The effects of pediatric cardiac surgery on long-term outcomes and neuropsychological development

Ph.D. Thesis

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1. INTRODUCTION

In recent years, improvements in medical treatments, non-invasive imaging, surgical techniques, advances in cardiopulmonary bypass surgery and pediatric intensive care have allowed more than 90% of children born with congenital heart disease (CHD) to reach adulthood. The overall mortality of this patient population has decreased by 31% over the last twenty years, however, it is still higher, then mortality related to other congenital malformations. The quality of life of grown-up survivors is continuously improving, but in some aspects it will never reach the level of the healthy population. The most remarkable indicator of the quality of care was the mortality rate for several years, but considering, that survival has reached a plateau regarding some malformation types (PDA, septal defects, pulmonary stenosis), the improvement of survival is due to the recovery of those operated with complex cardiac diseases (transposition of the great vessels, univentricular heart). Considering these factors, it was suitable to introduce other factors than mortality for characterizing and predicting the postoperative outcomes. Quality of life, neurocognition, rehospitalisation rates, social and behavioural adaptation are all well describing the future development of these children. Postoperative cardiac and extracardiac complications have a great influence on hospital stays, morbidity and mortality also. The occurrence of complications was related to different factors, like cyanotic states, long lasting cardio-pulmonary bypass, elevated lactate levels, higher need for intraoperative inotropic support, complex surgeries, long-term mechanical ventilation or intensive care unit stays. The number of patient having complications in different cardiac surgery centres is not necessarily different, the deviation between the institutions is due to the quality of postoperative care. High-volume centres have well-established therapeutic protocols regarding the recognition and care for the most complicated cases, thus improving the long-term outcomes.

After early surgical corrections, physically healthy grown-up survivors may still face the consequences of the neuronal and psychological injuries they might have suffered during the perioperative period. Cardiac surgery and perioperative complications also have been linked to dysfunctional behaviours and psychological abnormalities such as coping difficulties, social relation problems and attention-deficit/hyperactivity disorder (ADHD). Even though the aetiology of the above mentioned disorders is multifactorial, several studies reported a significantly higher morbidity for this disorder among cardiac

surgery patients, especially after aortic arch repairs and corrections of great artery transposition. Children with congenital heart disease have been reported to be at a 30% higher risk for inattention and hyperactivity disorder compared to healthy individuals. Importantly, while nearly half of the surgically treated patients need remedial school services when reaching adolescence, cardiac patients' ADHD symptoms are often under-diagnosed and thus under-treated. Unfortunately, there is no clear medical protocol regarding intraoperative cerebral protection either. Different neuroprotective operative management strategies, such as the use or the duration of deep hypothermic circulatory arrest may have less influence on behavioural outcomes than had been assumed previously. In line with this assumption, other studies showed that genetic abnormalities seem to have an impact on the neurodevelopment of neonatal cardiac surgery patients. Other factors such as complexity of the heart disease or additional genetic malformations or even the patient's age at surgery may also be significant predictors for psycho-behavioural outcomes. To date, studies examining the association between ADHD symptomatology and cardiac surgery in children have not considered the age of patients at operation and / or included healthy individuals as a control group. Further, studies have mostly relied on the parents' evaluation of ADHD symptomatology only, not considering the children's perceptions of their own symptoms.

2. OBJECTIVES

The aim of the present study was to discover the consequences of pediatric cardiac surgery, focusing especially on the short-, and long-term effects of chylothorax and the behavioural and neuropsychological outcomes of these patients.

1. We aimed to identify the short-term effects of rarely occurring chylothoraces after pediatric cardiac surgery, including mortality rates and different complications.
2. We aimed to identify the effects of chylothorax on the long-term survival and postoperative outcomes.
3. We aimed to establish an efficient therapeutic algorithm, adapted for the Hungarian pediatric cardiac surgery population, in the treatment of severe postoperative chylothorax.

4. We aimed to determine the effects of cardiac surgery on the future behavioural outcomes, especially focusing on coping strategies of children.
5. We aimed to identify the role of the age at surgery in the future incidence of ADHD symptoms.

3. METHODS

The analysis of chylothorax and behavioural development was investigated with separate methods, but from the same institutional database.

