals due to technical reasons.
Data are expressed as median (25-75 percentile).

	Pre1	XC1	XC6	XC9	DC3
Glucose					
Control	100,0 (-)	72,1(56,9-88,7)	19,7(8,1-45,5)	28,0(10,7-49,0)	139,0(133,9-275,0)
n	4	4	3	4	4
Allopurinol	100,0 (-)	87,4(82,0-182,9)	27,2(25,4-52,6)	31,1(10,7-38,5)	140,7(119,2-231,8)
n	4	4	4	4	3
Pyruvate					
Control	100,0 (-)	115,4(111,3-120,9)	56,1(44,6-62,8)	60,9(46,4-65,5)	112,3(85,6-121,1)
n	4	4	3	4	4
Allopurinol	100,0 (-)	115,1(103,2-245,4)	68,6(48,8-75,6)	49,7(40,8-56,4)	93,0(84,0-151,8)
n	4	4	4	4	3
Lactate					
Control	100,0 (-)	124,6(119,5-147,6)	462,8(257,4-903,6)	514,2(276,8-1138,7)	407,0(286,4-1306,1)
n	4	4	3	4	4
Allopurinol	100,0 (-)	102,4(97,4-251,7)	349,3(304,8-427,4)	375,7(339,9-435,6)	419,3(333,0-612,3)
n	4	4	4	4	
Lactate/Pyruvate					
Control	100,0(-)	111,3(99,7-127,4)	842,7(515,8-1577,8)	838,5(572,2-1822,3)	336,0(334,6-1163,2)
n	4	4	4	4	3
Allopurinol	100,0(-)	93,4(87,8-102,5)	462,1(444,3-875,1)	762,0(610,8(1064,5)	398,1(351,0-473,1)
n	4	4	3	4	4
Glycerol					
Control	100,0(-)	77,4(75,3-89,5)	138,9(107,8-178,1)	181,0(129,6-214,6)	200,0(145,1-318,3)
n	4	3	4	4	3
Allopurinol	100,0(-)	86,7(74,6-96,6)	104,5(96,1-105,4)	122,7(115,0-127,2)	186,0(139,1-202,8)
n	3	4	3	4	4
Glutamate					
Control	100,0(-)	71,1(60,3-165,3)	43,24(18,3-110,1)	41,4(25,2-63,2)	39,1(15,0-200,9)
n	4	4	4	4	3
Allopurinol	100,0(-)	129,4(58,2-222,3)	55,11(43,7-57,7)	59,3(15,1-141,0)	42,1(13,4-93,6)
n	4	4	3	4	4
Spinal cord flux					
Control	100,0 (-)	38,6(30,0-51,3)	60,7(32,6-86,2)	40,9(24,6-60,7)	94,9(48,6-154,8)
n	4	4	4	4	4
Allopurinol	100,0(-)	59,1(33,2-92,3)	58,4(24,0-93,5)	48,1(23,8-65,9)	59,1(20,0-122,5)
n	4	4	3	3	3

Figure 1.A-1.D:

Fig. 1.A: Glucose levels expressed as per cent changes from basal values.

Fig. 1.B: Lactate-pyruvate ratio expressed as per cent change from basal values.

Fig. 1.C: Glycerol levels expressed as per cent changes from basal values.

Fig. 1.D: Glutamate levels expressed as per cent changes from basal values.

The figures 1.A-D all have the same format and depict the time-course of the measured concentrations of metabolites. The ordinate is per cent change from basal values, with the values for the first ten minutes of the basal period all recalculated to 100. Pre1-Pre3, XC1-XC9 and DC1-DC3: samples drawn every ten minutes during the 30-minute basal period (Pre), 90-minute cross-clamping period (XC) and during the 30 minutes after declamping (DC) respectively. The continuous line connects the measurements for the allopurinol-treated group and the broken line the measurements for the control group. (For 25-75 percentiles, see Table 2.)

