

THESES OF DOCTORAL (PhD) DISSERTATION

**NEUROLOGICAL COMPLICATIONS OF OPEN HEART SURGERIES
AND
LEGAL AND ETHICAL ASPECTS OF HEART OPERATIONS**

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Intoduction

1. Iatrogenic complications emerging during heart surgery

Modern heart surgery can achieve surprisingly good results in correcting various cardiac diseases. Despite the fact that the technological conditions of such operations have improved at a fast rate, the risks of interventions are still considerable. Even the most perfectly performed operations can be accompanied by complications. In the case of elective surgery, physicians can make arrangements in advance to prevent certain complications such as loss of blood, thrombosis, respiratory failure, infections and disturbed wound healing. However, while surgeons make efforts to save the sick heart they may cause iatrogenic damage to another important organ or system. This may lead to the development of symptoms which engrave the patient's condition, worsen the process of healing, thereby lengthening hospitalisation, make rehabilitation more difficult; in certain cases it may cause serious deterioration of the patient's health and may even lead to the patient's death. Among them, damage to the central nervous system (CNS), more closely to the brain, is of special importance. A recently discovered condition defined as 'critical illness polyneuropathy' is often associated with open heart surgery, and hypoxic liver damage, renal failure and certain forms of disseminated intravascular coagulopathy (DIC) can also be listed here.

It has been an established fact now that damage to the CNS in association with heart surgery is of multifactorial origin. An important role has been attributed to embolisation, the so-called low cardiac output syndrome (LCOS), low perfusion pressure and absence of pulsatile flow during extracorporeal circulation (ECC) and other factors such as the type and duration of the operation, the patient's age, presence of associated diseases, postoperative treatment, etc.

2. Description of the religious community known as Jehovah's Witnesses

Medical interventions have serious ethical and legal aspects. This especially holds true for the surgical field, including heart surgery. One of the crucial ethical problems is to do with the surgical treatment of the members of the religious community known as Jehovah's Witnesses. Cardiac surgery in this group of patients poses special difficulty to surgeons, since

these patients refuse any kind of blood or blood product. The roots of the religious community Jehovah's Witnesses go back to the 19th century. It was founded by Charles Taze Russell in 1870. Originally the members researched the Bible and chose their name in 1931. Currently, their churches are found in over 235 countries of the world. According to data from 2005, there are approximately 6 600 000 members of the community worldwide, the calculated membership in Hungary being approximately 22 000. The community has declared that blood transfusion was against the divine laws, therefore the members refuse to accept blood and blood products including autologous blood transfusion on religious and conscientious grounds. These principles, which also apply in the case of their children, were based on the interpretation of four parts of the Bible and published in 1945. According to the teachings of the Bible, blood is sacred to God, it means life in God's opinion, therefore it must not be administered into the body in any form. According to the current approach, whole blood, RBCs, WBCs, thrombocytes, plasma, freshly frozen plasma and cryoprecipitates are not desirable while other fractions (albumins, globulins, FVIII and FIX coagulation factors, thrombocyte factor 4, haemoglobin and its substitutes such as PolyHeme and Hemopure, erythropoietin, interferons and interleukins) are not necessarily refused. Since the Bible does not contain references of these products basically derived from blood, they can be applied and the followers of this religion are allowed to conscientiously decide whether they accept them or not. Since 1980, organ and bone marrow transplantations have been individually decided about. Haemodilution, the use of intraoperative cell saver, the heart-lung machine, dialysis and plasmapheresis have also been accepted.

Since 1985, conscious attempts have been made to reduce the quantity of preserved blood during heart operations at the Department of Cardiac Surgery, Medical and Health Science Center of the University of Debrecen (UD MHSC). Routine use of haemodilution was accepted first, which was followed by the introduction of a complex method including changes in the operative techniques supplemented by the use of drugs. Experience obtained in bloodless operations are presented in the current theses.

Goals

Since 1990 until today, approximately 16 thousand open heart operations have been made at the Centre of Cardiac Surgery of MHSCUD, their mortality rate being 5-6%. The autopsy of the deceased was performed at the Department of Forensic Medicine UD MHSC. I did or supervised the post mortem examinations. The aim of the examinations was to learn about the harmful effects of open heart surgery on the CNS and reveal their effect mechanism.

I searched answers to the questions listed below:

1. The investigations were aimed at mapping the damage to the CNS accompanied by macroscopic and histological changes in open heart surgery with ECC.
2. In the possession of the clinical details and post mortem findings I searched for etiological factors that played a role in the development of brain damage.
3. Which of the four brain-specific enzymes – aldolase, LDH, PK and LAP – exhibit activity changes in the liquor in patients undergoing open heart surgery and suffering brain damage during the operation.
4. Is there any relationship between the (macroscopically and histopathologically detectable and classifiable) type and degree of brain damage and changes in enzyme activity?