A total of 1,664 consecutive pediatric patients undergoing heart surgery were admitted to our cardiac ICU between January 2004 and December 2008. During this period, 24 patients had and 1,640 did not have chylothorax. Therefore, we extended patient data collection for the occurrence of chylothorax for 10 years. The incidence of chylothorax has been reported as the percentage of an indexed type of surgery between 2002–2012. The study was approved by the Regional Ethical Committee and the Institutional Review Board (25980/2012/EKU). A propensity-matched statistical method allowed for analyses of two groups of patients with similar characteristics.

The diagnosis of chylothorax was made on biochemical testing and a positive chest X-ray: pleural spaces with high levels of triglycerides (>110 mg/dL), proteins (>20 g/L), and lymphocytes (>80% of cells). Patients with solely transudate formation were excluded. The cardiac surgical procedures were graded by applying risk adjustment for the congenital heart surgery (RACHS) scores. The vasoactive inotropic scores (VIS) were calculated as: dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100× epinephrine dose (μg/kg/min) + 10× milrinone dose (μg/kg/min) + 10,000× vasopressin dose (U/kg/min) + 100× norepinephrine dose (μg/kg/min). The in-hospital endpoints were mortality, serious morbidity and resource utilization. This latter includes the need for mechanical ventilation, the length of ICU and in-hospital stays and the need for renal replacement therapy. We defined mortality as in-hospital death from any reason, including children who died after having been transferred to another hospital. Postoperative low cardiac output syndrome [LCOS; clinical signs (tachycardia, hepatomegaly, cardiac arrest), with a base excess lower than −4 mmol/L or a lactate level higher than 2 mmol/L in two consecutive arterial blood samples, a urinary output lower

than 1 mL/kg/hr, a maximum VIS higher than 20, or the need for mechanical circulatory support]; pulmonary failure (non-infectious and non-vascular oxygenation problems, such as atelectasis, pneumothorax, chylothorax, phrenic paresis); renal failure (need for peritoneal dialysis or haemodialysis) and infection (catheter-related and deep sternal wound infection, positive hemoculture or sepsis) were considered to be adverse outcomes. Neurological events, such as convulsion without previous anamnesis, haemorrhage or cerebral infarction demonstrated on cranial imaging, were also included as complications. We assessed the long-term outcomes and complications. The follow-up period ended on November 15, 2016 and was 11.6 years for chylothorax and 10.6 years for control groups. During this follow-up period, the number and outcomes of the reoperations, morbidities, neurodevelopmental outcomes, confirmed thrombophilia and/or thromboembolic events were also recorded.

The investigation of behavioural disorders was approved also by the local institutional review board and was performed upon participants and parents giving informed consent.

The surgery group enrolled patients with congenital heart disease who underwent at least one cardiac surgery before 2012. (n=80) at the Pediatric Cardiac Centre of the Hungarian Institute of Cardiology and agreed to participate. The control group included children who underwent an ambulatory investigation because of accidentally detected heart murmurs but later were identified as healthy (n=62 for the behavioural assessment and n=53 for ADHD investigation). The mean elapsed time between the first cardiac operation and survey administration was 10,5 years (SD±2,3) among those undergoing surgery. The demographic and perioperative medical data were retrieved retrospectively from the institutional medical record. Medical variables included the length of the intensive care unit- (ICU) and overall hospital stay; length of the surgery and length of extracorporeal circulation (ECC) needed while surgical interventions were made. Further, length of aortic cross-clamp use and the risk adjustment system for congenital heart surgery (RACHS) score were also reported. Queries were administered prospectively upon check-up of the surgery groups in preschool- and primary school-age, while patients of the control group were assessed as part of their ambulatory medical examination.

For the analysis of cyanotic states, we defined two different subgroups among the operated children. The first subgroup included patients with univentricular heart and those

with anomalies requiring total cavopulmonary connection (TCPC) as final procedure (TCPC or cyanotic group). After an early palliative surgery (usually shunt-procedure), these children lived in mild cyanotic states at least for a year, until the final corrective surgery could be done. The second subgroup included patients with ventricular septal defects (VSD) with no cyanosis perioperatively (VSD or acyanotic group). For the analysis of ADHD symptomatology, we divided the surgery patients according to their ages: surgery performed before and after completing 3 years of age.