Figure 1.A

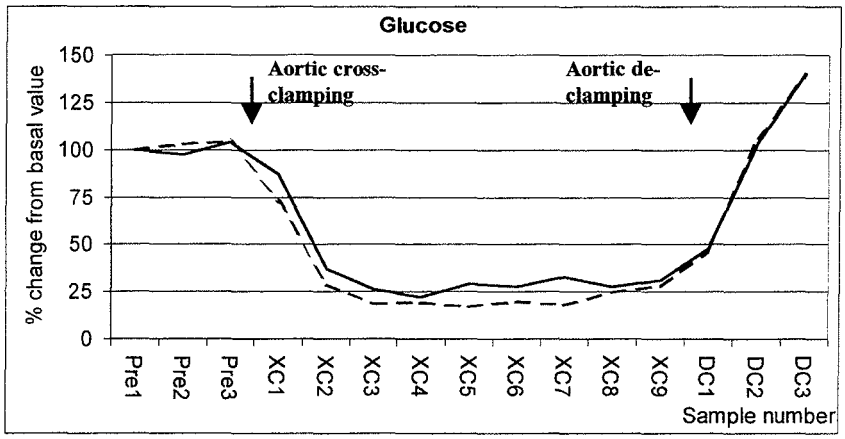


Figure 1.B

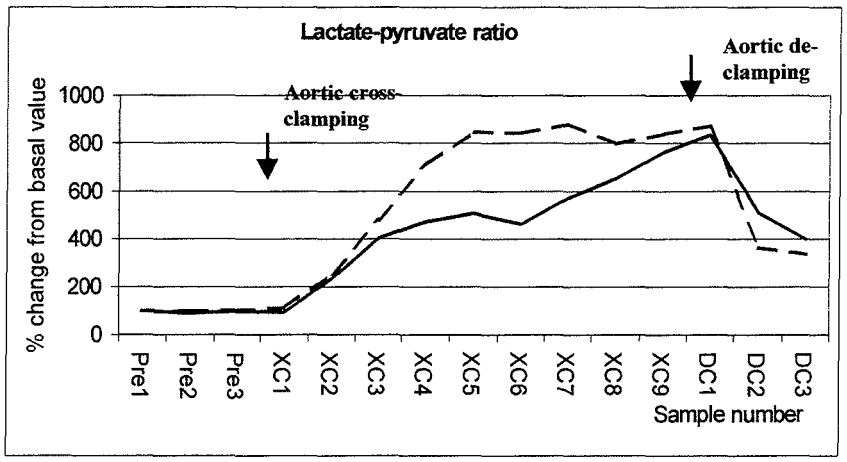


Figure 1.C

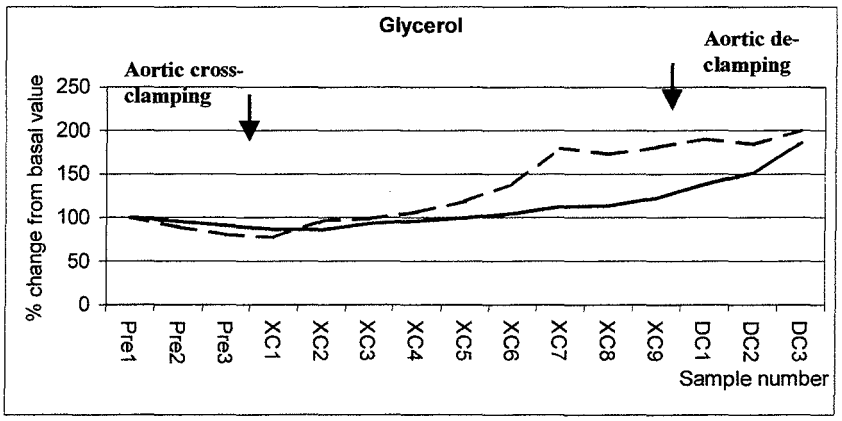
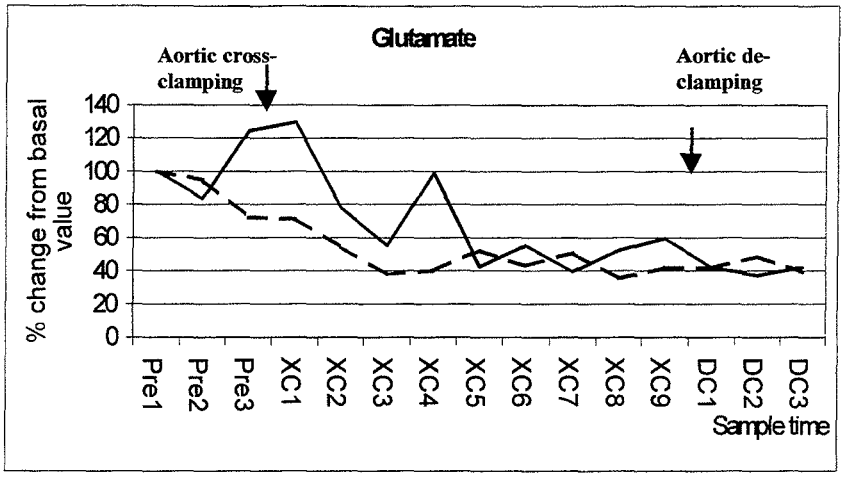


Figure 1.D


Glutamate
Aortic cross-clamping
Aortic de-clamping
% change from basal value
140
120
100
80
60
40
20
0
Pre1
Pre2
Pre3
XC1
XC2
XC3
XC4
XC5
XC6
XC7
XC8
XC9
DC1
DC2
DC3
Sample time

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