In the second part of my investigations, I wanted to reveal the following:

1. Can open heart surgery be safely carried out in patients belonging to the community of Jehovah's Witnesses without violating their religious beliefs, principles and rights?
2. I wanted to survey how the Hungarian Constitution and Hungarian laws related to the issue of "bloodless" healing – including the treatment of the underaged – in elective and acute surgery.

Patients and Methods

1.1 Patients

Sixty patients having undergone open heart surgery at the Centre of Cardiac Surgery of MHSCUD who died in the perioperative period or before the 30th postoperative day in the period of January 1990 and May 1992 were included in the morphological and histopathological study (mortality: 703/60 – 8.6%). The details of 40 patients have been used in our cumulative results. Based on the clinical documents, extensive irreversible brain damage was only mentioned in one patient before death.

Fourteen patients were included in testing the enzymes of CSF at the Department of Forensic Medicine of UD MHSC. Eleven of them died at the Centre of Cardiac Surgery of UD MHSC after heart surgery; the control group included three deceased who died of drug intoxication, chronic heart failure and pneumonia.

Investigation into the aetiology of complications affecting the CNS: in the 15-month period of 1993 and first quarter of 1994, 601 patients underwent open heart surgery at the Centre of Cardiac Surgery, 30 of them died during the operation and in the postoperative period. The ten deceased who had been diagnosed of having extensive irreversible brain damage before they died were included in the study. Their details were classified as follows: age, sex, functional stage by the NYHA classification, basic and associated diseases (diabetes mellitus, hypertension, angina pectoris, arteriosclerosis, coronary sclerosis, AMI in their history). Special attention was paid to the type of the intervention as it may have played a basic role in the development of complications affecting the CNS. During autopsy and histopathological investigations, we looked for morphological changes which may have caused brain damage.

1.2. Macroscopic investigation of cerebral slices

We examined frontal cerebral slices both fresh and fixed in 4% buffered formaldehyde solution for 24 hours. Doing the macroscopic analysis, we paid special attention to signs of oedema, atrophy, location and appearance of haemorrhage and softening, the course of intracranial vessels and the spaciousness of cerebral ventricles.

1.3. Histopathological investigation of cerebral tissue

The samples, sized 2x2x0.5 cm each, were taken from the central gyrus, cortex on the border of the parietal and occipital lobes, hippocampus, internal capsule, pons and cerebellum. The samples were fixed in 4% neutral formaldehyde solution. The sections from samples embedded in paraffin were stained using Hemalaun eosin and applying two special techniques known as Woelcke myelin staining and Nissl staining.

1.4. Investigation of cerebrospinal fluid

Cerebrospinal fluid was obtained from the cerebellomedullary cistern of the deceased, using a sterile syringe. After the macroscopic examination of CSF (clear or bloody) the fluid was stored at -70°C until further analysis. Enzyme activity measurements were performed immediately after the samples were thawed. Each measurement was carried out in a HP 8453 Hewlett Packard spectrophotometer.

Enzyme activities were determined using the optimised standard method and kits provided by SIGMA. The measurements were performed in duplicates.

2.1. Selection of patients

Between 1984 and May 1999, twenty-four heart surgery patients from the religious community of Jehovah's Witnesses were selected for the investigations, because only these patients had had clear documentation of their religious background. There were 17 females and 7 males among them. Their mean age and weight were 54.1 years (25-70 years) and 59.7 kg (45-98 kg) at the time of the operation. Surgery was indicated owing to congenital malformation, acquired valvular disease, coronary stenosis and combined valvular and coronary disease in 3, 11, 7 and 3 patients, respectively.

2.2. Surgical conditions

Except for one case, each patient underwent open heart surgery with ECC support. Also, with the exception of one case, a membranous oxygenator was used. The operating surgeons followed the protocol standardised earlier at the Centre of Cardiac Surgery. The liquid filling the device did not contain blood products and its mean quantity was 1375 mL (1000-1650 mL). Moderate haemodilution and hypothermia (28-33°C) were maintained

during the operation. The myocardium was protected with cold (+4°C) crystalloid cardioplegic solution. Aprotinin was used to reduce bleeding. The mean duration of ECC was 114 minutes (33-236 minutes); on average, the aortae were clamped for 75 minutes (17-182 minutes). For 8-16 hours after the operation, blood drained from the chest via a tube was collected in the tank of the oxygenator under sterile conditions and continuously reperfused to the patient.

The patients declared that they refused to receive any blood or blood product by their own free will.

2.3. Postoperative treatment

After the operation, iron supplementation and folic acid had to be given in case low haemoglobin and haematocrit values were found; in two cases erythropoietin was administered.