The tests completed by the participants were the following:

1. For the behavioural and coping strategy assessments, the Youth Self Report (YSR), as a modified version of the CBCL query, and the Ways of Coping Questionnaire (WOC) were used. The YSR is formed by 6 subscales: social problems (I), anxiety and depression (II), somatization (III), attention disorder (IV), deviant behaviour (V) and aggressive behaviour (VI). The first two subscales together are measuring internalization problems, while the fifth and sixth subscales the externalization difficulties. The original WOC questionnaire is a 68-item query, created by Lazarus et al. Dimensions of coping are defined 7 subscales, summed into 2 major scales: the problem-focused and the emotion-focused way of coping. In this study we used the shorter, 22-item version questionnaire, created by Kopp and Skrabski and adapted specifically for the Hungarian population. The first three subscales belong to the problem-focused coping (problem analysis, cognitive restructuring, adaptation), while the other four are making part of the emotion-focused strategies (emotion motivated actions, positive reassessment, escape-avoidance, seeking for social support).
2. For the examination of ADHD symptoms two subsequent subgroups were defined. In the first, children were enrolled if having surgery before 3 years of age (n=54), while the second subgroup included those who received operation at a later age (n=26). Two tests were performed: the ADHD Rating Scale IV, completed by parents, and the Attention Disorders Subscale ($CBCL_{AD}$ Subscale IV), out of the six subscales of the CBCL. This latter was completed by both parents and children. Internal reliability of the scale was good for scores provided by parents (Cronbach's alpha = 0.82) and suboptimal but acceptable for scores provided by patients (Cronbach's alpha = 0.63). Beyond the total score (ADHD

RS_{TOT}) of the ADHD Rating Scale IV, this 18-item instrument provides two subscale scores pertaining to attention-disorder (ADHD RS_{AD}) and hyperactivity-impulsivity (ADHD RS_{HI}) symptoms. Internal consistency was excellent both for the two subscales (Cronbach's alphas = 0.95) and the total (Cronbach's alpha = 0.97) scores.

The follow-up ended on 15th November 2016. During this period reoperations, other morbidities, later complications, neuropsychological, behavioural and ADHD related symptoms were registered. Major variables examined were the length of ICU and in-hospital stay, operation times, extracorporeal circulation (ECC) times, cross-clamp times and Risk Adjustment for Congenital Surgery Scores (RACHS).

Statistical analysis

The results are expressed as counts and percentages as well as the mean and standard deviation (SD) for categorical and continuous variables, respectively. The demographic and perioperative differences between patients were compared basing on a χ^2-test, Fisher's exact test and *t*-tests, as appropriate.

Due to the differences in baseline characteristics, the group with chylothorax and control group were not comparable with respect to important covariates. We established a propensity score model for the two groups; thus, we minimized differences and reduced the bias resulting from the study design. The propensity score was constructed using a multivariable logistic regression model, with chylothorax as the binomial dependent variable and all of the measured covariates that could be related to chylothorax (14 variables) as predictor variables and which were: age (days), RACHS points, preoperative ICU stay (days), preoperative need for inotropes, preoperative need for captopril, CPB time (minutes), aortic cross-clamp time (minutes), operation time (minutes), nasal temperature (degree Celsius), deep hypothermic cardiac arrest (DHCA), need for nitric oxide, fluid balance, need for RBC transfusion and need for aprotinin.

The variables had a $P<0.2$ value in the univariate analysis. The Hosmer-Lemeshow test and c-index were used to measure the model's reliability and predictive ability, respectively. The receiver operating characteristic curve's c-index (area under the curve)

was 0.8345, and the Hosmer-Lemeshow C statistic was 11.3, with a P value of 0.183 (8 degrees of freedom).

Chylothorax patients were matched to patients without this complication with similar propensity scores. A 1:1 nearest-neighbour greedy matching without replacement to form pairs using calipers was applied. The width was equal to 0.2 of the SD of the logit of the propensity score. The 48 matched pairs were analysed for differences in their baseline characteristics and outcome variables. We realized that the treatment options were different in patients with a vascular ring. Therefore, in the tables reporting postoperative and long-term complications, these six patients and their pairs were excluded. The standardized differences were estimated to evaluate the effectiveness of balancing the baseline characteristics between the two groups. The standardized differences were between −0.1 and 0.1 across the 14 baseline covariates. All of the tests were two-sided, and the endpoints and measured covariates were compared with a nonparametric-test for continuous variables and McNemar's test for the categorical data. SPSS 21 statistical software (SPSS, Chicago, IL, USA) was used. A P value of less than 0.05 was considered statistically significant. The follow-up extended from the day of discharge to the date of death or censoring, and its median was computed using the Kaplan-Meyer method.