Results

1.1. General characteristics of patients in the morphological and histopathological groups

Twenty-nine males and eleven females were examined. The males' mean age was 49.4 years, while the females were 60.8 years old on average. In 19 patients, surgery was indicated because of coronary disease, in 16 cases the problem was caused by valvular disease, while in 4 cases combined coronary and valvular disease and in 1 case atrial septal defect lay in the background of the operation.

1.2. Perioperative and postoperative conditions

Of the patients included in the study, 11 people died in the perioperative period or shortly after the operation. One patient survived until the 60th, another one until the 52nd postoperative day. Among the remaining 27 patients having undergone surgery, postoperative survival was 7 days.

According to the operation records, the mean period under ECC support was 193 minutes, while the aortae were clamped for 95 minutes on average.

1.3. Macroscopic changes of the brain

In the cerebral slices, macroscopic oedematous swelling of various degrees could be seen in each case. In 28 cases, this was the only difference observable for the naked eye. In 4 patients, bleeding cortical foci developed while in 7 cases, in the deep regions of the cerebral hemispheres focal emollition of the white matter developed. Extensive destructive cerebral bleeding and global emollition of the white matter developed in one case each. In both cases, necrosis was of such a great degree that only the margins of histological structures could be recognised during the histological investigation.

1.4. Microscopic changes of the brain

Cerebral oedema of various degrees was always found in the histological samples of the brain. In mild oedema cases, swelling appeared pericellularly, around the oligodendroglia cells (Buscaino sign). In more severe cases of oedema, widened perivascular space (Virchow-Robin space) and spongy degeneration of the white matter could be observed. Microgliosis could also be observed occasionally, which was suggestive of a necrobiotic state; furthermore, the histological investigation revealed clearly visible karyopyknosis. In three cases, cerebral oedema was accompanied by vascular congestion. White softened foci of microscopic size were detected in the samples obtained from the internal capsule and pons. Staining disappeared from them and, in four cases, Woelcke myelin staining revealed demyelination. Histological investigations confirmed minute focal cortical haemorrhages suggestive of microembolism. In one of the aforementioned cases, these became macroscopically visible; under the microscope, the process was accompanied with expressed haemorrhagic necrosis. In one patient, the histological investigation of the cortical macroscopic emollition justified the presence of angiomatous malformation. Haemangioma appeared to be similar to loose bunches of vascular bundles in the nervous tissue.

2.1. General characteristics of patients included in the enzyme investigation

The mean age of the 14 patients (5 females and 9 males) was 65.5 years. We looked for two specific factors of risk in the patients' history: hypertension and diabetes mellitus, which we could find in nine and two cases, respectively. In seven patients surgery involved CABG, in two cases heart valve implantation and in one case the combination of the two

were performed. In one patient the chest was explored due to aorta dissection, without any other intervention. The three patients in the control group died of intoxication, chronic circulatory failure and pneumonia.

2.1. Perioperative and postoperative conditions

The duration of the hypoxic period is clearly shown by the length of aortic clamping time (ACT) and ECC. Mean ACT and ECC were 81.1 and 121 minutes, respectively. The shortest ACT lasted for 13 minutes, while the longest was 125 minutes; in the case of ECC, the relevant figures were 41 and 220 minutes.

Survival after the operation was 7.7 days on average, one of the patients died on the day of the operation. The longest surviving patient was lost on the 23rd postoperative day. The events of the postoperative period were not identical: cardiac failure emerged in some patients, while the others developed an AV block, bradycardia, malignant ventricular rhythm disturbance, respiratory failure, haemorrhagic or neurological complications, all of which led to serious cerebral perfusion disturbance or oxygen deficiency.

2.3. Macroscopic changes

Oedematous swelling was present in all of the patients, and, in 13 cases, this was the only macroscopic change. Extensive emollition was found in the cortex and white matter of the left hemisphere in one case. The course of intracranial vessels was normal but in the majority of the patients (11 cases) they were sclerotic. CSF was clear in each case.

2.4. Histological changes

Cerebral oedema was found in each patient. In mild oedema, pericellular swelling around the oligodendroglial cell (Buscaino sign); in severe oedema, however, the widened perivascular space appeared as spongy degeneration of the white matter. Reactive microgliosis was justified in 6 patients (necrobiotic state: clearly visible neurones with signs of nuclear pyknosis). Focal haemorrhage was detected in one case.

2.5. Enzyme activities

The enzyme activity of aldolase in the liquor was extremely high in one case, its somewhat more moderate but still significant increase was found in 3 more cases. The increase in aldolase was parallel to the increase in LAP activity. Paradoxically, significant increase in LDH and PK enzyme activities was associated with low or normal aldolase and LAP values. The highest measured aldolase values were as follows: 26.178 U/L (normal: 2-8 U/L), in the case of LAP, the relevant figure was 19.081 U/L (normal: 1.2-3 U/L), the highest LDH was 883.6 U/L (normal: 125-236 U/L), the highest PK value was 833.3 U/L (normal: 6-19 $\mu\text{mol/L}$), while the lowest figures were 3.531 U/L, 0.385 U/L, 32.2 U/L and 6.51 U/L respectively.

3.1. Patients' general characteristics in the group chosen for the study of causes leading to damage of the CNS

Of the ten deceased, six were women and four men, their mean age being 56 years. Seven patients had undergone CABG operation and two of them simultaneously received prosthetic heart valves. In one case, the artificial valve was required due to secondary cardiomyopathy and subsequent left ventricular dilatation. An emergency operation was performed in one case due to the rupture of the ventricular septum (VSD). In another case the excision of pseudoaneurysm (scar) was done.

3.2. Perioperative and postoperative conditions

Circulatory collapse requiring resuscitation took place in four patients. In six patients severe hypotension ensued after surgery and they had to be treated and fitted with catecholamine and intra-aortic balloon pump, respectively. Respiratory failure and imperfect saturation values were noted in three cases. The autopsy findings revealed postinfarction scarring of the myocardium in six patients, three of which also developed perioperative infarctions. Two of four patients, all of them with diabetes mellitus in their histories, developed hyperglycaemia. Four anuria cases were identified, one of which was due to primary disease, the others were classified as secondary problems resulting from hypotension and decreased filtration pressure. Two patients had gastrointestinal haemorrhage; one of the bleedings was the sign of generalised multi-organ damage and it actually emerged as terminal

ischaemic mucosal bleeding. In the other case, the bleeding was preceded by long-term tube-feeding. In three of the deceased intracranial atherosclerosis was quite expressed.

116/1993. Clinically, the patient developed left lateral hemiplegia and became sopor-comatous afterwards. On autopsy, the cortex of the parietal and occipital lobes in the right hemisphere were found to contain haemorrhagic foci of embolic origin and, on both sides, the basal grey nuclei were affected by hypoxic necroses without bleeding.

424/1993. Clinically, the patient had ARDS, and cardiac arrest on two occasions. The autopsy revealed grave diffuse cerebral oedema and signs of impaction in the cerebellar tonsils and the area of the hippocampus.

522/1993. The patient's circulation collapsed during the operation and, based on the clinical neurological examinations, he/she was declared brain-dead. The autopsy of the brain revealed right cerebral necrosis accompanied with extremely grave generalised atherosclerosis.

954/1993. Diffuse hypoxic brain damage, which, in part, was thought to be of metabolic origin, developed during the operation. Autopsy and histological investigation confirmed changes suggestive of the acute hypoxic damage of the cortex and basal grey nuclei.

1066/1993. Neurological tests could not detect cortical functions. Autopsy showed diffuse hypoxic brain damage and necrosis. There were secondary linear haemorrhages in the pons and grave basal arterial sclerosis could also be observed. The myocardium was affected by extensive subacute infarction and scars of previous infarction(s).

74/1994. Two days after the operation, the patient developed left lateral hemiplegia. A neurologist made the initial diagnosis of pontomesencephalic embolism. On autopsy, white emollition of 2 cm in diameter was found in the pons, the myocardium was affected by dorsal subacute MI, and severe sclerosis of the vertebral and basilar arteries was also detected.

135/1994. The patient did not come round after the operation. Autopsy revealed diffuse brain damage, anterolateral subacute myocardial infarction and state of post-pseudoaneurysmal excision.

248/1994. On the second postoperative day, the patient developed right lateral facial paresis and anisocoria. On autopsy pontomesencephalic and cortical circulatory failure was found. In addition, expressed myocardial degeneration was also detected.

279/1994. A few hours after the operation, the patient had ventricular fibrillation. He was resuscitated several times but had clinical symptoms of diffuse cortical damage. Autopsy revealed cerebral atrophy, diffuse hypoxic damage and cerebral oedema. Extensive inflammation and adhesions of the thoracic organs and postinfarction scarring of the heart were also detected.

320/1994. The patient developed hemiplegia 2 days after the operation with bulbar involvement and symptoms of diffuse brain damage later on. On autopsy, extensive white softening of the pons, extensive embolic softening of the left cerebral cortex and diffuse hypoxic damage were identified. The largest diameter of Gortex patch in the interventricular septum was found to be 7 cm. The myocardium appeared degenerated and the patient also had bilateral bronchopneumonia.