For the analyses of behavioural and ADHD characteristics we used the SPSS 23.0 software (SPSS, Chicago, IL, USA). On the univariate level, ANOVA, chi square tests, and t-tests were performed to compare participants across surgery status (no cardiac surgery, surgery under 3 years of age, surgery above 3 years of age). On the multivariate level, the general linear model procedure was used to investigate the role of cardiac surgery and its timing in predicting the five indictors of ADHD severity [$CBLC_{AD}$ (child), $CBLC_{AD}$ (parent), ADHD RS_{AD}, ADHD RS_{HI}, ADHD RS_{TOT}] used as separate dependent variables. All multivariate analyses were controlled for sex and age at survey completion. The length of hospital and ICU unit stay was analysed along cutting points that may affect psychological status. We observed the significance by methodical stepping, by setting cut-off points at postoperative day 5, 10, and 20. The effect sizes were shown by Cohen d-values and etha-square values.

4. RESULTS

The effects of chylothorax on short-, and long-term outcomes

During the 10-year period, 48 patients had chylothorax after pediatric cardiac surgery, and its incidence was 1.2%. One patient had chylothorax preoperatively and one patient had additional significant anomalies in the area of the esophagus and the larynx. Chylothorax was observed between the first (3 patients, 6.2%) and 29th (1 patient, 2%) postoperative days. The highest incidence of chylothorax was observed on the second postoperative day (7 patients, 14.6%). Seven patients (14.6% of the chylothorax population) died during the in-hospital stay. Causes of death were, in 2 of the cases infection with consequent severe septic states; in 2 other cases, untreatable low-output syndrome; in 1 case fatal respiratory failure due to a residual pulmonary vein obstruction, which could not have been resolved by a surgical procedure; in 1 other case fatal thrombotic complications, followed by a superior vena cava syndrome and in 1 case irreversible pulmonary hypertension with acute respiratory failure after pleurodesis. In the control group mortality rate for the same period was 4.8% (80 patients of 1,640). Among the chylothorax patients, eleven had genetic abnormalities (3 Down's syndrome, 3 Di-Giorge's syndrome, 1 IgA deficiency and 1 VACTERL, 3 minor anomalies). High postoperative venous pressures (central venous pressure above 18 mmHg) were observed in 23 patients (48%). We had two cases (4.2%) in which the central venous cannulation was the possible cause of ductal injury. After excluding those who had chylothorax after a vascular ring operation (6 patients), the propensity score matching yielded 42 pairs of patients in our database. The exclusion of vascular ring patients was necessary because chylothorax in these cases was most likely due to intraoperative iatrogenic injury of the thoracic duct (considering the anatomical region operated), thus first-line therapy consisted in surgical correction.

Before propensity matching, we found higher values of the perioperative variables in patients with chylothorax: these children were younger than the control patients (308.1±688.2 days vs. 1056.4±1510.7 days, $P<0.001$), had higher RACHS points (3.1±1.2 vs. 2.4±1.1, $P<0.001$), and their CPB times were significantly longer (143.4±48.1 min vs. 104.1±83.5 min, $P<0.001$). Patients with chylothorax required more blood products (54.5±54.3 ml/kg vs. 27.5±37.9 ml/kg, $P=0.003$) and were treated with a greater volume in the first 72 hours (31.9±34.5 mg/kg vs. 20.3±26.1 mg/kg, $P=0.025$). Chylothorax patients needed higher doses of inotropes and nitric-oxide intraoperatively

(11±23 ug/kg vs. 180±11 ug/kg, P=0.016 and 14±29 vs. 102±6, P<0.001, respectively). After propensity matching, we could not determine any significant difference in our statistically balanced system regarding the pre-and intraoperative variables.

There were no significant differences in the postoperative mortality and composite mortality. The occurrence of pulmonary failure (23±54.8 vs. 9±21.4, P=0.001) was higher in the chylothorax group. They also required prolonged mechanical ventilation (M=238, IQR 91–456 vs. M=121, IQR 68–247, P=0.002), but the neurological events, LCOS and renal failure did not differ significantly between the groups. The lengths of the ICU and in-hospital stays (M=14, IQR 7–20 vs. M=7, IQR 4–11, P=0.049 and M=32, IQR 23–40 vs. M=23, IQR 15–28, P=0.01) were longer in the chylothorax group compared to the matched population.