4.1. *Mortality in the Jehovah's Witnesses group of patients*

Of the 24 patients who underwent surgery, two died in the early postoperative period, i.e. within 30 days after the operation. A condition known as low cardiac output syndrome developed in a 53-year old patient who had an emergency operation for a coronary artery due to unstable angina. Despite mechanic circulatory support, the patient died on the second postoperative day. Another patient aged 66, who had undergone aortic and mitral valve implantations, lost consciousness because of cerebrovascular complications. He/she developed anuria and pneumonia, and eventually died owing to multi-organ failure on the eighth postoperative day.

Following aortic valve prosthetic surgery, a patient required long-term artificial respiration for which conicotomy had to be performed. As his/her condition improved, the patient was transported to the intensive care unit of the regional hospital, but he/she died of septic complications six weeks after the operation.

4.2. *Perioperative and postoperative complications in the Jehovah's Witnesses group of patients*

Non-fatal complications emerged in three cases. On the second and ninth postoperative days, pericardium fenestration had to be performed in two patients owing to accumulation of fluid in the pericardium, which caused threatening tamponade. Because of excessive

bleeding, re-sternotomy had to be done in one patient in the postoperative hours. The bed of mammary arteries was the source of bleeding, it was treated and the haematoma was removed. Owing to the low, life-threatening haemostatus, the patient was reformed and he/she agreed to a life-saving blood transfusion prior to the operation. Five units of RBC mass had to be transfused.

Drug therapy was started in twelve patients because their parameters concerning haemostatus were significantly decreased, although not life-threatening. Eight of them were given 3x1 tablet of Tardyferon and 3x2 tablets of folic acid each. Four of the patients were treated with 3x1 tablet of Sorbifer Durules and 3x2 tablets of folic acid each. In the case of two patients, the aforementioned medications had to be supplemented with erythropoietin.

Each of the patients was given LMWH subcutaneously in the postoperative period. Although it increased the risk of haemorrhage, but its administration was indicated in patients requiring prolonged anticoagulant therapy until their therapeutic international normalised ratio (INR) was achieved. Similarly, patients having undergone bypass surgery were given LMWH treatment during recuperation (4-5 days on average). High or subtherapeutic INR values, or pathologically prolonged coagulation time posing a high risk of bleeding were not found. Thromboembolic complications were not found either.

4.3. Postoperative follow-up

The 21 survivors could be followed up for an average of 37.6 months (2-172 months). Mean hospitalisation was 15 days (10-28 days), while postoperative hospitalisation lasted for 11 days (8-26 days) on average. Preoperative parameters were as follows: haemoglobin (Hgb) 134.2 g/L (112-166 g/L), haematocrit (Htc) 36% (35-50%). The greatest decrease in haemostatus was seen during ECC: Hgb 74 g/L (51-113g/L), Htc 23% (16-37%), which could be explained for by haemodilution. Values measured immediately after the operation showed improvement: Hgb 104 g/L (65-145 g/L), Htc 27.1% (17-40%). The values decreased again on the first postoperative day, postoperative bleeding and haemolysis being the possible explanation. From the second day on, slow increase in Hgb and Htc values were seen. At about the 5th postoperative day, the values reached the level of those measured immediately after surgery. Further slow but continuous increase had been noted until the patients were discharged.

Thrombocyte count dropped sharply after the operation, partly because of the well known, diluting power and destructive effect of ECC on thrombocytes. The lowest thrombocyte count was found on the third postoperative day, after that it reached the initial preoperative value relatively fast and exceeded it after the seventh postoperative day. On the day of discharge from hospital, values exceeding the initial ones by 30-40% were documented.

The patients' condition gradually improved after the operation, their functional NYHA stage changed from 3.06 to 1.62.

Discussion

During the postmortem examinations, the following observations were made about patients having undergone open heart surgery: a) Diffuse and focal brain damage can equally occur in association with cardiac surgery. b) They can emerge either as haemorrhage or emollition. c) To all likelihood, there are multifactorial causes in the background, but the damage usually results from generalised hypoxia, embolisation or the combination of the two. d) It is the low cerebral perfusion pressure that may contribute to diffuse damage, while focal changes are due to embolisation. e) Vascular disease is supposed to predispose to the emollition of cerebral white matter, while haemorrhagic and embolic complications in the cortex are more common in patients with defective valves. f) Diabetes and hypertension are extremely high factors of risk.

1.1. Pathomechanism of complications affecting the CNS

It has been an established fact today that complications affecting the CNS during open heart surgery are multifactorial, i.e. they can emerge for several reasons.

1.1.1. Theory of embolisation

The majority of proofs found in the investigation of the causes of complications affecting the CNS support the theory of embolus formation. Even the high rate of embolisation detected by transcranial Doppler examination (TCD) is underestimated since TCD is capable of detecting only a fraction of all embolisations. Detailed histological investigations suggest that the rate of embolisation affecting the brain during CABG may be as high as 15 million. In our investigations we noticed minute focal haemorrhages in the cortex. As they usually develop

due to microembolisation they are also considered to be embolic complications. Similarly to our findings, Braekken *et al.* have reported that cortical focal haemorrhages occur more commonly after heart valve operations. It appears that embolisation is rarely of thrombotic origin if the rules of anticoagulation therapy are followed carefully. It is more likely, that the “sources” of embolisation consist of air bubbles escaping from intravenous cannulae, syringes, or heart-lung machines, fragmented tissue coming off during the intervention, or aluminium and silicone granules from the oxygenator.

Interestingly enough, the majority of microembolisations are detected at a stage of the operation when the patient is on a heart monitor, i.e. ECC, and no surgical manipulation is going on. Really, the introduction of operations without a heart engine device has led to a significant decrease in the frequency of microembolisations, but despite the expectations, the number of ‘cerebral events’ has not decreased dramatically and patients undergoing off-pump surgery may not be exempt from the decrease in their neurocognitive functions. Factors independent of ECC are also likely to be high factors of risk. This idea has been supported by an observation: patients with a decrease in their postoperative neurocognitive functions do not suffer from fewer microembolisations than the ones who do not have cognitive functional disturbance. Therefore, cognitive functional disturbance cannot be explained for by embolisation.

1.1.2. Theory of low perfusion pressure

It was as early as in the 1960s that low blood pressure developing during ECC was supposed to play a role in the formation of CNS complications. Based on several investigations it appears that, despite hypothermia, high perfusion pressure or high partial O₂, the EEG often becomes isoelectric at a perfusion pressure of 50 mmHg. Therefore, it is highly recommended that the mean arterial pressure exceeds 50 mmHg during ECC support, to ensure the cerebral perfusion capable of maintaining spontaneous EEG activity at least. 50 mmHg appears to be a highly underestimated value. According to the literature, this autoregulation range falls between 60 mmHg and 150 mmHg of mean arterial pressure (MAP). In case MAP falls below 60 mmHg, O₂ extraction increases and when compensation is over, irreversible brain damage may develop. According to recent studies even MAP at 60 mmHg is not enough to keep the perfusion in the brain at the level of those with normal pressure. Since, it is hypertensives who have to undergo heart operation in the majority of the

cases, the drop in their blood pressure results in a significant deficit of cerebral perfusion. Our investigations suggest that the damage in confluent cerebral emolition and cases with destructive cerebral haemorrhage accompanied with red cerebral malacia resulted from cerebral hypoperfusion rather than embolisation because a) in the majority of cases, it did not occur at the typical location (internal capsule), but in the cortex, b) the patients had been given circumspect anticoagulant treatment. This has been confirmed by the observations by our team and Maruyama *et al.*: the source of the embolus could only be found in one case. Supposedly, the etiology of global cerebral ischaemic necrosis is similar; according to the clinical details, it was caused by prolonged ECC time or generalised cerebral circulatory failure, which had developed for a different reason.

1.1.3. Theory of reperfusion

Based on the investigations by Stockard *et al.*, the pressure applied during reperfusion and the neurological outcome are in good correlation with each other. Although ischaemia can directly damage the neurones, many presume that a no-reflow phenomenon is found in the background that should be started by the vascular mechanism, when swollen endothelial and perivascular cells cause a significant decrease in intravasal perfusion, the parenchymatous stage developing afterwards.

1.1.4. Other theories

Not only the decrease in cerebral blood flow but also the duration of decreased blood flow play an important role in the development of the damage. The mean age of the patients examined by us was under 60 years, therefore no conclusions could be made of the higher risk in old people. Since the risks of an operation are determined by the basic disease, factors of risk, patient's functional stage, type of operation, patient's age, etc. together, the use of the Euroscore system allows for assessing the risk of an intervention in a certain patient prior to the operation. Follow-up investigations confirm that the patient's age is perhaps of the greatest importance.

Based on our results the follow-up of ARDS, AV block, PM therapy, resuscitation, etc. is highly important as they greatly contribute to further deterioration of the brain having suffered from hypoxia earlier. It appears, that patients with high blood glucose concentration

are definitely worse at tolerating relative cerebral hypoxia than those with normal blood sugar level. In the case of hyperglycaemia the brain requires more oxygen and is more sensitive to poor oxygen saturation. In patients with normal blood sugar level, cerebral damage basically involved haemorrhagic softening which was supposedly of embolic origin.

1.2. Role of enzyme investigations in diagnosing brain damage

Several studies have highlighted that trauma to the brain has contributed to a significant increase in aldolase, LDH, LAP and creatin-kinase BB isoenzyme (CK-BB) activities in the cerebrospinal fluid. Although the conditions and complications of open heart surgeries cannot be considered synonymous with cerebral traumas, the brain is also exposed to a kind of trauma during open cardiac surgery.