We used early surgical treatment in patients with vascular ring operations. In the majority of cases, after establishing the diagnosis, conservative therapy was started. For those patients who were refractory to the monogenic formula diet and cessation of breast feeding, MCT-TPN therapy was initiated. Twenty-nine patients who did not respond to TPN therapy received octreotide infusion, started with higher loading doses of 8-10 ug/kg/hour and de-escalated gradually after resolution. Dosing in this manner, octreotide infusion resulted in the resolution of CTX in 48 hours in 11 patients (23%). One patient had an anaphylactic reaction to octreotide and acute pleurodesis was performed. In 17 patients (35%), non-responding to octreotide therapy in 48 hours we proceeded with thoracic drainage with the continuation of octreotide infusion for at least 24 hours. This strategy resulted in CTX resolution in 11 (23%) cases. 6 children however, did not show any regression of CTX after 24 hours of chest drainage and continuous octreotide infusion, thus we decided to proceed with surgical intervention. The majority of deaths occurred after the ineffectiveness of conservative therapies, where surgical interventions could not have been avoided (5 patients 12%).

During the long-term follow up, neither octreotide treatment nor surgical ligation were associated with increased mortality (log-rank P=0.54 and P=0.91, respectively). The mean survival times were 11.2 years (95% CI: 9.9–13.4 years) and 10.6 years (95% CI: 8.7–12.5 years) in the chylothorax group and control group, respectively (log-rank test: 0. 47). During the long-term follow-up period, additional 3 patients have died in the

chylothorax group [10 patients (23.8%) during the 10 years] and 12 patients (28.2%) in the control group. Causes of death in the chylothorax group were in 1 case pneumonia induced septic shock and in 2 cases a cerebrovascular event—1 intracranial haemorrhage with consequent herniation and 1 ischemic complication). In the chylothorax group, two-thirds of patients needed at least one reoperation within the first 2 years, which was slightly more than in the control group. During the follow-up, 4 patients had thromboembolic complications (2 had confirmed thrombophilia) in the chylothorax group, while three events were observed in the control group. Neurologic complications (hypoxic cerebral lesions diagnosed by MRI) and epilepsy were frequent in both groups. In the chylothorax group, phrenic palsy occurred more frequently (N=5, 11.9%; N=1, 2.3%, P<0,001). During the 49 reoperations, chylothorax did not reoccur.

Behavioural outcomes

In the examination of behavioural outcomes 80 children undergoing cardiac surgery and 62 healthy controls were included. The mean age of patients during the psychological analysis was 11.5±3.4 years for the operated (47.5% male, 52.5% female) and 11.3±3.5 years for the control groups (58% male, 42% female), with no significant difference between them. The distribution of the different congenital malformations was the following: septum defects (n=15; 18.75%), valve defects (n=15; 18.75%), aortic coarctation with valve disease and/or septum defect (n=5; 6.25%), transposition of the great arteries (n=9; 11.25%), anomalies needing total cavopulmonary connection (TCPC) repair (n=20; 25%), tetralogy of Fallot (n=7; 8.75%), other (n=9; 11.25%). Exclusion criteria were: moderate or severe mental retardation syndromes (Down-syndrome, DiGeorge syndrome), traumatic head injuries, premature birth, extreme low weight at birth (<2500 grams), lack of parental consent. The average RACHS score was 2.5±0.7, the mean ICU stay was 5.9±6.7 days and the mean in-hospital stay was 8.7±10.6 days. Among the 80 operated children 38 were cyanotic preoperatively, while 42 were not. The 80 patients underwent a total of 150 surgeries. Reoperations included in the analysis were planned. 14 patients needed delayed chest closure (17.5%).

For the analysis of the influencing effect of cyanotic states, operated patients were divided in two different groups, considered as homogenous according to the type of the malformation. The first group included patients with incomplete and univentricular

circulation, needing TCPC as final reconstruction (cyanotic group). These children lived for 2-3 years with moderate cyanotic state after an early primary palliation. The second group included patients with VSD, with no cyanosis preoperatively (acyanotic group).