In the current study, we try to find a relationship between the enzyme activity changes in CSF of four brain-specific enzymes (aldolase, LDH, pyruvate kinase and LAP) and the macroscopically and histopathologically detectable and classifiable cerebral damage. CSF samples from each patient showed more or less rise in enzyme activity. We could observe that values for the two pairs of enzymes – LDH-pyruvate kinase and aldolase-LAP – changed parallel to each other. Increased aldolase and LAP activity was best observed in patients suffering from diabetes and hypertension which is suggestive of the fact that hypertensives and diabetics can tolerate hypoxia to a lower degree. According to Japanese researchers, neurological complications emerge more often if patients spend more time with their aorta clamped or supported by ECC during cardiac surgery, the duration being in close correlation with the frequency and severity of neurological complications. Our enzyme activity investigations do not always confirm the above: interestingly enough, extremely low LAP activity was detected in our only leukoencephalomalacia patient, who had the gravest brain damage. The results for the four enzymes and the macroscopic and histological changes of the brain brought up the idea that CABG operations pose a greater risk than heart valve surgeries do. This has also been confirmed by Japanese authors. Owing to the low number of cases, we cannot come to farfetched conclusions, but studying the results according to the above ideas it can be presumed that brain-specific enzymes are sensitive markers of the degree of brain damage – and studying a representative (large and heterogeneous) group of

patients, using relevant statistic methods, values of enzyme activity could serve as excellent prognostic markers for those having undergone open heart surgery.

1.3. Role of postmortem examinations in quality control (QC) of heart surgery

In the era of the rapid development of diagnostic imaging techniques, many question the necessity of autopsy in making an accurate diagnosis. Experience, however, shows that we need detailed information about the deceased after heart surgery in order to decrease unwanted complications and learn a lesson from cases assessed poorly in the past. This involves the definition of the exact cause of death and recognition of perioperative complications. Both can be achieved by autopsy and the subsequent investigations. In the past, postmortem examinations were widely accepted as standard methods in analysing the cases of death in health care facilities. In contrast, today, the number of postmortem investigations has decreased dramatically. To decide if this change in approach was good or not, the prospective study by Rastan *et al.* on patients deceased after cardiac surgery may give the answer. Comparing clinical and autopsy results they found that the clinical diagnoses were incorrect or incomplete in several cases. Regarding total mortality, clinicians gave a wrong diagnosis for the cause of death in 30% of the cases. This figure may appear high at first glimpse but it may be explained by the fact that dissections of problematic cases are usually requested, new information as well as the exact causes are expected to come after autopsy. One cannot neglect the fact that clinicians and pathologists approach the basic disease and its complications differently, and there is also a difference in specifying the immediate cause of death.

Conclusion

In the case of open heart operations, the histological changes of the brain result from generalised hypoxia, embolisation or the combination of the two. To decrease the incidence of complications it is desirable to decrease the period while the patient receives ECC support. It is also necessary to ensure adequate blood pressure and cerebral circulation during the whole of the operation in addition to determining and eliminating the sources of embolisation. Further investigations into the possible factors of risk and their capacity to increase morbidity and mortality are necessary to detect patients at risk prior to the operation. Since certain

factors of risk cannot be removed during the operation, attempts have been made to apply pharmacological prophylaxis of the CNS by administering instenon or Nycomed® perioperatively.

2. Experience of open heart surgery in patients belonging to Jehovah's Witnesses; ethical and legal aspects of the intervention

Cardiac surgery in this group of patients poses special difficulty to surgeons, since these patients refuse any kind of blood or blood product, including autologous transfusion. No wonder that interest in bloodless surgical technique has been growing. The safety of bloodless operations has greatly increased due to careful surgical techniques, special attention paid to haemostasis, availability of aprotinin, reduction of perfusion liquid and increased protection of coagulation factors. In the study period, 24 patients belonging to Jehovah's Witnesses were operated on at the Centre of Cardiac Surgery, UD MHSC. Experience has shown, that despite all the efforts by medical science (including careful surgical techniques, antihemorrhagic aprotinin treatment or administration of erythropoietin to support blood production) bloodless heart operations can only be made relatively safe if the patient's weight before the operation exceeds 20 kg, Hgb is over 100 G/L, Htc exceeds 35% and the patient is not predisposed to haemorrhage, does not have liver, kidney, blood or haemopoietic diseases or multiorgan disease in his/her history. Similarly to the international findings, we have also found that the haemostatus values were the lowest during ECC, if the perioperative period was considered. Htc should not be less than 15%. In summary it can be concluded that the cardiac surgical treatment for Jehovah's Witnesses can be given safely using a few special techniques different from the 'routine protocol' even in interventions posing serious surgical risks. Neither stroke, AMI, atrial fibrillation, prolonged artificial respiration, acute renal failure nor re-exploration due to bleeding are more common among them. Our multivariate analysis has also pointed out that postoperative mortality and intensive care are also similar to those in the control group.