The WOC questionnaire revealed significantly lower scores in problem-focus coping (problem analysis $p=0.007$, conformity $p<0.001$) in the operated group compared to the healthy control (operated 10.7±8.1 points vs. control 14.5±6.1, $p=0.002$). The emotion-focused coping scores were also significantly lower among the operated patients (operated 9.6±6.9 points vs. control 13.6±4.9, $p=0.026$), especially in the field of seeking emotional balance (operated 2.3±1.9 vs. 3.8±1.9 points, $p<0.001$). We have also found significant difference between the TCPC and the control groups in seeking social support (operated 4.9±1.5 vs. 3.1±1.5 points, $p=0.017$) and the emotion-focused coping subscales (operated 10.4±4.4 vs. control 13.6±4.9 points, $p=0.03$);

Between the acyanotic and the control groups we have found remarkable differences in problem-focused coping (problem analysis $p=0.013$; conformity $p=0.02$) and the emotional balancing subscale, resulting in lower scores in the acyanotic operated group. Reoperated patients reached significantly lower scores in all fields of problem-focused coping (problem analysis 2.4±3.1 vs. 4.2±2.5 points, $p=0.035$; cognitive restructuring 2.8±3.5 vs. 5.8±2.9 points, $p=0.003$; conformity 1.6±2.1 vs. 4.9±1.9, $p<0.001$; problem-focused coping subscale 8.4±8.2 vs. 14.9±5.4, $p<0.001$) and in some fields of the emotion-focused coping subscale (emotional balancing 1,4±1,9 vs. 3.2±1.8, $p=0.003$; seeking social support 1.6±2.2 vs. 3.8±1.4, $p<0.001$). Reoperated children had higher scores on the escape-avoidant behaviour subscale (reoperated 2.9±1.3 vs. 1.3±1.6 points, $p=0.002$). Escape-avoidance was also strengthened by longer mechanical ventilation times (>4 days 4.9±1.8 vs. <4 days 3.1±0.88; $p=0.007$), delayed chest-closure (delayed 5.5±1.41 vs. primary closure 3.0±1.75; $p<0.001$) and in-hospital stay longer than 20 days (>20 days 4.3±1.8 vs. <20 days 3.1±1.8; $p=0.02$). ICU stay longer than 5 days resulted in higher problem analysis scores (>5 days 5.7±2.4 vs. <5 days 3.9±2.5; $p=0.006$) and escape-avoidant behaviour (>5 days 4.2±1.7 vs. <5 days 2.7±1.8; $p=0.002$).

According to the YSR there was no significant difference between operated patients and the control, neither in internalization or externalization symptoms. Examining the influence of the cyanotic states, we have found significantly higher scores regarding somatization in the TCPC group (TCPC 2.9±3.2 vs. control 1.4±2.1, $p=0.049$)

compared to the control. The difference was not remarkable between the acyanotic group and the control. Among operated children, short-term ICU stay has significantly strengthened the internalization symptoms (>5 days 1.9±1.7 vs. <5 days 3.2±2.9; p=0.017).

Attention deficit hyperactivity disorder

In the analysis of ADHD symptomatology 80 operated (26 above and 54 under 3-years of age) and 53 healthy control patients were involved. There was no statistically significant difference among the three study groups in terms of participants' sex. However, those undergoing surgery later in life were older at survey completion (medium effect size) than members of the control group or who were operated on below the age of 3 for the first time ($CBLC_{AD}$ F=1,89, p=0,156, η^2= 0,028; YSR_{AD} F=4,463, p=0,013, η^2= 0,064; ADHD RS_{AD} F=9,716, p<0,001, η^2=0,130; ADHD RS_{HI} F=7,640, p<0,001, η^2= 0,105; ADHD RS_{TOT} F=7,92, p<0,001, η^2=0,109]. Between the two surgically treated groups, there were statistically significant differences in the length of hospital stay (medium effect size), the number of operations (medium effect size), and the frequency of perioperative cyanosis (large effect size); in all three cases, values were higher (less favourable) for children who were first operated below 3 years of age. In terms of ADHD symptomatology, those undergoing surgery later in life had higher ADHD symptom scores across all five indicators than the other two subgroups; however, the difference did not reach statistical significance in case of the Child Behaviour Checklist's Attention Disorders Subscale. The magnitude of the differences was small ($CBCL_{AD}$) or moderate (YSR_{AD}, ADHD RS_{IA}, ADHD RS_{HI}, ADHD RS_{TOT}). In terms of the prevalence of diagnosable ADHD symptom severity, those undergoing surgery later in life had higher prevalence rates than the other two subgroups. The difference did not reach statistical significance in case of the Child Behaviour Checklist's Attention Disorders Subscale (although the effect size indicator suggested a moderate difference), while in the case of the ADHD Rating Scale–IV, the difference was statistically significant and the effect size was large (YSR_{AD} F=3,920, p=0,022, η2=0,058; $CBCL_{AD}$ F=1,566, p=0,213, η^2 =0,024). Results of the omnibus tests from the multivariate analyses indicated that surgery status was a significant predictor of most indicators of ADHD symptomatology even after controlling for sex and age at survey completion, with effect sizes in the small to medium

range. Similar to the bivariate analyses, the only ADHD symptom severity indicator regarding which surgery status was not a statistically significant predictor was the Child Behaviour Checklist's Attention Disorders Subscale. Observed power for the surgery status variable ranged from 0.43 ($CBCL_{AD}$) to 0.75 (YSR_{AD}). Regarding all ADHD symptom severity indicators, the post hoc tests indicated that the symptoms of those treated surgically above 3 years of age were more severe than not only the control group but also of those who were treated surgically at a younger age; and with some exceptions, these differences were statistically significant (ADHD RS_{AD} F=9,759, p<0,001, η^2 =0,132; ADHD RS_{HI} F=8,756, p<0,001, η^2 =0,120; ADHD RS_{TOT} F=8,846, p<0,001, η^2=0,121). Interestingly, the control group and those treated surgically under 3 years of age did not differ significantly across any of the five ADHD symptom severity indicators according to the post hoc tests.

5. CONCLUSIONS

In the present study we examined the short-, and long-term consequences of pediatric cardiac surgery. We demonstrated the effects of chylothorax on the long-term survival after pediatric cardiac surgery and we described the behavioural and neuropsychological outcomes of this specific patient population. The new findings detailed in this dissertation are the following:

1. Chylothorax is a serious but rare complication after pediatric cardiac surgery in Hungary. Its short-term consequences consist in prolonged need for mechanical ventilation, increased intensive care unit and in-hospital stays. Despite, short-term mortality rates do not differ from non-chylothorax patients.
2. During the long-term follow-up, we did not observe significantly higher mortality rates among patients with chylothorax compared to non-chylothorax children, not even when considering subsequent morbidities and different therapeutic modalities. Despite the prolonged hospital stay and the fluctuating course of the disease, the long-term prognosis is good. After reoperations, the complication did not reoccur in any of the cases, regardless of the complexity of the surgical procedure.

3. Based on the experience of the present study, we propose a clearly structured, centre-based therapeutic algorithm, with an optimized resource utilization for the treatment of chylothorax. The algorithm starts with a median-chain triglyceride diet with halted breast feeding and / or parenteral nutrition in all cases where clear surgical causes can be surely excluded. In non-responder cases, octreotide infusion can be safely introduced by using higher loading doses followed by a gradual de-escalation strategy. Physical elimination of the chyle by chest drainage can be included in any stage of the algorithm as a supportive strategy, in case if respiratory distress occurs and invasive ventilation cannot be stopped or it is needed to be restarted. Surgical intervention is proposed to be used only in very well-considered refractory cases, as morbidity and mortality may be particularly high.
4. Coping strategies and psychological adaptation of children who underwent open heart surgery under the age of 3-years, significantly differ from healthy population in several aspects. Operated children had difficulties in the mobilization of both emotion-, and problem-focused coping. Long-term hospital stays resulted in increased somatization, while multiple reoperations led to an escape-avoidant behaviour. Children living with a long-term incomplete circulation are liable to develop maladaptive emotion-focused coping strategies, while patients undergoing surgery with an acyanotic malformation have difficulties in the activation of problem-focused coping and social adaptation.
5. The neuropsychological outcome following pediatric cardiac surgery strongly depends on the current stage of an age-related neurodevelopment. We have found a significantly higher incidence of ADHD symptomatology among children undergoing surgery after 3-years of age, despite that they had less reoperations and incomplete circulation compared to younger patients. Possible causes include better neuronal plasticity and active synaptogenesis in neonates and infants.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

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Further publications

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