In an ideal case, the intervention can be completed successfully without the administration of blood or blood product. Should circumstances require the administration of blood or blood product, the treatment of the patient puts extra ethical and conscientious load on the attending physician. We must respect the patients' conviction that the acceptance of

blood products deprives them of immortality. At the same time, however, the declaration of refusal of blood transfusion signed by the patient does not lift the physician's responsibility in case it is proved that the deterioration of the patient's health or his/her death was due to a missed transfusion. This situation may be a special problem for an active physician because it is not clear how to match the doctor's duty, responsibility and rights in such cases.

The standpoint of Hungarian legislation on this issue is as follows:

After adequate information free of threat and compulsion an able patient has the right to decide whether or not he wishes to have recourse to health care and decide which interventions he agrees to or refuses during the treatment. Should he suffer serious damage or even die due to missed therapy the patient can only refuse treatment in a declaration.

An incapable patient or one limited in his ability is represented by his legal representative or the person appointed by him. In case the treatment is refused by the appointed person in such a way that the health of the incapable patient or patient limited in his ability will be negatively affected, the law includes authoritative measures and, by means of the jury, it can immediately supply the missing agreement. This is the point where a health care provider faces the moral and ethical responsibility when and how to use the law, authoritative measures and turn to a jury.

It should be remembered that the term 'bloodless operation' does not mean that blood components are not administered either. According to the Watchtower Society it is prohibited to give the patients blood and certain blood products, while other products, also made from blood, are allowed. Currently the Watchtower Society teaches that only those blood products are allowed which are capable of crossing the placental barrier during pregnancy. However, the interpretation and use of this teaching appears to be somewhat outdated today: medical science has got several proofs to support that practically all blood components cross the placental barrier. It is also questionable if it is only the blood components of small fraction that are allowed by the Watchtower Society. Albumin, for instance, is allowed although it constitutes 2.2% of the volume of blood while the prohibited WBC and platelet fractions are found in 1.0% and 0.17%, respectively. Moreover, haemoglobin, which is also allowed, constitutes 14.8% of the volume of blood. Further contradictions are discovered if one takes

the case of haemophiliacs. The Watchtower Society does not give its followers the permission to have their own blood products frozen. At the same time, however, to treat haemophiliacs, large quantities of blood should be collected and frozen and it is approved. This problem may be solved using coagulation factors prepared by the recombination technique, but its use is limited by the considerable costs.

Summary

The dissertation gives an account of the investigation into cases when patients having undergone open heart surgery at the Department of Cardiac Surgery of UD MHSC died. Special attention was paid to complications affecting the central nervous system (CNS) in the first place. A separate chapter was devoted to interventions performed in the case of Jehovah's Witnesses, and also the legal and ethical problems of such operations.

In my study, I have surveyed the damage to the CNS accompanied with macroscopic and microscopic changes during open heart surgery supported by ECC. In the knowledge of the clinical course of the disease and findings of autopsy I looked for the causes of brain damage. I studied which of the four brain-specific enzymes (aldolase, LDH, PK and LAP) shows activity changes in the CSF due to brain damage suffered during the operation. Is there any relationship between the type and extent of brain damage and the changes in enzyme activity? Can open heart operations be safely performed in Jehovah's Witnesses without the violation of their religious beliefs, principles and rights? I studied what the constitution and laws of the Republic of Hungary say about the "bloodless" treatment given to Jehovah's Witnesses.

The postmortem examination of patients having undergone open heart surgery enabled us to observe the following: Both diffuse and focal brain damage may emerge in association with heart surgery. This can appear both as haemorrhage and emollition. Multifactorial causes are likely to be in the background of brain damage, but the changes basically result from generalised hypoxia, embolisation or the combination of the two. Low cerebral perfusion pressure and embolisation are blamed for diffuse brain damage and focal changes, respectively. Vascular disease causes the emollition of cerebral white matter, while valvular diseases may result in embolic changes of the cerebral cortex. Diabetes, hypertension and old age – and especially their combination – present a high factor of risk. Surgical treatment of Jehovah's Witnesses poses a special problem, since they refuse any blood and blood product, including autologous transfusion. However, the cardiac surgical intervention of Jehovah's Witnesses can be safely performed by using a few special techniques developed based on the 'routine protocol'. The Hungarian Constitution and laws strictly outline the standard operating protocols in these cases.